

PQM Good Manufacturing Practices Assessments and Dossier Review, India

August 9-12, 2010

Trip Report

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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 and Dr. Kennedy M. Chibwe traveled to India to perform Good Manufacturing Practices (GMP) assessment of the Svizera Labs Private Ltd. facilities to assess their compliance with the World Health Organization (WHO) GMP main principles for pharmaceutical products.

The assessments revealed that the Svizera Labs facility is operating in a state of control regarding compliance with the WHO Good Manufacturing Practices for pharmaceuticals.

The PQM team also met with Lupin and Cipla to discuss current and future collaborations and PQM technical assistance.

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Key Words

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

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Acronyms

DOTS	Directly-Observed Treatment, Short-course
DQI	Drug Quality and Information Program
GMP	Good Manufacturing Practices
PQM	Promoting the Quality of Medicines Program
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

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 WHO with their "Expressions of Interest" for the WHO Prequalification Programme.

Executive Summary

The following is a summary of the assessment audit of Svizera Labs in India conducted by PQM to assess the firm’s capabilities regarding compliance with World Health Organization current Good Manufacturing Practices (WHO cGMPs) main principles for pharmaceutical products.

Key Observations

Svizera has systems in place as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture finished TB pharmaceutical products. However, the audits also revealed that Svizera has minor objectionable observations regarding compliance with the WHO cGMPs for finished pharmaceutical products. These observations applied to Quality System, Facilities and Equipment System, and Laboratory System.

Dossier review

PQM reviewed Svizera dossiers that are in different stages of completion, focusing on the Ethionamide 250 mg tablets dossier that will be finalized and submitted to WHO before September 2010. The others dossiers will be submitted after completing activities regarding bioequivalence studies.

Source of Funding

This trip was supported by Core funds for TB.

Overview of Activities

August 9-10, 2010

Visit to Svizera: The PQM team visited Svizera Labs to perform cGMP assessments of the facilities and review dossiers. (See *Annex* for audit agenda).

The assessment audit was performed using the general scheme of the systems approach for auditing the manufacture of pharmaceuticals, and included coverage of the:

1. Quality System, which includes the overall compliance assessment of GMP, internal procedures, and specifications.
2. Facilities and Equipment System, which includes the activities of the firm in providing an appropriate environment and necessary resources to manufacture pharmaceutical products.

3. Materials System, which includes 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, which includes the measures and activities used to control the manufacture of pharmaceuticals, in-process sampling and testing, and process validation.
5. Packaging and Labeling System, which includes the controls used in the packaging and labeling of finished goods.
6. Laboratory Control System, which includes 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 assessment audit revealed that Svizera has systems in place as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture finished TB pharmaceutical products. However, the audits also revealed that Svizera has minor objectionable observations regarding compliance with the WHO cGMP's for finished pharmaceutical products. These observations applied to Quality System, Facilities and Equipment System, and the Laboratory System, which are described below:

1. Manufacturing area doors from sifter, loading, and paste area and main hallway do not seal properly to avoid cross-contamination. Correctives action had been taken by placing a plastic cover with tape; however, a permanent repair should be done.
2. Secondary packaging area carton coding is performed manually in line. The auditor observed some carton stamps were not legible, and there was no well-established inspection interval for the stamping material. Also, there was no vendor qualification of the ink supplier.
3. The chemical testing laboratory fume hood was not adequate for handling of chemicals. A performance check of the hood showed no extraction flow.
4. Review of recall procedures showed no mock recall had been done to evaluate the effectiveness of recall.



The PQM team visits Svizera

August 11, 2010

Visit to Lupin: The team visited Lupin Ltd. to discuss the Capreomycin 1000 mg powder for injection dossier re-submission status and future collaborations for other second-line TB applications to WHO. Capreomycin activities are on hold until senior management decides if a new API supplier will be selected. Lupin will share with PQM the WHO queries for the accepted dossiers for Protionamide tablets 250mg, Cycloserine tablets 250mg tablets, and Ethionamide tablets 250mg for technical assistance, as needed.



The PQM team visits Lupin

August 12, 2010

Visit to Cipla: The team visited Cipla to discuss future collaborations for second-line TB applications to WHO. Cipla has 36 products approved by WHO and 20 in the pipeline. Cipla expressed frustration with the lack of quality documentation from the API source related to their Capreomycin and Ethionamide dossiers, asking if PQM can help on this. PQM will follow up to see how assistance can be provided. Cipla agreed to share with PQM the WHO queries regarding their dossier applications for second-line TB. The PQM team also discussed Cipla's zinc acetate monograph (donated to USP for publication) analytical method validation.



The PQM team visits Cipla

Next Steps

Svizera

- Svizera will send 250 mg tablets Ethiomine dossier to PQM for review prior to submission in August.

Lupin

- PQM will work with Lupin on current dossiers in active status with WHO prequalification.
- Lupin will inform PQM of the future of the Capreomycin 1000mg powder for injection dossier, following the senior management decision.

Cipla

- PQM will work with Cipla on Capreomycin 1000mg powder for injection and Ethionamide 250mg tablets current dossiers in active status with WHO prequalification.
- Cipla will pursue method validation for zinc acetate and work with PQM for possible cross-validation.

Audit Agenda Tentative Audit Plan

Date:	August 9-10, 2010
Products	General cGMP Audit for TB products
Morning 08:30	<p><u>Opening meeting with manufacturer 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>
09:30	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) • Complaint 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>
	<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. <u>HVAC and Dust Control system:</u> • Qualification/Requalification/Monitoring the HVAC + Dust Control System • Inspection of the HVAC + Dust extraction technical area <u>Water purification system:</u> • 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>Compressed air system</u></p> <ul style="list-style-type: none"> • Qualification/Requalification/Monitoring of the Compressed Air systems
17:00	Summary of observations for the day