

GMP Assessment and Discussions on WHO Prequalification with Eight Manufacturers

Mumbai and Pune, India

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Trip Report

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PROMOTING THE QUALITY OF MEDICINES

Executive Summary

Mr. Toledo traveled to India to visit the following eight manufacturers:

1. Shalina Laboratories Pvt. Ltd.
2. Svizera Labs Pvt. Ltd.
3. Concept Pharmaceutical Ltd.
4. Bliss GVS Pharma Ltd.
5. Abbott Healthcare Pvt. Ltd.
6. Kilitch Drugs, Ltd.
7. Simpex Pharma Pvt. Ltd.
8. Nexgen Healthcare Pvt. Ltd.

Mr. Toledo performed an assessment of Shalina's implementation of Good Manufacturing Practices (GMP). This assessment was performed using the World Health Organization (WHO) inspection procedures approach for auditing the manufacture of pharmaceuticals. The assessment revealed that the firm has the systems in place as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture finished TB pharmaceutical products. All the non-compliances and opportunities for improvement observed during the assessment are listed in a full confidential report for the manufacturer.

In addition to the assessment, meetings were held with the other manufacturers to discuss their dossier compilation status and the technical assistance that PQM can offer the companies in the process of obtaining WHO prequalification (PQ).

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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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- Mr. Gagan Harch, Bliss GVS Pharma, General Manager
- Mr. Kishore Shintre, Abbott Healthcare, General Manager
- Mr. Atul Bhopal, Nexgen Healthcare, Marketing Manager
- Nr. Naresh Santhanan, Simpex Pharma, General Manager
- Mr. Yugin Gupta, Concept Pharmaceutical, Executive Director
- Mr. Anthony Boni and Dr. Maria Miralles at USAID Headquarters in Washington, D.C.
- PQM administrative staff and editors

ACRONYMS

API	Active Pharmaceutical Ingredient
CAPA	Corrective and Preventive Action
FPP	Finish Pharmaceutical Product
GMP	Good Manufacturing Practices
PAS	Para-Aminosalicylic Acid
PQM	Promoting the Quality of Medicines Program
RA	Regulatory Affairs
TA	Technical Assistance
TB	Tuberculosis
USAID	United States Agency for International Development
USFDA	United States Food and Drug Administration
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). PQM assists countries to implement anti-TB medicine quality monitoring, and in 2008, began providing technical assistance (TA) 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 (PQ) Program.

Purpose of Trip

The purpose of the trip was to:

- Conduct GMP assessment of Levofloxacin manufacturing activities at Shalina Laboratories Pvt. Ltd. and provide TA on Good Manufacturing Practices (GMP) compliance.
- Visit Abbott Healthcare Pvt. Ltd. to follow up on the status of Capreomycin and Kanamycin dossier compilation and discuss their WHO PQ application.
- Visit Concept Pharmaceutical to discuss dossier compilation requirements for WHO PQ.
- Visit Bliss GVS Pharma Ltd. and Kilitch Drugs Ltd. to discuss future collaboration for products to be submitted to WHO PQ.
- Visit Svizera Labs Pvt. Ltd. to discuss the status of Capreomycin, Levofloxacin, Ethionamide and Cycloserine dossiers to be submitted to WHO PQ.
- Visit Kilitch Drugs Ltd. to discuss future collaboration for products to be submitted to WHO PQ.
- Meet with Simpex representatives regarding Levofloxacin.
- Visit Nexgen Ltd. to discuss future collaboration for products to be submitted to WHO PQ.

Source of Funding

This trip was funded by USAID for Core TB.

Overview of Activities

Manufacturer	Products	Status	Next Steps
Kilitch	Capreomycin Finished Pharmaceutical Product (FPP)	<ul style="list-style-type: none"> • Working with artesunate injection and the dossier will be submitted in the next 2 months. • Injectable facility was sold to Akorn (US pharmaceutical company) and will be phased out within one year. • Planning to manufacture Capreomycin and other 2nd line TB products with a contract manufacturer in Bhiwadi, India next year. 	<ul style="list-style-type: none"> • PQM will continue to support Kilitch for Capreomycin PQ. • PQM will conduct a GMP baseline assessment of the 2nd line TB contract manufacturer by August.
Shalina	Levofloxacin 500mg	<ul style="list-style-type: none"> • Discussed and reviewed Levofloxacin dossier with RA personnel at Shalina headquarters in Mumbai. Dossier will be submitted to WHO PQ by August. • Assessed facilities in Pune. The assessment revealed that the firm has the systems in place as well as the 	<ul style="list-style-type: none"> • PQM will continue to support Shalinas and plan dossier training for RA personnel by July 2012. • PQM will send Levofloxacin

		capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture TB FPP. A confidential report was sent to Shalina for corrective and preventive action (CAPA) plan implementation.	reference standard + impurities for analytical method development activities by mid-May.
Bliss GVS	Levofloxacin 500mg	<ul style="list-style-type: none"> Presented PQM TA support for 2nd line TB medicines manufacturers. Bliss is working toward PQ of Artesunate suppositories and Artemeter/Lumefantrine tablets. After meeting with PQM, Bliss management was interested in developing Levofloxacin 500mg tablets for PQ by 2013. 	PQM will support Bliss on Levofloxacin product development.
Concept	Capreomycin FPP Cycloserine FPP Ethionamide FPP Kanamycin FPP Levofloxacin FPP Moxifloxacin FPP Prothionamide FPP	After PQM's presentation, Concept wants to work with PQM and would like to fast track the process for the following: <ol style="list-style-type: none"> 1. Capreomycin, powder for injection 1g, vial 2. Cycloserine, capsule 250mg 3. Ethionamide, tablet/capsule 250mg 4. Kanamycin, powder for injection 500mg or 1g, vial 5. Levofloxacin, tablet 250 mg or tablet 500mg 6. Moxifloxacin, tablet/capsule 400mg 7. Prothionamide, tablet/capsule 250mg 	<ul style="list-style-type: none"> PQM will provide comparator products starting with Levofloxacin by mid-May. PQM will visit the manufacturing facility in Aurangabad (Chittegaon) to conduct a baseline GMP assessment and dossier compilation training by July.
Svizera	Ethionamide FPP Cycloserine FPP Levofloxacin FPP Capreomycin FPP	<ul style="list-style-type: none"> Svizera is working with 1st line TB 4FDC and 2 FDC that are in good position to reach PQ in the next two months. The facility already passed a WHO PQ inspection and bioequivalence (BE) studies have been accepted. 2nd line TB products (Ethionamide, Cycloserine, Levofloxacin, and Capreomycin) need active pharmaceutical ingredient (API) quality information to finalize dossier compilations. 	<ul style="list-style-type: none"> PQM will provide support to Svizera regarding 2nd line TB API quality information procurement from Chinese and Korean manufacturers. PQM will plan dossier compilation training for Svizera RA personnel by July.
Abbott	Streptomycin FPP	<ul style="list-style-type: none"> Discussed Streptomycin project status and status of the dossier: <ol style="list-style-type: none"> 1. Module 1 completed 2. Module 2 waiting for API 	<ul style="list-style-type: none"> PQM will continue to provide support to Abbott toward PQ. PQM will provide

		<p>information</p> <p>3. Module 3 to be finished with validation information</p> <p>4. Module 4 N/A</p> <p>5. Module 5 to be finished later</p> <p>6. Dossier will be submitted by early 2013</p>	<p>comparator products and reference standards by the end of May.</p> <ul style="list-style-type: none"> • PQM will conduct a GMP baseline assessment of the new facility by July.
Simpex	<p>Levofloxacin FPP</p> <p>Terizidone FPP</p> <p>Prothionamide FPP</p> <p>PAS FPP</p>	<ul style="list-style-type: none"> • Met with Simpex management to outline PQM TA and discuss Levofloxacin, Terizidone, Prothionamide, and PAS projects. • Management will discuss the projects and PQM TA with Directors and will revert to PQM in the coming weeks. 	<ul style="list-style-type: none"> • PQM will continue to support Simpex regarding project readiness. • PQM will provide comparator products and reference standards, if they decide to go forward.
Nexgen		<ul style="list-style-type: none"> • Visited facility to tour the laboratories and discuss PQM support for 2nd line TB manufacturers. • Nexgen is compiling a Streptomycin dossier for Abbott and has a good regulatory record with the USFDA with 16 ANDA submissions and 56 registration dossiers in other countries. • Nexgen management is very interested in developing a Cycloserine FPP in the next year. 	<ul style="list-style-type: none"> • PQM will continue working with Nexgen regarding the Abbott application • PQM will support Nexgen if they decide to go forward with Cycloserine FPP project.

Conclusion

This visit to India was successful by introducing PQM's technical assistance to seven manufacturers and conducting a baseline GMP assessment and dossier discussions for one additional manufacturer. With PQM assistance, one company expects to reach WHO PQ for two dossiers in the coming months, and PQM will continue to support the other manufacturers toward WHO PQ.