Good Manufacturing Practices Assessment of Hizon Laboratories and Meeting with Lloyd Laboratories

Manila, Philippines

September 23-27, 2013

Trip Report

Mr. Edwin Toledo
Senior GMP Specialist

Promoting the Quality of Medicines
Implemented by U.S. Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: (+1) 301-816-8165
Fax: (+1) 301-816-8374
Email: ert@usp.org

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PROMOTING THE QUALITY OF MEDICINES

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Executive Summary

Staff from the Promoting the Quality of Medicines (PQM) program traveled to Manila, Philippines, to conduct a Good Manufacturing Practices (GMP) assessment at Hizon Laboratories for compliance with World Health Organization (WHO) GMP requirements in the manufacture of Levofloxacin tablets.

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

1. Quality System, which includes the overall compliance assessment with Good Manufacturing Practices, internal procedures, and specifications.
2. Facilities and Equipment System, which includes the activities of the firm that provide an appropriate environment and resources needed in the manufacture of pharmaceutical products.
3. Materials System, which includes the measures 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 related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the firm's stability program.

The objective in using this audit approach is to provide the most comprehensive GMP 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 GMPs for the manufacture of finished pharmaceuticals.

The PQM assessment audit revealed that Hizon Laboratories has the capabilities, knowledge, and skills necessary to manufacture finished Levofloxacin products. The audit also revealed, however, that Hizon had some objectionable observations regarding compliance with the GMP's for finished pharmaceutical products related to utilities and infrastructure that will be addressed during the coming months. These observations will strengthen the firm's quality systems in order to comply with WHO GMP requirements.

In addition, PQM visited Lloyd Laboratories to discuss their interest in receiving technical assistance for various products toward WHO Prequalification.

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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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- Anthony Boni and Maria Miralles at USAID Headquarters in Washington, D.C.
- PQM administrative staff and editors

ACRONYMS

AHU	Air Handling Unit
CAPA	Corrective and Preventive Action
DQ	Design Qualification
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
HEPA	High-Efficiency Particulate Air
HVAC	Heating, Ventilation, and Air Conditioning
IQ	Installation Qualification
OQ	Operational Qualification
OOS	Out of Specifications
PQ	Performance Qualification
PQM	Promoting the Quality of Medicines Program
SOP	Standard Operating Procedures
TA	Technical Assistance
TB	Tuberculosis
UDAF	Unidirectional airflow
USAID	United States Agency for International Development
USP	U. S. Pharmacopeial Convention
VMP	Validation Master Plan
WHO	World Health Organization
WP	Water Purification

Background

Tuberculosis (TB) is a global concern, and the Promoting the Quality of Medicines (PQM) program, funded by the United States Agency for International Development (USAID) and implemented by the U.S. Pharmacopeial Convention (USP), 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 quality monitoring of anti-TB medicines and, in 2008, began providing technical assistance (TA) to interested manufacturers of anti-TB medicines in the preparation of the medicine dossiers they submit to the World Health Organization (WHO) with their "Expressions of Interest" for the WHO Prequalification Programme.

Purpose of Trip

The purpose of the trip was to:

- Conduct GMP assessment at Hizon Labs for the manufacturing of Levofloxacin tablets; and,
- Visit Lloyd Laboratories, Inc., to discuss PQM technical assistance for second-line anti-TB products.

Source of Funding

This trip was funded by the Global Health Bureau for Core Tuberculosis.

Overview of Activities

Assessment of Hizon Laboratories

Item	Description	
Date	September 23-25, 2013	
Specific Objectives	Perform pre-procurement GMP assessment of Hizon Labs	
Chi Key Personnel	Lucita Y. Soriano, Senior Vice President–Plant Operations, Hizon Laboratories Joy A. Valle, Vice President–Technical Services, Hizon Laboratories Jennifer K. Uy, Executive Director–Technical services Harry J. Arnedoval, Quality Assurance Manager Leonora V. Tison, Quality Assurance Coordinator Annabelle G. Esguerra, Validation Manager Jennifer G. Villanoza, Vice President–Manufacturing Operations	
Agenda	See *Annex 1* for the Hizon GMP assessment agenda	
Areas Evaluated	• Quality assurance • GMP for pharmaceutical products • Sanitation and hygiene • Qualification and validation • Complaints • Product Recalls • Contract production and analysis	• Training • Personal hygiene • Premises • Materials • Utilities • Documentation • Good Practices in Production

	• Self-inspection • Personnel	• Good Practices in Quality Control
Key Findings	The PQM assessment audit revealed that Hizon Laboratories has the capabilities, knowledge, and skills necessary to manufacture finished Levofloxacin products. The audit also revealed, however, that Hizon had some objectionable observations regarding compliance with the GMP's for finished pharmaceutical products related to utilities and infrastructure that will be addressed during the coming months. These observations will strengthen the firm's quality systems in order to comply with WHO GMP requirements.	
Conclusions	Based on the documents reviewed, personnel met, and manufacturing premises audited, the assessment reveals that Hizon will need to make improvements in its infrastructure and utilities in order to comply with WHO GMP requirements. The above deficiency should be addressed with an immediate Corrective Action and Preventive Action (CAPA) plan in no more than six months.	
Next Steps	• Hizon to complete CAPA by April 20, 2013 • Hizon to start compiling dossier per PQM recommendations.	

Meetings with Lloyd Laboratories

As the management of Lloyd Laboratories had expressed interest in participating in the PQM technical assistance program for second-line anti-TB medicines, Mr. Edwin Toledo met with them to further discuss what technical assistance PQM could provide for their existing facility and for a new plant in Pondicherry, India.

Conclusion

Overall, the company was very receptive and eager to receive PQM technical assistance for Levofloxacin, Moxifloxacin, and Amikacin. The management is committed to investing in a facility upgrade in a timely manner as would be required to comply with WHO GMP requirements.

Next Steps

1. PQM will sign a confidentiality agreement with Lloyd Laboratories.
2. PQM will send a list of manufacturers of active pharmaceutical ingredients to Lloyd for Levofloxacin, Moxifloxacin, and Amikacin by October 31.
3. PQM will conduct GMP assessments of Lloyd's manufacturing sites as they progress with the projects.

Annex 1

Hizon Assessment Agenda

Activity
Day 1
<u>Opening meeting with key personnel:</u> • Introductions of all personnel • Hizon presentation • Confirmation of proposed inspection plan/schedule • Levofloxacin project status
Facility Tour: • Receiving raw material and packaging materials • Raw Material and Packaging Material Warehouse • Utilities, HVAC, water purification, compressed air, boilers, electricity generators • Manufacturing Areas
Facility Tour continuation • Finished Products Warehouse • Shipment • Quality Control • Chemistry Analysis (SOP, Specifications, Records) • Microbiological Analysis (SOP, Specifications, Records) • Stability Studies (SOP, Specifications, Records)
Summary of observations for the day
Day 2
Document Review - Quality Management System review: • 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 • Validation Master Plan • Equipment Qualification • Pest Control

Activity
• Batch Records • Maintenance Program • Calibration Program • Supplier Qualification • Internal Audits • Change Control • Recalls from the Market • Complaints Management • Deviation Management • Annual Product Review for the products in focus for 2011 & 2012
<u>CONTINUE -</u> **Document Review - Review of Plant Layout and Utilities (HVAC, Dust control, Water purification, and Compressed air system):** **1. HVAC and Dust Control system:** • Qualification/Requalification/Monitoring the HVAC & Dust Control Systems • Inspection of the HVAC + Dust Extraction technical areas **2. Water purification system:** • WP system drawings and summary of specifications and capacities • Qualification/Requalification/Monitoring the WP system (Sampling and trend analysis) • Inspection of Water Generation and Purification System installations **3. Compressed air system:** • Qualification/Requalification/Monitoring the Compressed Air systems **4. Equipment qualification and preventive maintenance:** • Equipment qualification/Requalification (DQ, IQ, OQ, and PQ for major equipment) • Calibration • Preventive maintenance schedules and records **5. Validation:** • Validation Master Plan (including status and planned) • Process validation and revalidation for the product in focus • Cleaning validation **6. Review of BMRs:** • SOP on batch review and batch release Review of BMRs for selected batches
Summary of observations for the day and closing meeting with company representatives
Day 3
Levofloxacin dossier discussion and compilation
Summary of visit and Next Steps