

USP DQI Good Manufacturing Practices Assessment and Dossier Review

India

March 16-26, 2009

Trip Report

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The United States Pharmacopeia Drug Quality and Information (USP DQI) Program, funded by the U.S. Agency for International Development (USAID) under cooperative agreement HRN-A-00-00-00017-00, provides technical leadership to more than 30 developing countries to strengthen their drug quality assurance programs, ensure the quality of medicines and promote public health. USP DQI helps build local, national and regional capacity to improve the standards of drug manufacturing and distribution, reduce the impact of infectious diseases, mitigate the effects of the HIV/AIDS epidemic, and advance the appropriate use of medicines. This document does not necessarily represent the views or opinions of USAID. It may be reproduced if credit is given to USP DQI.

Abstract

The DQI team (Dr. Souly Phanouvong and Mr. Edwin Toledo) conducted a visit to Kilitch Drug Limited and Lupin Limited, in Paonta Sahib and Mumbai, India, to evaluate the progress of their corrective actions to comply with World Health Organization (WHO) Good Manufacturing Practices (GMP) standards in manufacturing Capreomycin powder for injection and to provide assistance in compiling additional information to respond to the WHO Prequalification queries.

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Key Words

Kilitch Drug Limited (KDL), Lupin Limited (LL), Good Manufacturing Practices, Validation, Standard Operating Procedures, Capreomycin Powder for Injection, Dossier, Prequalification.

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Acronyms

AED	U.S. Academy for Educational Development
CAP	Corrective Action Plan
DMF	Drug Master File
DOTS	Directly-Observed Treatment, Short-course
EOI	Expression of Interest
FDC	Fixed Dose Combination
GDF	Global Drug Facility
GLC	Green Light Committee
GMP	Good Manufacturing Practices
KDL	Kilitch Drug Limited
LL	Lupin Limited
MCH	Maternal and Child Health
POUZN	Point-of-Use Water Disinfection and Zinc Treatment program
HP	Himachal Pradesh
QA	Quality Assurance
QC	Quality Control
UNOPS	United Nations Office for Project Services
USAID	United States Agency for International Development
USP DQI	United States Pharmacopeia Drug Quality and Information Program
WHO	World Health Organization

Background

Tuberculosis, a global concern for many decades, is now compounded by the development of multidrug-resistant tuberculosis (MDR-TB) – strains of tuberculosis that are resistant to both isoniazid and rifampicin. The situation has been exacerbated by the emergence of extensively drug resistant tuberculosis (XDR-TB), which is described as resistance to isoniazid, rifampicin, and two or more of the six classes of second-line anti-tuberculosis drugs.

USP DQI 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, in 2001, at the request of USAID and WHO, USP developed pharmacopeial 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. USP DQI also assists countries in the Mekong Subregion to implement anti-TB drug quality monitoring and helped develop and deliver joint regional and national training courses on TB drug management for Central Asian countries and Russia. USP DQI also disseminated drug information on MDR-TB and TB/HIV co-infection to help improve drug selection and treatment.

In 2007, USAID asked USP DQI to assist the Global Drug Facility (GDF) and the Green Light Committee (GLC) to increase the number of manufacturers of good quality second-line anti-TB drugs that are WHO prequalified. In response, USP DQI assisted GDF and GLC to design a questionnaire to include with request to manufacturers to submit Expressions of Interest (EOI) in the WHO prequalification process. These facilitate the evaluation of manufacturers of priority second-line anti-TB drugs (capreomycin, kanamycin, and para-amino salicylic acid) that may be eligible for and interested in becoming WHO prequalified. Through these collaborative efforts, the manufacturers selected will receive technical assistance to improve their GMP compliance.

In February 2008, USP DQI visited Kilitch Drug Ltd (KDL) – a sub-contractor of Lupin Ltd (LL) and manufacturer of capreomycin powder for injection – to conduct a GMP inspection and provide guidance on compiling dossiers to submit to the WHO Prequalification Programme. The DQI team found 40 GMP-related deficiencies and recommended that KDL implement corrective actions. Following DQI assistance in dossier compilation and review, LL submitted the capreomycin dossier to WHO in September 2008. WHO has accepted the application for review.

Purpose of Trip

The USP DQI team visited KDL and LL to perform assessments of their compliance with GMP standards and dossier status in the manufacturing of capreomycin powder for injection toward WHO prequalification. USP DQI conducted a full GMP audit to evaluate KDL corrective actions implementation and to help LL address WHO prequalification queries. USP DQI also discussed with LL a possible collaboration to develop pharmacopeial monographs for prothionamide and ethionamide. Meetings were held with USAID/India, the United Nations Office for Project Services (UNOPS), and the Academy for Educational Development (AED) to debrief officials and the team also met with zinc gluconate manufacturers for monograph collaboration (see *Annex 1* for the Visit Agenda).

Source of Funding

This trip was supported by USAID core funds for Tuberculosis and Maternal and Child Health.

- **Overview of Tuberculosis-related Activities**

Monday, March 16, 2009

Meeting with USAID/India Mission: The USP DQI team met with Mr. Robin Mardeusz (Population Health & Nutrition Officer) from the Office of Population Health & Nutrition, USAID/India, to discuss the details of the trip. The team provided details of the technical assistance USP DQI is providing to LL and KDL on the capreomycin dossier and GMP compliance (see *Annex 2* for the Audit Agenda). The team met with Dr. Rajiv Tandon, Chief of the Mission's Maternal and Child Health team to discuss the possible involvement of USP DQI in rolling out zinc sulfate for pediatric diarrheal diseases in India. Dr. Tandon explained to the team that zinc has been rolled out in the private sector by AED and requested information on any findings regarding zinc quality. Dr. Tandon also requested ideas on how DQI could assist.

Next steps:

1. Should the need arise, Mr. Mardeusz will inform USP DQI of anti-TB drug quality issues in India and discuss possible technical assistance requirements.
2. USP DQI team will send this trip report to Mr. Mardeusz and bullet points to Dr. Tandon.

Meeting with UNOPS: The team later met with Mr. Sesay Murtada, Senior Pharmaceutical Product Supply Chain Officer, and Mr. Sridharan Rangachari, National Procurement Officer, at UNOPS to discuss the technical assistance that USP DQI is providing to second-line anti-TB manufacturers and explore a possible collaboration in the identification of good quality anti-TB manufacturers as possible candidates for USP DQI technical assistance in GMP and dossier preparation. Mr. Murtada and Mr. Sridharan were interested in USP DQI assistance in anti-TB dossier preparation and will be helping to identify manufacturers willing to pursue WHO prequalification.

Next steps:

1. USP DQI team will send this trip report to Mr. Murtada and Mr. Sridharan.
2. UNOPS will discuss with USP DQI possible manufacturers of second-line anti-TB drugs that may be interested in WHO prequalification.

Wednesday, March 18, 2009

The team traveled from Delhi to Paonta Sahib, Sirmour (H.P.), and stayed in Dehradun, where they met with the management KDL to discuss and plan for the assessment.

Thursday-Friday, March 19-20, 2009

The team visited the KDL manufacturing site and met with Mr. Paresh Metha, Technical Director, Mr. M.M. Agashiwala, Sr. Vice President, and KDL site management to evaluate the progress of their compliance with GMP standards in manufacturing capreomycin powder for injection and to provide assistance in compiling additional information to respond to the WHO Prequalification team's queries related to the manufacturing activities of the finished dosage form of capreomycin. The USP DQI GMP evaluation covered the air handling unit, water purification system, compressed air system, starting materials stores, production rooms, packaging area, QC laboratory, and capreomycin formulation. All KDL GMP standing issues had been addressed to the satisfaction of the DQI inspection team, and the company is ready to receive a WHO Prequalification visit.

The DQI team went through each of WHO's queries with the responsible staff of KDL and a representative from LL, Mr. P.M. Judhav, Corporate QA, and provided guidance on what information and support documents should be included in the responses. Most queries pertinent to the finished dosage form of capreomycin by KDL have been addressed. Queries related to active pharmaceutical ingredient (API) are to be addressed by LL headquarters in Mumbai.

Monday-Tuesday, March 23-24, 2009

The team visited LL in Mumbai and met Mr. Jadav Prabhakar, Corporate QA; Ms. Mansi Haldankar, Manager – Regulatory Affairs; and the Regulatory Affairs personnel to review the API of capreomycin dossier and help them address the queries from WHO (See *Annex 3* for the agenda). USP DQI also discussed with LL whether the company would be interested in providing analytical methods on prothionamide and ethionamide to DQI for use in developing pharmacopeial monographs for these products. LL Regulatory Affairs personnel expressed interest in providing their analytical methods but need concurrence from senior management. They will inform DQI of their decision once they have consulted with the appropriate management staff. USP DQI and LL agreed on the response to WHO and next steps.

Next Steps:

1. LL team to contact the capreomycin API vendor, North China Pharmaceutical Huasheng Co., requesting the following documents/information:
 - a. The Drug Master File (DMF) should include detailed information, including specifications, on the container closure system of the API.
 - b. Description on the microbiological monitoring program used during routine production and media fills.
 - c. Certification that the material (capreomycin API) is free from risk of Bovine Spongiform Encephalopathy and Transmissible Spongiform Encephalopathy.
2. USP DQI to schedule a conference call in May 2009 with LL to discuss progress.
3. LL to add capreomycin impurities testing and force degradation study results to the dossier.
4. LL to include last stability results (9 months stability) in capreomycin dossier.
5. LL to update capreomycin specifications to include vials and stopper ID test along with required in process tests.
6. LL to discuss with R&D possible collaboration in the development of a prothionamide tablets monograph.

Next Steps

1. Ensure that LL submits the remaining data on API DMF by May 2009.
2. Follow up with LL and KDL on any assistance they may need in relation to capreomycin submission.
3. Schedule a conference call with LL by May to discuss prothionamide tablets monograph development.

• Overview of Maternal and Child Health-related Activities

Monday, March 16, 2009

Meeting with AED: The team met with Mr. Deepak Saksena, Country Director of Public-Private Partnerships for Health, AED/India Office, who is working on the POUZN project to roll

out zinc in India. The team discussed collaborating on zinc gluconate/acetate syrups monograph procurement from local manufacturers and how USP DQI can help in India's zinc activities. Mr. Saksena agreed to contact FDC Pharmaceuticals (local zinc manufacturer) to ask if they are interested in working with USP DQI to develop a compendial monograph for zinc syrups. Mr. Saksena also requested that USP DQI perform testing of zinc syrups developed by Daffohils Pharmaceutical, a small company that has extensive rural coverage in Uttar Pradesh State where AED is implementing a campaign to sensitize rural chemists and medical practitioners to prescribe zinc and ORS for diarrhea management as an effective replacement for antibiotics and anti-diarrheals. USP DQI agreed to the request and explained how to send the samples by courier.

Next steps:

1. USP DQI to perform testing on zinc sulfate syrup from Daffohils Pharmaceutical.
2. Mr. Saksena to contact FDC for zinc gluconate/acetate syrups monograph collaboration.

Tuesday, March 17, 2009

Meeting with Shalaks Pharmaceuticals Ltd: The team met with Mr. Vinod K.Nangia, Managing Director, Mr. Raj Wirmani, Director, and Mr. Mahesh Jaidka, TOSC Pharmaceutical General Manager (the "Shalaks team") to discuss possible collaboration on zinc gluconate syrup monograph development. The Shalaks team agreed to send the technical information and samples of their zinc gluconate syrup with a courier on March 21, 2009 to the DQI team. USP DQI was pleased with Shalaks' initiative and conducted a walk-through of their facilities to understand their manufacturing process and zinc syrup capabilities.

Shalaks is a small manufacturing company located in New Delhi focusing on drug formulations and personal care products. They manufacture ointments, creams, and solutions including Chlorhexidine solution 4%. Zinc gluconate syrup production is sub-contracted to TOSC International Pvt. Ltd., also a local pharmaceutical manufacturer in Delhi. Shalaks/TOSC's manufacturing facilities are adequate for their manufacturing activities; however, a detailed assessment will need to be done to assure full compliance with WHO GMP requirements.

Wednesday, March 25, 2009

The team visited FDC Ltd. and met with Ms. Jwala Naik, Marketing Manager, to explain USP DQI's role in zinc activities and discuss possible collaboration on zinc gluconate/acetate syrups monograph development. Ms. Jwala agreed to discuss the USP DQI proposal with FDC R&D Management and will communicate any decision to DQI in May 2009.

• Conclusion

USP DQI objectives of the trip were met; WHO queries regarding capreomycin dossiers were properly addressed and KDL is implementing the corrective actions recommended by DQI in compliance with WHO guidelines. LL has to follow up with its capreomycin API vendor in China for some additional critical documents to support complete responses to WHO queries. The USP DQI team provided compendial reference materials, a complete set of USP32-NF27 (approx. \$718), to LL to assist them in analyzing APIs and finished products; the company was very appreciative of the donation. The USP DQI team also received technical data for zinc sulfate syrup monograph development from Shalaks Pharmaceuticals.

Visit Agenda

Date	Time	Place	Contact
March16 (Monday)	10:0-11:00am	AED	Mr. Deepak Saksena
March16 (Monday)	3:30-4:30pm	USAID	Mr. Robin Mardeusz Dr. Rajiv Tandon
March16 (Monday)	7:00-8:00pm	UNOPS	Mr. Murtada Sesay Mr. Sridharan Rangachari
March17 (Tuesday)	7:30am-2:00pm	Shalaks Pharma	Mr. Vinod K.Nangia Shalaks Pharmaceuticals Pvt. Ltd.
March 18 (Wednesday)	All day	Travel to Paonta Sahib	N/A
March 19 (Thursday)	9:30am-4:30pm	Kilitch	Mr. Paresh Metha
March 20 (Friday)	9:30am-4:30pm	Kilitch	Mr. Paresh Metha
March 21 (Saturday)	All day	Travel from Paonta Sahib to Delhi	N/A
March 22 (Sunday)	All Day	Travel from Delhi to Mumbai	N/A
March 23-24 (Tuesday)	9:00am-4:00pm	Lupin	Ms. Pooja Baria
March 25 (Wednesday)	1:00-2:00pm	FDC	Ms. Jwala Naik
March26 (Thursday)	All Day	Travel to US	N/A

Audit Agenda
March 19-20, 2009
Product: Capreomycin for Injection

I. Introduction

- Introduce personnel (all)
- Purpose of the visit
- Review of compliance report
- Discussion of WHO prequalification process for Capreomycin

II. Warehouse, Plant, and Laboratory Tour

III. Compliance Report Documentation Review

1. Site Master File
 - Amendments, if applicable
 - Annual Report
2. Drug Registration and dossier

IV. Quality Systems

1. Master Batch Record Control and Review
2. Release Process
3. SOPs and Documentation Practices
4. Records and Sample Retention (Reserve sample program)
5. Change Control
6. Customer Notification Procedures
7. Training (GMP and job-specific)
8. Complaint System
9. Internal/External Audit Program
10. Investigation reports (will be selected during the audit)
11. Stability Program: procedure, Protocol and Summary of data
12. Rejects: Investigation
13. Quarantine product
14. General Manufacturing Procedures

Lupin Agenda

March 23-24, 2009

Products: Capreomycin, Prothionamide, Ethionamide, and Cycloserine

1. Introduce personnel (all)
2. Purpose of the visit
3. Discuss Capreomycin Dossier Status
4. Discussion on Prothionamide , Ethionamide and Cycloserine Dossier status
5. Discussion on Lupin collaboration for Prothionamide Tablets USP monograph development

Lupin Regulatory Affairs Personnel

Name	Position
Ms.Pooja Baria	Executive
Ms. Mansi Haldankar	Mansi Haldankar
Mr. Vinay Dadavarte	Manager RA
Mr. Jadav Prabhakar	Manager QA (contract manufacturer)
Mr. Ayyubshaha pure	Manager QA (contract manufacturer)