

DQI Good Manufacturing Practices and Dossier Assessment for Manufacturers of Zinc Sulfate Tablets and Chlorhexidine

Nepal

November 9-13, 2009

Trip Report

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About DQI

The United States Pharmacopeia Drug Quality and Information (DQI) Program, funded by the U.S. Agency for International Development (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. 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 DQI.

Abstract

DQI conducted a GMP and dossier assessment of the manufacturing process for zinc sulfate tablets at Deurali-Janta Pharmaceuticals (DJPL) in preparation for their Expression of Interest (EoI) to the World Health Organization (WHO) Prequalification Programme. DQI also performed an assessment of the manufacturing process for chlorhexidine cream and a review of the zinc tablets dossier at Lomus Pharmaceutical PVT (LPP).

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Key Words

Deurali-Janta Pharmaceuticals (DJPL), Lomus Pharmaceuticals Pvt (LPP), Good Manufacturing Practices (GMP), Validation, zinc sulfate, chlorhexidine, dossier, prequalification, World Health Organization (WHO)

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Acronyms

AED	Academy for Educational Development
CHD	Child Health Division, Ministry of Health and Population
DDA	Department of Drug Administration
DJPL	Deurali-Janta Pharmaceuticals Pvt. Ltd
DQI	Drug Quality and Information Program
EOI	Expression of Interest
GMP	Good Manufacturing Practices
LPP	Lomus Pharmaceutical PVT
MCH	Maternal and Child Health
MOH	Ministry of Health
NPL	Nepal Pharmaceutical Laboratory, Pvt. Ltd.
ORS	Oral Rehydration Solutions
POUZN	Point-Of-Use Water Disinfection and Zinc Treatment
TA	Technical Assistance
UNICEF	United Nations Children Fund
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

It is estimated that diarrheal diseases cause more than three million deaths of children in developing countries each year and contribute substantially to malnutrition in surviving children. Diarrheal episodes of longer duration, commonly called “persistent diarrhea,” have the greatest effect on these outcomes. Treatment of acute diarrhea with oral rehydration solutions (ORS) has become widespread, resulting in reduced mortality from dehydrating diarrheas, but has not resulted in any decrease in the duration of episodes or their consequences, such as malnutrition. Furthermore, adherence to recommendations regarding fluid therapy in children with diarrhea is poor because caregivers want to reduce the duration of illness, often leading them to use antibiotics and other treatments of no proven value.

Two well-documented determinants of diarrheal duration are low weight-for-age and decreased cell-mediated immunity. A common determinant of both of these factors is zinc deficiency, thought to be prevalent in children in developing countries. Zinc supplementation was shown to reduce the duration and severity of childhood diarrhea in randomized controlled trials; consequently, the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) now recommend its use in the management of diarrheal diseases.

In support of WHO and UNICEF, the Drug Quality and Information Program (DQI) developed pharmacopeial monographs for zinc sulfate tablets and zinc syrup. DQI has also provided technical assistance to the zinc global task force in the area of drug quality control, particularly by identifying manufacturers of zinc tablets and syrups that have been certified in Good Manufacturing Practices (GMP). To ensure that available zinc products are of high quality, DQI performs GMP assessments and audits of zinc sulfate manufacturers and assists them in the process of achieving WHO pre-qualification status.

Purpose of Trip

Mr. Toledo visited Deurali-Janta Pharmaceutical Pvt. Ltd. (DJPL) in Katmandu, Nepal to assess their progress on GMP compliance in the manufacturing process of zinc sulfate tablets toward WHO pre-qualification status. Mr. Toledo also visited Lomus Pharmaceuticals Pvt. (LPP) to evaluate the progress on chlorhexidine cream development and to review the zinc sulfate tablets dossier. In addition, several meetings were held with USAID/Nepal, the Department of Health Services, Child Health Division; Department of Drug Administration (DDA); and the Academy for Educational Development (AED) to debrief officials on the manufacturers’ progress toward WHO GMP compliance and the capacity of local manufacturers to produce quality zinc sulfate tablets and chlorhexidine products.

Source of Funding

The trip costs were supported by USAID PE 3.1.6.6 Maternal and Child Health.

Overview of Activities

Monday, November 9, 2009

Meeting with AED

Mr. Toledo met with Mr. Peter Oyloe, Resident Advisor, N-MARC and POUZN Project; and Rajeeb Satyal, Public-Private Partnerships Advisor to discuss Nepali manufacturer GMP status and the visit agenda (see *Annex I*). Mr. Toledo discussed details of the technical assistance (TA) that DQI is providing to Nepali manufacturers. The AED staff gave information about their programs, and Mr. Toledo agreed to meet again at the end of the trip to give a summary of the meetings and to provide AED with a list of the next steps.

Meeting with USAID Maternal and Child Health (MCH) Team

Mr. Toledo and Mr. Oyloe met with Mr. Clifford Lubitz, Deputy Director, Office of Health/Family Planning, and Ms. Linda Kentro, Health Development Specialist, Office of Health/Family Planning (hereafter “MCH team”) to brief them on DQI activities with Nepal manufacturers. The USAID MCH team were pleased with DQI assistance and requested that Mr. Toledo evaluate and send chlorhexidine product specifications manufactured at Lomus Pharmaceutical that will be used for cord washing to prevent sepsis.

Tuesday, November 10, 2009

Meeting at Department of Drug Administration

Mr. Toledo, Mr. Oyloe, and Dr. Pranita Bhatta, Zinc Manager from MITRA SAMAJ (a non-profit organization based in Nepal) met with DDA Director Dr. Radha Raman Prasad to discuss DQI GMP activities with Nepali manufacturers. Dr. Radha was pleased with DQI assistance and reference standard donation and requested GLP training for the Nepal National Laboratory and more help with the reference standard program.

Meeting at Child Health Division of the Department of Health Services

Mr. Toledo and Dr. Bhatta met with Mr. Satish Bista, Senior Public Health Officer from the Department of Integrate Management of Childhood Illness, and Mr. Lila Bikram Thapa Nutrition Chief from Child Health Division (CHD) to update them on DQI activities and Nepali manufacturers’ status. Both were pleased with the updates and the quality of the manufacturers’ products. CHD is purchasing zinc tablets from local manufacturers for the zinc roll out. DQI reiterated the offer to support testing additional samples from local manufacturers to monitor the quality as part of the tendering exercise.

Wednesday-Thursday, November 11-12, 2009

Visit to Lomus Pharmaceuticals PVT

Mr. Toledo visited LPP headquarters and met with Pradeep Jung Pandey, Managing Director and Chairman, to brief him on DQI activities at LPP, then visited the manufacturing facility to discuss the zinc sulfate tablets dossier status and chlorhexidine formulations. LLP’s zinc dossier will be submitted to WHO by the second quarter of 2010. Mr. Toledo briefed LLP on zinc dossier compilation and made some recommendation on how to prepare the required documentation. LLP is still working with chlorhexidine formulations and decided to manufacture only a lotion, based on an acceptability study performed by AED (Chlorhexidine lotion formulated by LLP was accepted by the majority of the mothers participating in the field study in Nepal; WHO is waiting on the results from the study in Bangladesh in early 2010 to issue recommendations on the use of Chlorhexidine for cord care). Mr. Toledo reviewed the chlorhexidine lotion formulation and quality data and made some recommendations on stability and product quality specification requirements. Mr. Toledo also requested chlorhexidine samples to be tested at USP laboratories.

Friday, November 13, 2009

Visit DJPL Pharmaceutical

Mr. Toledo met with DJPL management to discuss zinc tablets dossier compilation in light of WHO requirements and visited DJPL’s new facilities, which are under construction. Mr. Toledo reviewed DJPL’s zinc dossier and made some recommendations to improve its quality. DJPL is working actively on dossier compilation and plans to submit by the end of December and will continue addressing WHO’s new requirements related to biowaivers and flavor acceptability

tests. The new GMP manufacturing facility will be finished by January 2010 and commissioned by March 2010.

Next Steps

- DQI (and the successor program, Promoting the Quality of Medicines “PQM,” which is also implemented by USP) will continue providing TA to DJPL on WHO queries related to the zinc dossier.
- DQI/PQM will visit DJPL in FY10 to evaluate their new manufacturing facility in light of WHO GMP requirements.
- DQI/PQM will continue providing support to LLP for zinc dossier compilation and chlorhexidine quality attributes.

DQI Visit Agenda — November 9–13, 2009

Date	Time	Place	Contact
November 9 (Monday)	10:00am-3:30pm	AED/POUZN Office	Peter and Team
November 9 (Monday)	3:00pm-4:00pm	USAID	Mr. D. P. Raman
November 10 (Tuesday)	11:30pm-12:30pm	Department of Drug Administration office	DDA Director Radha Ramen
November 10 (Tuesday)	02:00am - 03:00 pm	Child Health Division Chief/Nutrition Chief	CHD Director Dr. Shyam Upreti Nutrition Chief
November 11 (Wednesday)	10:00am-04:00pm	Lomus pharmaceutical zinc sulfate	Lomus Marketing Director Mr. Prajwel Raj Pandey
November 11 (Thursday)	10:00am-04:00am	Lomus pharmaceutical chlorhexidine	Lomus Marketing Director Mr. Prajwel Raj Pandey
November 12 (Friday)	10:00am to 5:30pm	DJPL factory	Mr. Hari Bhakta Sharma