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

Nepal

January 12–23, 2009

Trip Report

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About USP DQI

The United States Pharmacopeia Drug Quality and Information (USP 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. 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

USP DQI conducted a follow-on GMP assessment audit of the manufacturing process for the manufacture of zinc sulfate tablets at Deurali-Janta Pharmaceuticals (DJPL), Nepal Pharmaceutical Limited (NPL), and CTL. Also, an initial assessment of the manufacturing process for zinc tablets and chlorhexidine solution was conducted at Lomus Pharmaceutical PVT (LPP) in Kathmandu, Nepal January 12- 23, 2009. The inspection covered the air handling units, water purification systems, compressed air systems, starting materials stores, production rooms, packaging areas, quality control (QC) laboratories, zinc sulfate tablets, and chlorhexidine solution formulations.

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Key Words

Deurali-Janta Pharmaceuticals (DJPL), Nepal Pharmaceutical Limited (NPL), CTL, Lomus Pharmaceuticals Pvt (LPP), Good Manufacturing Practices, Validation, Standard Operating Procedures, zinc sulfate tablets, Prequalification

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Acronyms

AED	Academy for Educational Development
BMR	Batch Manufacturing Records
BPR	Batch Packaging Records
CAP	Corrective Action Plan
CHD	Child Health Division, Ministry of Health and Population
CHX	Chlorhexidine
CTL	CTL Pharmaceutical Laboratory Pvt. Ltd.
DDA	Department of Drug Administration
DJPL	Deurali-Janta Pharmaceuticals Pvt. Ltd
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HVAC	Heating**,** ventilation, and air conditioning
LPP	Lomus Pharmaceutical PVT
MOH	Ministry of Health
NPL	Nepal Pharmaceutical Laboratory, Pvt. Ltd.
OOS	Out-of-Specifications
ORS	Oral Rehydration Salts
POUZN	Point-Of-Use Water Disinfection and Zinc Treatment
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
TA	Technical Assistance
UNICEF	United Nations Children Fund
USAID	United States Agency for International Development
USP DQI	United States Pharmacopeia Drug Quality and Information Program
VMP	Validation Master Plan
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 United States Pharmacopeia Drug Quality and Information Program (USP DQI) developed pharmacopeial monographs for zinc sulfate tablets and zinc syrup. USP 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 zinc products made available are of high quality, USP 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

USP DQI conducted the visits to DJPL, NPL, and CTL, in Kathmandu, Nepal to assess their progress on GMP compliance in the manufacturing process of zinc sulfate tablets toward WHO pre-qualification status. USP DQI also conducted a full GMP audit at Lomus Pharmaceutical to identify any gaps in the systems and help the manufacturer pursue WHO pre-qualification for zinc sulfate products and chlorhexidine. In addition, several meetings were held between USP DQI and USAID/Nepal, the Nepal Department of Health Services, Child Health Division, Department of Drug Administration (DDA), and 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 Program Element 3.1.6.6 Maternal and Child Health.

Overview of Activities

Tuesday, January 13, 2009

Meeting with AED

Mr. Toledo met with Mr. Rajeeb Satyal, Public-Private Partnerships Advisor, and Mr. Peter Oyloe Resident Advisor N-MARC and POUZN Project, to discuss the Nepali manufacturers GMP status and the visit agenda (see *Annex 1* for the visit agenda). Mr. Toledo discussed details of the technical assistance that USP DQI is providing to Nepal manufacturers and the audit process (see Annex 2 for the audit agenda). AED staff gave information about their programs, and the team agreed to meet again at the end of the trip to summarize the audits and meetings and to provide AED with a list of the next steps. Mr. Toledo and Mr. Oyloe departed for DDA.

Meeting at Department of Drug Administration

Mr. Toledo and Mr. Oyloe met with the new DDA Director, Dr. Radha Raman Prasad, to discuss USP DQI GMP activities with Nepali manufactures. Dr. Radha was pleased with USP DQI's assistance and requested Good Laboratory Practices (GLP) training for the Nepal National Laboratory to strengthen their capabilities and help with the reference standard program. Mr. Toledo and Mr. Oyloe were invited to tour Nepal National Medicine Laboratory facilities with Dr. Radha. During the tour, Mr. Toledo noticed that the laboratory needs improvement in equipment, supplies, and facilities. The laboratory personnel are very motivated; however, they work with limited resources, too little training, and inadequate facilities to fulfill their mandate.

Meeting with USAID MCH Team

Mr. Toledo and Mr. Oyloe met with USAID/Nepal officials Mr. Clifford Lubitz, Deputy Director, Office of Health/Family Planning; Mr. Dharmapal P. Raman, Health Program Manager Specialist, Office of Health/Family Planning; Ms. Sharon Arscott-Mills, Senior Public Health Advisor, and Mr. Pangday Yonzone, Program Specialist (hereafter the "MCH team") to brief them on USP DQI activities with Nepal manufacturers. The MCH team was pleased with USP DQI's assistance and requested Mr. Toledo to evaluate chlorhexidine product specifications manufactured at Lomus Pharmaceuticals that will be used for cord washing to prevent sepsis. Mr. Toledo also communicated to the MCH team the DDA's request for assistance. The MCH team explained that the funding allocated to USP DQI for Nepal activities was only for GMP technical assistance and that, at this moment, there are no plans to initiate additional activities in Nepal because there are not enough funds available.

Thursday-Friday, January 15-16, 2009

Visit to Lomus Pharmaceutical PVT

Mr. Toledo visited Lomus Pharmaceuticals headquarters and met with Mr. Pradeep Jung Pandey, Managing Director and Chairman, to brief him on USP DQI activities at Lomus, then visited the manufacturing facility to evaluate the development of zinc sulfate tablets and chlorhexidine formulations and to conduct a detailed GMP inspection that covered the air handling unit, water purification system, compressed air system, starting materials stores, production rooms, packaging area, QC laboratory, and zinc sulfate tablets formulation (see *Annex 3* for LPP audit findings). Lomus is formulating zinc sulfate tablets on 10mg and 20 mg presentation as well as a zinc sulfate oral solution.

Friday, January 16, 2009

Meeting with Dr. Stephen R. Hodging

Mr. Toledo and Mr. Oyloe met with Dr. Stephen R. Hodging, Chief of Party for Nepal Family Health Program, to discuss the chlorhexidine project in Nepal. Chlorhexidine (CHX) has been a widely used disinfectant over the past half century and is approved for use in Nepal both as a surface disinfectant and for topical application. It is widely used in hospitals and is available in consumer formulations through the retail sector. As well as being broad-spectrum, CHX has the property of adhering strongly to skin and providing continuing antibacterial effects for hours or even days, depending on the concentration used. Trials are been conducting in Nepal to assess the ease of use and acceptability with several different application procedures or formulations. Lomus Pharmaceuticals is currently developing both formulations (CHX solution and lotion) for this trial and will be able to finish in the next of month. A pilot study using tubes of CHX lotion and a small plastic bottles of solution, both at a concentration of 4%, will begin in early March in Banke district.

Sunday, January 18, 2009

Meeting at Child Health Division (CHD) of the Department of Health Services

Mr. Toledo and Mr. Oyloe met with Dr. Bhim Acharya, Section Chief, to update him on USP DQI activities and GMP compliance of Nepalese manufacturers. Dr. Acharya was pleased with the manufacturers' GMP status and quality of their products. Nepal CHD is launching a zinc roll-out using Nutriset products; however, they will use local manufacturers' products during the next Phases. USP DQI reiterated support for testing additional samples from local manufacturers to monitor their quality.

Monday, January 19, 2008

Visit NPL Pharmaceutical

Mr. Toledo visited NPL management to discuss the implementation of the corrective action plan (CAP) recommended by USP DQI during the last inspection. NPL management provided a presentation with details on how the CAP was implemented. Mr. Toledo agreed with how NPL addressed the deficiencies in a timely manner. (See *Annex 4* for NPL CAP implementation)

Tuesday, January 20, 2009

Visit DJPL Pharmaceutical

Mr. Toledo met with DJPL management to discuss the implementation of the CAP recommended by USP DQI during the last inspection. DJPL management provided evidence of the implementation, and Mr. Toledo toured the facilities. DJPL has been investing capital to improve their premises with a new water purification unit, a new compress air unit, and two new buildings that will be fully operational during the next year. Mr. Toledo commended DJPL management's commitment toward quality and encouraged them to continue improving quality systems. (See *Annex 5* for DJPL CAP implementation)

Wednesday, January 21, 2009

Visit CTL Pharmaceutical

Mr. Toledo visited the CTL manufacturing site to discuss the implementation of the CAP recommended during the last inspection. CTL has been investing capital updating their system:

new water purification unit pipes made from stainless steel 316 (one of the WHO GMP recommended materials for purified water systems) were installed, a new HPLC was purchased, and most of the findings were addressed in a timely manner. Mr. Toledo congratulated CTL management for their commitment toward quality and encouraged them to continue bringing up their quality system. (See *Annex 6* for CTL CAP implementation)

Thursday, January 22, 2009

Meeting with AED

Mr. Toledo visited the AED office in Kathmandu and met with Mr. Satyal and Mr. Oyloe to discuss both the outcomes of the assessments/audits and a follow up action plan that includes yearly GMP inspections of zinc tablets manufacturers, quality testing of new batches of zinc tablets, post-marketing surveillance of zinc tablets in the market, and technical assistance to prepare local zinc manufacturers to achieve WHO/UNICEF prequalification. The group also discussed possible future collaborations and activities such as GMP assessments for manufacturers of oral contraceptives formulations in light of the WHO prequalification program's new expression for interest for manufacturers of selected oral contraceptives.

Friday, January 23, 2009

Meeting with USAID MCH Team

Mr. Toledo and Mr. Oyloe met with the MCH team to debrief them on the activities with Nepal manufacturers. Mr. Toledo explained how the manufacturers had improved their quality systems dramatically and are willing to pursue WHO prequalification for zinc sulfate, even though they are not receiving help to market their products and the CHD will not use local products during zinc roll-out. Mr. Toledo also explained Lomus GMP status and CHX formulations activities. Mr. Raman and Mr. Yonzone were pleased with USP DQI's technical assistance.

Conclusion

Based on the areas re-inspected, and the corrective actions programs in place as part of USP DQI recommendations, Deurali-Janta Pharmaceuticals Pvt. Ltd., Nepal Pharmaceutical Pvt. Ltd., and CTL Pharmaceuticals meet USP zinc sulfate quality standards and are operating at an acceptable level of GMP compliance for local zinc sulfate tablets manufacturing, as recognized by local regulatory authorities. The companies are willing to submit expressions of interest for zinc sulfate product evaluation in response to the invitation from the WHO Prequalification Program. Lomus Pharmaceuticals' GMP status is in compliance with local GMP standards; however, they need to implement some corrective actions and finish zinc sulfate and CHX formulation development in order to pursue WHO prequalification.

Next Steps

- USP DQI will continue providing GMP TA to DJPL, NPL, CTL, and LPL on dossier compilation.
- USP DQI will test samples of zinc sulfate from Lomus Pharmaceuticals.
- DJPL, NPL, and CTL will continue to address USP DQI CAPs and submit new action plans.
- USP DQI will plan a visit to Nepal zinc and CHX manufacturers by January 2010 to evaluate their progress

Annex 1

USP DQI Visit Agenda — January 13–23, 2009

Date	Time	Place	Contact
January 13 (Tuesday)	10:00am – 3:00pm	AED/POUZN Office	Mr. Oyloe and Team
January 13 (Tuesday)	3:00pm - 4:00pm	DDA	Dr. Radha Raman Prasad Shah, Director DDA
January 13 (Tuesday)	4:30pm - 5:30pm	USAID	Mr. D. P. Raman
January 15 (Thursday)	11:00am - 5:30pm	Lomus Pharmaceuticals Zinc Sulfate	Mr. Prajwel Raj Pandey
January 16 (Friday)	11:00am - 6:30pm	Lomus Pharmaceuticals Chorhexidine	Mr. Prajwel Raj Pandey
January 18 (Sunday)	11:00am - 12:00pm	Child Heath Division	Dr. Bhim Acharya Section Chief
January 19 (Monday)	10:00am - 5:30pm	NPL factory	Mr. Mahendra B Amatya
January 20 (Tuesday)	11:00am - 5:30pm	DJPL factory Visit	Mr. Hari Bhakta Sharma
January 21 (Wednesday)	10:30am - 5:30pm	CTL factory	Mr. Shrestha
January 22 (Thursday)	10:00am - 12:30pm	POUZN Team (Follow-up action plan)	AED team
January 23 (Friday)	10:00 am - 11:00am	USAID debrief at AED office	Mr. D. P. Raman

Annex 2

Audit Agenda

Products: Zinc Sulfate Tablets and CHX

I. Introduction

1. Introduce personnel (all)
2. Purpose of the audit (assessment)
3. Brief review of manufacturing processes used for zinc sulfate tablets and CHX

II. Warehouse, Plant and Laboratory Tour

III. Documentation Review

1. Site Master File
   a) Amendments, if applicable
   b) 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

V. Facilities and Equipment System

1. Air Handling Units – Qualification, Maintenance and Operation (room differential pressures)
2. Water System – Qualification, Sanitization procedure, monitoring and specifications (for all types of water)
3. Manufacturing and Packaging Equipment
   a) Equipment Cleaning Logbook
   b) Preventive Maintenance and Calibration System
   c) Equipment Qualification
4. Pest Control and Housekeeping
5. Environmental
   a) SOP for sanitary design of the transferred equipments

VI. Materials Management

1. Segregation of Materials and FIFO
2. Temperature and Humidity Control
3. Raw Material Receipt, Sampling and Release Procedures
4. Status Control, Storage of Raw Materials and Issuance to Production
5. Control, Storage Labeling and Shipping of Finished Goods (including containers handling)
6. Procedures for Rejected Materials and Destruction
7. Identification of Components
8. Inventory of Materials
9. Storage under Quarantine (location)
10. Raw Materials – Representative Samples Collected, Tested Using Appropriate Means
11. Visual Identification /Inspection

VII. Review of Production and Packaging Systems

1. Batch Record Review Manufacturing and Packaging
2. SOP Cleaning and Line/Equipment Clearance
3. General Manufacturing Procedures
4. Yield and Accountability of Product
5. Reprocessing Procedures
6. In-process Controls and In-process Storage
7. Cleaning Validation (Mfg and Pkg)
8. Process Validation
9. Computer Validation
10. Equipment Qualification
11. Procedure for Labeling Control (storage, issuance, reconciliation and destruction).
12. Environmental Control during Packaging
13. Drum Sealing and Packaging

VIII. Laboratory Control Systems

1. Sampling/Sample Receipt/Handling/Storage/Documentation
2. Reagents and Solutions Preparation/Standardization/ Control/ Documentation
3. Reference Standards – Preparation/Control and Documentation
4. Laboratory Data Documentation, and Review
5. Product and Raw Material Test Methods
6. Testing (In-process and Finished Product) and Release Practices
7. Chromatography Practices
8. Laboratory Equipment Maintenance and Calibration
9. Laboratory Equipment Qualification
10. Laboratory Investigations and Out-of-Specification Result Handling
11. SOP for Reduced Testing (if applicable)
12. Analytical Methods Validation – Accuracy, Precision, Specificity, Linearity, Ruggedness, Limit of Detection and Limit of Quantization
13. Microbiological Testing, if applicable
14. Impurities – Current Impurity Profiles (drug substances along with the acceptable specifications).

15. Handling of Hazardous Materials
16. Procedures and Specifications for In-process Testing

Annex 3

Audit Findings

Lomus Pharmaceutical Pvt (LPP)

The inspection involved the following **key personnel** from LPP:

Dr. Dhama Prasad	General Manager
K. Sarat Kumar	Deputy General Manager
Sarmila Amatya	Assistance QA Manager
Bhesh Raj Shahi	Production Officer
Gyamendra K Ray	Engineer
Raj Kumar Korki	QC Officer
Prajwal Jung Pandey	Marketing Director

General information for LPP

Name of manufacturer	Lomus Pharmaceuticals, Pvt. Ltd
Physical address	Gothatar, Nepal
Postal address	P, Lomus House Chour, Lazimpat , Kathmandu, Nepal
Telephone number	+977-1-443696
Fax number	+977-1-4436395
Summary of activities of manufacturer	Manufacturing of products in the following dosage forms: - tablets, coated or uncoated - capsules - powder - liquid (syrups) - suspensions - hormones - penicillin - creams
Scope of inspection	Inspection of the manufacturing of Zinc Sulfate Tablets and Chlorhexidine formulations with special emphasis on dossier, validation/qualification of manufacturing process, equipment and utilities
Date of inspection	January 15 and 16, 2009
Program	PE 3.1.6.6 Maternal and Child Health

Summary LPP

Lomus is one of the largest manufacturing companies for pharmaceutical formulations in Nepal and is an ISO 9001 and ISO 14001 certified private limited company. Established in 1986, it is situated at Gothatar, 7 km away from Kathmandu zone. It has a main building for oral external, a dermatological unit, a beta-lactam products unit, and a hormones manufacturing unit.

The site has 90 people on staff; 82 in the production area and 8 in the QC/QA departments.

This was the first time the company has been inspected by a USP DQI team. The objective of the inspection was to verify compliance with WHO GMP, in the framework of the prequalification program on priority essential medicines regarding the manufacture of zinc sulfate tablets and chlorhexidine products. USP will also provide technical assistance in dossier compilation based on WHO guidelines and local requirements.

The inspection covered all areas of activity related to the manufacture of the dosage form tablets and liquids:

- Quality assurance;
- Facilities: HVAC, compressed air, water system, and electrical power back-up system;
- Storage areas;
- Sampling and dispensing areas;
- Granulation, compression, mixing, and primary and secondary packaging;
- Quality control and microbiological laboratories.

Lomus GMP Status	
Quality assurance	A quality assurance system was implemented and maintained. The QA and QC units were independent from production. QA personnel were involved in all production and QC activities.
Good manufacturing practices for pharmaceutical products	Good manufacturing practices were implemented and maintained. Manufacturing processes were clearly defined and reviewed. Manufacturing steps were recorded in Batch Manufacturing Documentation. Necessary resources were provided. Instructions and procedures were written in clear and unambiguous language.
Sanitation and Hygiene	The site's hygiene program covered personnel, equipment, materials, and premises. The hygiene measures in place at the time of the inspection were generally found to be sufficient to assure the prevention of contamination of the premises and product. However, manufacturing personnel gowning was drying outside on a line in an unhygienic manner.
Qualification and validation	The key elements of a qualification and validation program were clearly defined and documented in the Validation Master Plan. The VMP was a comprehensive document; it included the worst case principle and specified re-qualifications of the systems. Air handling unit was validated. However, the HEPA filter integrity test needs to be done and analytical method validation were not stability indicating.
Complaints	Complaints and other information concerning potentially defective products were reviewed according to written procedure and the corrective actions were taken. Lomus has a system to track and answer complaints in a timely manner
Product Recalls	Procedure for product recalls was available. Mock recall drill had been performed.
Contract production and analysis	No manufacturing was contracted out.

Self-Inspection	There were procedures to conduct self inspection on an annual basis. This procedure was comprehensive and covered all areas of production, quality control, quality assurance and engineering. There was a schedule with defined teams, and the record showed that the schedule was complied with. Vendor audits were part of the vendor approval and qualification procedure. Lomus uses a questionnaire for vendor qualification.
Personnel	The personnel met were well qualified to perform the duties assigned and had a high consciousness of GMP. There was an organization chart and job description to guide personnel. The responsibilities of the key personnel like head of production, head of quality control and head of quality assurance were well defined and there were personnel designated to deputize the key personnel in their absence. The responsibility for batch review and release was assigned to the head of the QA department.
Training	Training issues were covered in written SOPs. The company provides training at the time of recruitment, specific training relevant to area of deployment, and regular SOP training. Training comprehension was assessed by discussions and observation of performed activities.
Personal Hygiene	Personnel were trained in personal hygiene procedure and facilities were provided in the form of changing rooms, protective garments, and disinfectants. The facilities were generally adequate and the procedures were well enforced.
Premises	Buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance, and production operations. Facilities were designed to minimize potential contamination; the production area had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. There was also sufficient space for the movement of materials and personnel. There were separate personnel and material entrances. Temperature, relative humidity, and pressure differentials were regularly monitored and recorded. In general, the buildings were well-maintained and clean. However, the compression room needs to have the door fixed and differential pressure adjusted to maintain dust control. Dust was observed in the main corridor. The water purification system was fully validated. However, sampling point needs to be identified and the water system diagram at the site master file updated to include sampling points.
Equipment	Process equipment was installed and maintained in a way that minimizes risk of error and contamination. Preventive Maintenance program was in place and was followed. Cleaning SOPs and records were available. Production and quality control equipment were identified as to content and cleanliness status and appropriately indicated by labels. Equipment calibration schedule was established on an annual basis.
Materials	The procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials was available. Incoming goods and finished products were quarantined until tested and released by QC. However, warehouses do not have material location system as part of material management and temperature mapping.
Documentation	There was a procedure for preparation, review, approval and authorization of SOPs. For products reviewed, there was a master formula, specification of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results.
Good Practices in Production	Manufacturing and packaging procedures were well documented in batch manufacturing records (BMRs), batch packaging records (BPRs). Review of several BMRs, BPRs, and use and cleaning logs for rooms and equipment showed that the production processes were generally well executed, controlled and monitored.

Good Practices in Quality Control	In general, good practices in quality control were implemented and maintained. The quality control functions were independent of other departments. Adequate facilities, trained personnel, and approved procedures were available for all relevant activities. Batches of products were released for sale or supply only after certification by the authorized person or designated persons. Quality control personnel had access to production areas. Analyst competency list and training files were available. The QC staff was responsible for sampling and testing incoming starting and packaging materials, intermediates and final products. The QC equipment were qualified and calibrated and the methods used were also validated. Records of analysis were kept and could easily be retrieved. However, the HPLC was broken, there is no IR, and an Out of Specification SOP needs to be drafted.

Annex 4

Corrective Action Plan Implementation
Nepal Pharmaceutical Laboratory (NPL)

Deviation			Status
Sanitation and Hygiene	1	An integrated comprehensive program of sanitation and hygiene must be established that includes premises, equipment and apparatus, production materials and containers, equipment cleaning and disinfection.	Sanitation and Hygiene was initiates as per SOP. Corrective action acceptable
Qualification and Validation	2	Validation Master Plan is missing.	VMP was prepared (NPL/VMP/001-65. Corrective action acceptable
	3	Air Handling Unit is not fully validated. Validation of particle only done at rest conditions.	Revalidation of AHU has been done. Corrective action acceptable
	4	Major manufacturing equipment, such as granulators, blenders, tablet machines, fluid bed dryers, and coating machines, are not qualified.	Qualification on some Mayor manufacturing equipment is done and on going for others as per VMP. Corrective action acceptable
	5	Water purification system is not fully validated.	Revalidation has been done Corrective action acceptable.
	6	Compressed air equipment is not validated.	Qualification Started (Contractor is ACE International). Corrective action acceptable
	7	Cleaning procedures for equipment are not fully validated. Cleaning protocol needs to be finished and implemented.	Cleaning Validation protocol was drafted and is in implementation phase. Corrective action acceptable
	8	Zinc tablets manufacturing process is not fully validated. A minimum of three batches is needed.	Validation report was available. Corrective action acceptable
	9	Zinc sulfate development report needs to include justification of preservative use with stability data.	Preservative had been removed from formulation. Corrective action acceptable
	10	Packaging lines cleaning is not fully validated.	Under Development. Pending
	11	Fluid bed dryer filter bag cleaning procedures are not validated.	Under Development. Pending
Product Recalls	12	The company does not have a designated area for recalled material, and no mock recalls have been made to assess the effectiveness of the company's recall program or the readiness of the recall team. Mock recalls help identify any gaps in traceability or problems that might have developed in the procedures.	Mock recall has been done. Corrective action acceptable
Training	13	Yearly GMP training program is not in place for the employees.	Yearly GMP training has been established. Corrective action acceptable
	14	A training program needs to be established for all employees.	

Personal Hygiene	15	Personnel conducting visual inspections in the packaging area should also undergo periodic eye examinations.	Eye checkup report was available. Corrective action acceptable
Premises	16	Secondary packaging material store is not adequate. Material needs to be segregated. Inventory system is not operational.	Segregation was done and inventory system is now operational. Corrective action acceptable
	17	Storage for liquid raw material is not adequate. Segregation needs to be put in place. The area had other non-liquid materials on top of the barrels. A system for liquid spills need to be put in place (trenches)	Segregation was done. Spill system done. Corrective action acceptable
	18	Facility layout is not adequate; no logical flow of material, personnel and waste were observed.	Flow layout was corrected Corrective action acceptable.
	19	Floors in some areas of production should be changed to an appropriate seamless style that can be effectively cleaned.	Floors of production areas were change. Corrective action acceptable
	20	Premises do not have appropriate lighting. GMP regulations of Storage 50–100 Lux, Laboratory 300 Lux, and Processing and Filling/Packing 500 Lux.	Lux data collection was performed. Necessary step have been initiated. Pending
	21	Raw material storage needs segregation; areas for quarantine and rejected materials are not adequate or missing. Storage area lay-out not adequate. Humidity control not adequate.	Segregation has been done. Lay out is adequate now. Humidity is documented. Corrective action acceptable
	22	SOP for pest control needs to be revised to include a diagram of rodenticide stations around storage and manufacturing areas	Rodenticide stations are in place now. SOP was revised. Corrective action acceptable
	23	The production areas are generally ventilated with filtered air and were entered through airlocks in some areas. The necessary environmental and pressure differential controls were not carried out and recorded in all areas.	Pressured differential now recorded in all areas and condition had been improved. Corrective action acceptable
	24	Warehouses temperature mapping needs to be done	Temperature Mapping has been done. Corrective action acceptable
	25	The map of the warehouse contents needs to be updated, and the appropriate material-handling SOP updated to include the map.	Location Map is under process. Pending
Equipment	26	Procedures for issue, receipt, storage, and destruction of tablet punches and dies do not exist.	Procedure initiated and documented. Corrective action acceptable
	27	The grease container used to lubricate and protect punches and dies is not food grade, which can lead to product contamination. No materials used for operations, such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g., food grade) to minimize health risks.	Grease is now food grade Corrective action acceptable
	28	Non-dedicated manufacturing mayor equipment need validated cleaning method.	Cleaning validation was initiated as per VMP. Corrective action acceptable
	29	Fixed pipes on water system should be clearly labeled to indicate the contents and, where applicable, the direction of flow.	Labeling was done. Corrective action acceptable
	30	Installation Qualification and Operation Qualification has not been performed on the purified water system. Equipment layout and drawing are not adequate. Procedure for sampling of purified water did not specify sampling points and frequency of sampling/testing	Qualifications done. Layout available. Sampling points were made. Corrective action acceptable
	31	Fluid bed dryer and coating machine compressed air line need filters for particles that can contaminate products. Maintenance programs for filter change need to be put into practice.	Under process. Pending

Materials	32	The current version of the approved suppliers list needs to be updated, as it does not identify adequately whether the supplier was the original manufacturer or a trader or mediator.	Suppliers list has been update. Corrective action acceptable
	33	Supplier Audit program needs to be established and put into practice.	Yet to implement. Pending
	34	Warehouse inventory system is not adequate. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by the first expire, first-out rule.	Inventory systems now adequate. FIFO process is in practice. Corrective action acceptable
Good Practices in Production	35	The differential pressure system is not operational, as the pressure gauges are not calibrated.	Steps have been taken to initiate calibration. Pending
	36	The clean room classification is not met because they do not do particle counts.	Clean room classification has been done as per particle count. Corrective action acceptable
	37	Water system sanitation procedures are not adequate. Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological	Sanitation SOP established (SOP 173/400). Corrective action acceptable
Good Practices in Quality Control	38	No primary reference standards were found on site. Chemists used working standards from different suppliers. They had the certificates of analysis, but not the information to trace their production to official reference standards. The lab should request this information and annually inspect their suppliers to ensure that they are receiving high quality reference standards.	Primary reference standard had been purchased. DDA is providing secondary reference standards with certificates. Corrective action acceptable
	39	Improperly labeled or unlabeled solutions were observed in the lab. A large container of buffer and the unlabeled pH calibration solutions were observed. GMP requires all solutions to be labeled with name, analyst, date of production, and expiration date.	Measurement had been implemented to rectify the problem (training). Corrective action acceptable
	40	The working standards used in place of reference standards did not have the necessary storage conditions marked on them; all were in desiccators on the bench. Some items should have cold storage, and a solution marked “store at room temperature” was observed in the refrigerator.	Storage conditions are now provided for working standard as per label. Corrective action acceptable
	41	Additional storage space for reagents and solvents may be required. Hazardous chemicals are not separated from general storage.	Reagent had been relocate and separate from general storage. Corrective action acceptable
	42	No SOP on notebook usage was available. This SOP should cover the information required to be recorded for every analysis. The minimum information needed is: date, analyst, sample tested, reference standard, method and reference, conclusion, and other relevant information/observations not captured in the work sheets.	SOP is available now (SOP Q-106). Corrective action acceptable
	43	No SOP exists on significant digits.	SOP is available now (SOP Q-104). Corrective action acceptable
	44	No SOP exists for glass washing.	SOP available (SOP Q-026). Corrective action acceptable
	45	No SOP exists for use of the HPLC.	SOP available (SOP Q-013) Corrective action acceptable
	46	No SOP exists for assignment of expiration dates on solutions.	SOP Available (SOP Q-107) Corrective action acceptable
	47	Microbial quality of purified water was monitored following a sampling program; however, the laboratory does not conduct positive microbial control.	Positive microbial control has been started. Corrective action acceptable
	48	A written program for ongoing stability determination must be	Written program available (SOP

		drafted	Q-086) Corrective action acceptable
	49	Stability chambers are not validated.	Revalidation is done. Corrective action acceptable
	50	A detailed SOP for Out of Specification has to be drafted	SOP is available (SOP Q-093) Corrective action acceptable

Annex 5

Corrective Action Plan Implementation
Deurali-Janta Pharmaceuticals (DJPL)

Deviation			Status
Sanitation and Hygiene	1	An integrated, comprehensive program of sanitation and hygiene must be established that includes premises, equipment and apparatus, production materials and containers, equipment cleaning and disinfection.	Sanitation program has been established Corrective action acceptable
Qualification and Validation	2	Validation Master Plan is not adequate. Time-table for equipment validation-revalidation needs to be established.	Revalidation established. VMP revised. Corrective action acceptable
	3	Air Handling Unit is not fully validated.	Under process. Pending
	4	Major manufacturing equipment, such as granulators, blenders, tablet machines, fluid bed dryers, and coating machines, are not qualified.	Qualification had been started. Corrective action acceptable
	5	Water purification system is not fully validated	Completed. Corrective action acceptable
	6	Compressed air equipment is not validated.	New compressor installation under progress validation to follow. Pending
	7	Cleaning procedures for equipment are not fully validated. Cleaning protocol needs to be finished and implemented.	Cleaning master plan prepare. Validation started. Corrective action acceptable
	8	Zinc tablets manufacturing process is not fully validated. A minimum of three batches is needed.	Completed Corrective action acceptable.
	9	Packaging lines cleaning is not fully validated	Not started yet. Pending
	10	Fluid bed dryer filter bag cleaning procedures are not validated	Under process. Pending
Product Recalls	11	The company does not have a designated area for recalled material, and no mock recalls have been made to assess the effectiveness of the company's recall program or the readiness of the recall team. Mock recalls help identify any gaps in traceability or problems that might have developed in the procedures.	Pending
Self inspection	12	The procedure categorizes the deviations as critical/major/minor, but the corresponding corrective actions and follow-up are managed in the same manner, regardless of the classification	SOP revised Corrective action acceptable
Training	13	Yearly GMP training program is not in place for the employees.	GMP training implemented. Corrective action acceptable
Personal Hygiene	14	Personnel conducting visual inspections in the packaging area should also undergo periodic eye examinations.	Eye examination done Corrective action acceptable.
Premises	15	Facility layout is not adequate; no logical flow of waste material was observed	New facility under construction. Pending
	16	Floors in some areas of the first level of the production should be changed to an appropriate seamless style that can be effectively cleaned.	Long term plan .Pending
	17	Facility does not have a storage area for barrels of received materials.	Long term plan .Pending
	18	Facility does not have an appropriate storage area/cabinet for flammable materials	Long term plan .Pending

	19	Premises were not disinfected according to written procedures	Started following use of disinfectant and cleaning agent. Corrective action acceptable
	20	Premises do not have appropriate lighting. GMP regulations of Storage 50–100 Lux, Laboratory 300 Lux, and Processing and Filling/Packing 500 Lux.	Lighting within Lux limits. Corrective action acceptable
	21	Facility walls need to be painted with a non-peeling paint (epoxy) to assure good sanitation.	Painting is done Corrective action acceptable.
	22	Storage segregation areas for quarantine and rejected materials are not adequate or missing. Storage area layout is not adequate	New facility under construction. Pending
	23	SOP for pest control was not available. Rodenticide stations were missing around the storage and manufacturing areas.	SOP under revision. Corrective action acceptable
	24	The production areas are generally ventilated with filtered air and were entered through airlocks in some areas. The necessary environmental and pressure differential controls are not carried out and recorded in all areas.	Pressure differential now recorded. Corrective action acceptable
	25	The map of the warehouse contents needs to be updated, and the appropriate material-handling SOP updated to include the map.	Not done. Pending
	26	Thermometers and hygrometers need to be calibrated as per master schedule.	Thermometers and hygrometers calibrated. Corrective action acceptable.
	27	Calibration program is not adequate. A master calibration schedule needs to be followed.	Established Corrective action acceptable.
	28	Installation Qualification and Operation Qualification have not been performed on the purified water system. Equipment layout and drawing are not adequate. Procedure for sampling of purified water did not specify sampling points and frequency sampling/testing. Sampling point needs to be properly identified.	Completed. Corrective action acceptable.
Equipment	29	Procedures for issue, receipt, storage, and destruction of tablet punches and dies do not exist.	Established Corrective action acceptable.
	30	The grease container used to lubricate and protect punches and dies is not food grade, which can lead to product contamination. No materials used for operations, such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g., food grade) to minimize health risks	Pending
	31	Non-dedicated manufacturing equipment needs a validated cleaning method.	Included on Cleaning validation master plan. Corrective action acceptable.
	32	Fixed pipe on heat exchanger and boiler works should be clearly labeled to indicate the contents and, where applicable, the direction of flow.	Completed. Corrective action acceptable.
Materials	33	The current version of the approved suppliers list needs to be updated, as it does not identify adequately whether the supplier was the original manufacturer or a trader or mediator.	Pending
	34	Supplier Audit program needs to be established and put into practice	Pending
	35	Warehouse inventory system is not adequate. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by the first expire, first-out rule	FEFO rule is being followed. Corrective action acceptable.
Good Practices in Production	36	The differential pressure system is not operational, as the pressure gauges are not calibrated.	Pending
	37	The clean room classification is not met because they do not do particle counts	Pending

	38	The sampling in the dispensing boot is not validated	Pending
	39	Water system sanitation procedures are not adequate. Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological.	Pending
Good Practices in Quality Control	40	analytical balances should be placed on a non-vibrating bench (marble table) away from air conditioning outlets	Done Corrective action acceptable.
	41	Access to the QC lab was not restricted. The door has a lock, but it remains unlocked during business hours. Some sort of arrangement needs to be developed to restrict access to required personnel only.	Done Corrective action acceptable.
	42	No primary reference standards were found on site. Chemists used working standards from different suppliers. They had the certificates of analysis, but not the information to trace their production to official reference standards. The lab should request this information and annually inspect their suppliers to ensure that they are receiving high quality reference standards.	Primary standards received. Corrective action acceptable.
	43	Two calibration stickers were noticed on some instruments. The SOP does not require the application of these stickers, so this may be why previous stickers were not removed. The SOP should be updated to ensure chemists do not use equipment that is out of calibration.	SOP 458-00 updated Corrective action acceptable.
	44	Improperly labeled or unlabeled solutions were observed in the laboratory. A large container of buffer and the unlabeled pH calibration solutions were observed. GMP requires all solutions to be labeled with name, analyst, date of production, and expiration date.	Labeling corrected Corrective action acceptable.
	45	The working standards used in place of reference standards did not have the necessary storage conditions marked on them; all were in desiccators on the bench. Some items should have cold storage, and a solution marked “store at room temperature” was observed in the refrigerator.	Storage conditions for standards established Corrective action acceptable.
	46	The current monograph was not in use for zinc sulfate tablets. The specifications of the in-process sheet need to be updated; specifically, the disintegration procedure has been changed to less than one minute at 37 degrees, and their current procedure requires disintegration within 3 minutes at 20 degrees.	Zinc Tablets monograph implemented Corrective action acceptable.
	47	Additional space for storage of reagents and solvents may be required. Hazardous chemicals were not separated from general storage.	Pending
	48	No eye wash was observed; safety glasses were not used by the staff.	Eye wash operational now Corrective action acceptable.
	49	Reagent SOP required inspection of desiccant every fortnight; no logbook was available to document this inspection.	Log book maintained now Corrective action acceptable.
	50	No SOP on notebook usage was available. This SOP should cover the information required to be recorded for every analysis. The minimum information needed is: date, analyst, sample to be tested, reference standard, method and reference, conclusion, and any other relevant information/observations not captured in the work sheets	SOP 445-01 updated Corrective action acceptable.
	51	No SOP exists on significant digits.	SOP prepared (SOP 472-00) Corrective action acceptable.
	52	No SOP exists for glass washing	SOP Prepared (SOP 426-02) Corrective action acceptable.
	53	No SOP exists for use of the HPLC	SOP prepared (SOP 462-00) Corrective action acceptable.
	54	Microbial quality of purified water was monitored following a sampling program; however, the laboratory does not conduct positive microbial control	Positive control conducted Corrective action acceptable.

	55	A written program for ongoing stability determination must be drafted.	Stability program exists Corrective action acceptable.
	56	Stability chambers are not validated	Pending

ANNEX 6

Corrective Action Plan Implementation
CTL

Deviation			Status
Quality Assurance	1	Discuss and come to the conclusion for SOP for batch/lot numbering system of raw and packaging materials	Done Corrective action acceptable
	2	Prepare a SOP to handle process deviation.	Available Corrective action acceptable
	3	Secure the electronic records of production document to avoid unauthorized use.	Available Corrective action acceptable
	4	Specifications of excipients/diluents are to be prepared.	Done Corrective action acceptable
	5	Prepare master documents for all the products.	Available Corrective action acceptable
	6	Maintain the records of replacement of spare parts strictly.	Available Corrective action acceptable
Sanitation and Hygiene	7	Prepare and implement the qualification & validation protocol for sanitation-hygiene and general cleaning.	Available Corrective action acceptable
	8	Establish methods for cleaning of Inlet and HVAC terminal filters	Established Corrective action acceptable
	9	Make an arrangement for shoe covers for personnel entering into production area.	Shoe cover available Corrective action acceptable
	10	Make an arrangement for periodic eye examinations of personnel conducting visual inspections in the packaging area	Eye examination done Corrective action acceptable
	11	Work out the critical parameters for revalidation of process upon the change in materials, equipments and deviation in process itself.	Completed Corrective action acceptable
	12	Prepare a SOP and format for annual product review(APR) and implement from the end this fiscal year(2064-2065)	Format prepared Corrective action acceptable
Product Recalls	13	Allocate a place to store the returned drug products	Completed Corrective action acceptable
	14	Standard format for "Product Recall Record" is to be prepared.	Available Mock recall done Corrective action acceptable
Personnel	15	Provide training to newly recruited personnel.	Records available Corrective action acceptable
	16	Elastic should be fitted on the apron hand cuff. Caps should cover ears as well.(Design caps)	New design done Corrective action acceptable
	17	Syllabus for GMP training should be prepared. (Annually the training should be provided to all the staffs)	Done Corrective action acceptable
	18	Training should be provided to newly recruited staffs.	Done Corrective action acceptable
Premises	19	SOP for overall maintenance of premises should be prepared.	SOP available Corrective action acceptable
	20	Revise the SOP for pest control with the provision of rodenticide stations around storage and manufacturing areas	SOP available Corrective action acceptable
	21	Make an arrangement for necessary environmental and pressure differential control and recording in all areas	AHU validation done Corrective action acceptable

	22	Make an arrangement for warehouses temperature mapping.	Record available Corrective action acceptable
	23	Set an alert and action limits for HVAC.	Done Corrective action acceptable
	24	Make a provision for controlling the humidity in microbiological Lab.	Implemented Corrective action acceptable
Equipment	25	Prepare specifications of all production related machines on thebasis of provided manuals and machines themselves.	Available Corrective action acceptable
	26	Prepare and implement the SOP for calibrating volumetric flasks and pipette or use only the calibrated items.	Implemented Corrective action acceptable
	27	Operation and performance qualification of water system and production equipments/machines needed.	Qualified Corrective action acceptable
	28	Records should be maintained for equipments for cleaning and maintenance.	Implemented Corrective action acceptable
	29	Procedure for issue, receipt, storage, and destruction of dies should exist.	Implemented Corrective action acceptable
	30	Use food grade lubricant to protect and lubricate punches and dies.	Food grade lubricant being used Corrective action acceptable
	31	Maintenance programs for filter changing needs to be put into practice for fluid bed dryer and coating machine compressed air line.	Implemented Corrective action acceptable
	32	Master calibration schedule should be prepared.	Available Corrective action acceptable
	33	Prepare a SOP for maintenance.	Available Corrective action acceptable
	34	Start a practice of keeping the records of checkings of screens, sieves, punches and dies.	Records available Corrective action acceptable
	35	Prepare specifications of equipments/machines of production unit. Complete the specifications of all the instruments of QC.	Specifications available Corrective action acceptable
	36	Calibrate pressure gauges, count the particles on schedule.	In process
	37	Prepare a SOP for finished products	Sop available Corrective action acceptable
	38	Make an arrangement for continuous control of humidity & Temp in the storage	Done Corrective action acceptable
	39	Make an arrangement to store printed packaging materials in restricted area if possible with lockers	Corrective action acceptable Done
	40	Look a feasibility of keeping a dedicated booth for sampling purpose.	Sampling booth available Corrective action acceptable
	41	Discuss about the feasibility of allocating quarantine area for finished products.	In progress
	42	Prepare a SOP for general house keeping of Sanepa store. Keep into place the protective measures against insects, rodents and birds.	SOP available Corrective action acceptable
	43	Provide GMP training to warehouse personnel.	
	44	Update the list of suppliers and materials of their supply.	Available Corrective action acceptable
	45	Carry out assessment of prospective suppliers prior to place order. Begin the culture of re-evaluation of established suppliers as well.	Done Corrective action acceptable
Good Practices in	46	Make arrangements of quarantine also for others than raw materials.	Done Corrective action acceptable
	47	Start a practice of line clearance of secondary packaging room	In process

Production	48	Make proper arrangements to store the component allocated for the pre-coding.	Done Corrective action acceptable
	49	Discuss about the rationality of collecting samples of raw materials from all the containers and implement the findings of discussion.	In process
	50	Make necessary arrangements consulting with the relevant personnel to audit batch prior to release	Done Corrective action acceptable
Good Practices in Quality Control	51	Make necessary arrangements consulting with the relevant personnel to audit batches prior to release.	Done Corrective action acceptable
	52	Try to establish self life of raw materials on the basis of stability data and storage condition. On the basis of stability data and storage condition recommend suitable storage condition whenever necessary.	In process
	53	Issue written instructions for reprocessing procedure.	Done Corrective action acceptable
	54	Continue process of vendor evaluation and keep updated list of vendors.ted the	
	55	If new method of analysis is not official, then validate it. Prepare a validation scheme for all the instruments/equipments in the laboratory	In progress
	56	Practice of positive control should be adopted during analysis of water.	Done Corrective action acceptable
	57	Prepare a contract paper with outside laboratories for contract analysis.	Available Corrective action acceptable