USP DQI Good Manufacturing Practices Assessment for Manufacturers of Zinc Sulfate Formulations

Dar es Salaam, Tanzania
October 24-30, 2008

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 the U.S. Agency for International Development (USAID). It may be reproduced if credit is given to USP DQI.

Abstract

USP DQI conducted a Good Manufacturing Practices (GMP) assessment of the manufacturing process for zinc sulfate tablets and oral solutions at Shelys Pharmaceuticals Limited (SPL) and Zenufa Laboratories Limited (ZLL) in Dar es Salaam, Tanzania, October 24-30, 2008. The inspection covered the air handling units, water purification systems, compressed air systems, starting materials stores, production rooms, packaging areas, quality assurance (QA) documentation, quality control (QC) laboratories, and zinc sulfate formulations.

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Key Words

Shelys Pharmaceuticals Limited (SPL), Zenufa Laboratories Limited (ZLL), Good Manufacturing Practices, Validation, Standard Operating Procedures, Zinc Sulfate, UNICEF, Prequalification.

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Acronyms

AED	Academy for Educational Development
AHU	Air Handling Unit
BMR	Batch Manufacturing Records
CAP	Corrective Action Plan
DT	Dispersible Tablets
GMP	Good Manufacturing Practices
HVAC	Heating, Ventilation, and Air Conditioning
MBR	Master Batch Records
MOH	Ministry of Health
OOS	Out-of-Specifications
POUZN	Point-Of-Use Water Disinfection and Zinc Treatment
QA	Quality Assurance
QC	Quality Control
PIC	Pharmaceutical Inspection Convention
SPL	Shelys Pharmaceutical Limited
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
ZLL	Zenufa Laboratories Limited

Background

It is estimated that diarrheal diseases cause more than 3 million deaths of children in developing countries each year and contribute substantially to malnutrition in surviving children. Diarrheal episodes of long duration, commonly called persistent diarrhea, have the greatest effect on these outcomes. Treatment of acute diarrhea with oral rehydration solution has become widespread, resulting in reduced mortality from dehydrating diarrheas, but provides no decrease in the duration of episodes or their consequences, such as malnutrition. Furthermore, adherence to recommendations regarding fluid therapy 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. Furthermore, zinc supplementation was shown to reduce the duration and severity of childhood diarrhea in randomized controlled trials.

In order to help ensure that quality zinc products can be procured in developing countries, USP DQI performs GMP assessments and audits of zinc manufacturers to ensure that their products are of high quality. In order to help manufacturers achieve World Health Organization (WHO) pre-qualification status, USP DQI provides recommendations to them to strengthen their quality assurance systems and GMP programs.

In 2008, Shelys Pharmaceuticals Limited in Tanzania was invited by UNICEF to participate in the 2008 zinc tender. Their application is currently under evaluation.

Purpose of Trip

The primary purposes for the trip to Tanzania were to:

- Verify that Corrective Action Plan (CAP) recommendations were put in place by Shelys
- Provide GMP technical assistance (TA) in preparation for Pharmaceutical Inspection Convention (PIC) and UNICEF inspections
- Conduct a full GMP audit at Zenufa to identify gaps in the system and evaluate the zinc sulfate oral solution manufacturing process.

Source of Funding

This trip was supported by USAID Program Element 3.1.6. Maternal and Child Health.

Overview of Activities

Friday and Monday, October 24 and 27; and Wednesday, October 29, 2008
Meeting with Shelys Pharmaceutical Limited

The USP DQI team of E. Toledo and S. Bradby (hereafter “the team”) visited Shelys Pharmaceuticals – recently acquired by Aspen Phamacare Holdings, Africa's largest pharmaceutical firm – and met with Mr. Ashok Gupta, Manager, Regulatory and Formulation Development, to discuss standing GMP issues and verify the

implementation of corrective actions recommended during the last visit. The team performed 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. The team found that most of the standing issues were addressed in a timely manner, showing the commitment of Shelys' senior management toward the quality of the products manufactured at the site. (see *Annex 1* for the visit agenda and *Annex 2* for Shelys' GMP Status)

Saturday, October 25, 2008
Meeting with AED
The team met with Bongo Mgeni, Country Coordinator, AED-POUZN Project, to coordinate meetings with manufacturers and understand the status of zinc roll out in Tanzania. AED is working with local authorities to create demand for zinc in public and private sectors by raising awareness and offering education programs for health providers and care givers and through the adoption of zinc treatment in the "Integrated Management for Childhood Illnesses Guidelines."

Tuesday, October 28, 2008
Meeting with Zenufa Laboratories LTD
Zenufa Laboratories Ltd. was established in 2005 through a strategic collaboration with the Belgian Investment Company for Developing Countries (BIO). The facility was subsequently commissioned, validated, and qualified in June 2007 and began production in July 2007. Zinc sulfate oral solution is under development and will be available by July 2009.

This was the first time the company had been inspected by a USP DQI team. The objective was to verify compliance with WHO GMP, in the framework of the prequalification program on priority essential medicines, regarding the manufacture of zinc sulfate oral solution.

The inspection covered all areas of activity related to the manufacture of oral solutions, such as: the air handling unit, water purification system, compressed air system, starting materials stores, production rooms, packaging area, QC laboratory, and zinc sulfate oral solution formulation development. The team found that most of the GMP requirements were in place; however, Zenufa will not hold a Tanzania FDA GMP certificate until corrective measurements are accepted by the FDA (see *Annex 3* for ZLL GMP Status).

Thursday, October 30, 2008
Meeting with USAID
The USP DQI team met with Charles Llewellyn and Raz Stevenson to debrief them on the Shelys findings. Both representatives were pleased with the good news regarding Shelys GMP compliance status and reiterated their support of the zinc sulfate roll out.

Conclusion

Based on the areas inspected, and considering the findings of the prior inspection and the corrective actions programs in place in response to USP DQI recommendations, Shelys

Pharmaceuticals Ltd., Dar es Salaam, Tanzania is operating at an acceptable level of GMP compliance. Zenufa Laboratories will need to finish zinc sulfate oral solution development, comply with standing issues with the Tanzania FDA, and obtain a GMP certificate from local authorities.

Next Steps

- USP DQI will continue providing GMP and dossier TA to Shelys toward WHO prequalification for zinc sulfate.
- USP DQI will provide TA in GMP and dossier compilation to Zenufa toward WHO prequalification.
- In light of new expressions of interest for zinc sulfate tablets manufacturers issued by WHO in November 2008, USP DQI will plan a visit to Shelys by July 2009 to perform a mock GMP audit in preparation for the WHO audit.

Annex 1

USP DQI Visit Agenda — October 24-30, 2008

Date	Time	Place	Contact
October 24 (Friday)	11:30am - 4:30pm	Shelys	Ashok Gupta
October 25 (Saturday)	7:00pm	USP DQI/AED planning meeting	Bongo Mgeni
October 27 (Monday)	9:30am - 4:30pm	Shelys	Ashok Gupta
October 28 (Tuesday)	9:30am - 4:30pm	Zenufa	Dr. Kishor Athalye
October 29 (Wednesday)	9:30 am - 7:00pm	Shelys	Ashok Gupta
October 30 (Thursday)	10:00am -11:00am	USAID	Charles Llewellyn, Raz Stevenson,
October 30 (Thursday)	9:00pm	Travel to USA	

Annex 2

Shelys GMP Status

Name of manufacturer	Shelys Pharmaceuticals Ltd.
Physical address	New Bagamoyo Road, Mwenge Plot No.396 Block No.32 Dar es Salaam Tanzania
Postal address	PO Box 3016 Dar es Salaam Tanzania
Telephone number	+255 22 27 71715/6/7
Fax number	+255 22 27 72417
Summary of activities of manufacturer	Manufacturing of products in the following dosage forms: - tablets, coated or un-coated - capsules - powder (sachets) - liquid (syrups) - suspension
Scope of inspection	Second inspection of the manufacturing of zinc sulfate tablets with special emphasis on dossier, validation/qualification of manufacturing process, equipments, and utilities.
Date of inspection	October 24-27 and 29, 2008
Program	PE 3.1.6.6 Maternal and Child Health

Status	
Quality assurance	The QA system was maintained; however, raw material sampling is being done on 100% of the product until a formal plan to audit /qualify vendor is in place, including visits to the sites or third party inspection with the corresponding reports.
Good manufacturing practices for pharmaceutical products	The manufacturing and quality control processes were clearly defined and reviewed periodically. The manufacturing steps were specified in Master Batch Records (MBR). Actual records and recordings were made during manufacture. Instructions and procedures were generally written in clear and unambiguous language.
Sanitation and Hygiene	The facilities were found to be in a good state of cleanliness. Cleaning and sanitation were well established and covered the essential equipment, facilities, and rooms.
Qualification and validation	The key elements of the qualification and validation program were defined and documented in the Validation Master Plan (VMP). Water system, cleaning, and analytical methods are being qualified to comply with PIC requirements.
Complain	Shelys has a procedure for handling complaints which generally meets WHO GMP requirements. Complaints and other information concerning potentially defective products were reviewed.
Product Recalls	Procedure for product recalls was available. The company does not have a designated area for recalled material. The need to carry out mock recalls was indicated in the Standard Operating Procedure (SOP) for recalls; however, at the time of the inspection, the company had not yet performed a mock recall.
Contract production and analysis	Shelys Pharmaceuticals does not have any contract production at this time.
Self-Inspection	Self inspections were performed in accordance with a written procedure. The procedure included questionnaires, self inspection reports, and corrective and preventive actions (CAPAs). Self inspection findings were not classified. After completion of self inspection, a report was drawn up and necessary CAPAs were initiated.
Personnel	The company has a sufficient number of qualified personnel to carry out all the tasks for which the manufacturer is responsible. The personnel met during the audit were familiar with GMP practices.
Training	GMP training was covered in a written SOP. Comprehension of training content was assessed by discussions and observation of performed activities, as well as by written examination. The training program for 2008 was available. Training records were available for each employee summarizing the history of training received.
Personal Hygiene	The level of hygiene observed and the measures taken were in general sufficient.

Premises	In general, the buildings and facilities of the inspected plant were appropriately designed and were of a good standard with respect to work flows. Facilities were designed and maintained to minimize the risk of cross-contamination. QC laboratories were separated from the production areas.
Equipment	The process equipment was located, designed, and maintained to suit the operations to be carried out. Generally, the equipment was well maintained. Cleaning SOPs and records were available for the equipment. Equipment items were identified as to their contents and cleanliness status by appropriate labels.
Materials	Incoming goods and finished products were quarantined until tested and released by QA. Sampled containers were appropriately indicated.
Documentation	Documents were approved, signed, and dated by appropriate responsible persons. Documents were regularly reviewed and kept up-to-date. The management of the documentation system was well organized and facilitated easy retrieval during the inspection. Shelys still works on Laboratory SOP update.
Good Practices in Production	Production operations followed defined procedures in order to produce products of the requisite quality. Measures for the prevention of cross-contamination were in place. Line-clearance was performed and recorded before processing operations were started.
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.

Annex 3

Zenufa Laboratories Ltd GMP Status

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

Chief Executive Officer	Harvindersingh Alag
General Manager Operation	Dr. Kishor Athalye
Assit. General Manager	Vijay Kumar
Manager Production	Peter Saniwa
Manager QA	Nooresh Velani
Manager, QC	Suleman Mlungwana
Senior Production supervisor	Nageshwara Rao
Warehouse In Charge	Sanja Kadu
Maintenance Manager	Ankur Patel
Yogesh Durge	Plant Engineer
Head Microbiologist	Lukas Mwalewela
Human Resources Manager	Ndenkunde Kaaya

General Information for ZLL:

Name of manufacturer	Zenufa Laboratories Limited
Physical address	Nyerere Road, Kipawa Dar es Salaam, Tanzania
Postal address	P.O. Box 77914 DSM, Dar es Salaam, Tanzania
Telephone number	+255-22-218 2552 / 3
Fax number	+255-22-218-2551
Summary of activities of manufacturer	Manufacturing of products in the following dosage forms: – liquid orals – tablets – capsules
Scope of inspection	Inspection of the manufacturing of zinc sulfate oral solution development activities with special emphasis on validation/ qualification of manufacturing process, equipment, and utilities
Date of inspection	October 28, 2008
Program	PE 3.1.6 Maternal and Child Health

Status	
Quality assurance	A quality assurance system was implemented and maintained. The QA unit and QC unit were independent from production. QA personnel were involved in all the production and quality control activities. However, job descriptions for the QA manager's responsibilities were not available.
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. The storage and distribution of products ensured batch traceability. Records were made during manufacture. 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.
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. Generally, validations were considered to be appropriately performed.
Complain	Complaints and other information concerning potentially defective products were reviewed according to written procedure and the corrective actions were taken.
Product Recalls	Procedure for product recalls was available. However, no mock recall had been performed.
Contract production and analysis	No manufacturing was contracted out.
Self-Inspection	Self-inspection was performed in accordance with written procedure. Procedures included questionnaires on GMP requirements and main GMP items were covered.
Personnel	The personnel met during the audit were experienced, skillful, and conscientious. An organization chart was available. However, job descriptions for key personnel were not available.
Training	Training issues were covered in written SOPs. The company provides initial training at the time of recruitment, specific training relevant to area of deployment, and regular continuous SOP training. Comprehension of training content was assessed by discussions and observation of performed activities.
Personal Hygiene	All personnel passed medical examinations prior to and during employment. Persons with illness and open lesions were not allowed to work in areas where open products were exposed to the environment. All changing rooms were provided with photos describing the gowning procedures.

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.
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 equipments were identified as to content and cleanliness status and appropriately indicated by labels. Equipment calibration schedule was established on annual basis.
Materials	The procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials were available. Incoming goods and finished products were quarantined until tested and released by QC. Materials and products were generally stored in a proper manner. However, the lists of the approved vendors of the raw materials and packaging materials were not available in the warehouse. Zenufa needs to establish a qualification program for raw material vendors.
Documentation	Zenufa documentation system needs to be well-established and maintained to facilitate easy retrieval at the time of an inspection. Documents were approved, signed, and dated by the appropriate responsible persons.
Good Practices in Production	Production operations were done following clearly defined procedures. Deviations from instructions or procedures were done in accordance with an approved procedure. Necessary checks on yields and reconciliation of quantities were carried out.
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. OOS were evaluated and investigated in accordance with written procedure.