

Zinc Sulfate Tablets Manufacturing: GMP Assessment of CHI Pharmaceuticals and Meetings with other Nigerian Manufacturers submitting Expressions of Interest

Lagos and Abuja, Nigeria

June 24-28, 2013

Trip Report

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Executive Summary

In June 2013, staff from the Promoting the Quality of Medicines (PQM) program traveled to Lagos, Nigeria to visit local manufacturers who had submitted expressions of interest (EOIs) for technical assistance to manufacture zinc sulfate dispersible tablets and oral rehydration salts (ORS). Based on the EOIs received and responses to a manufacturer questionnaire, CHI Pharmaceuticals was identified as the only company currently manufacturing the products of interest and ready for a good manufacturing practices (GMP) assessment. PQM performed the assessment using the World Health Organization (WHO) inspection procedures approach for auditing the manufacture of pharmaceuticals. CHI Pharmaceuticals has the systems in place as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture zinc sulfate tablet finished pharmaceutical products (FPP) compliant with GMP.

PQM also visited six other Nigerian manufacturers who submitted EOIs but were not at the stage of being ready for a GMP assessment for these products. The visits to the other companies revealed that the manufacturers are at different stages in manufacturing and bringing to market zinc sulfate tablets and ORS. PQM will develop individual plans for technical assistance for each company.

In addition to the manufacturer visits, PQM traveled to Abuja, Nigeria to hold meetings with the Family Health Department of the Ministry of Health, National Agency for Food and Drug Administration and Control (NAFDAC), Clinton Health Access Initiative (CHAI), and the United States Agency for International Development/Nigeria (USAID/Nigeria) to brief them on PQM activities related to maternal and child health (MCH) pharmaceutical commodities.

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About PQM

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID’s response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical assistance to developing countries, PQM helps build local capacity in medicine quality assurance systems, increase the supply of quality medicines to priority USAID health programs, and ensure the quality and safety of medicines globally. This document does not necessarily represent the views or opinions of USAID or the United States Government. It may be reproduced if credit is given to PQM and USP.

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- Dr. Wapada Balami, Director Family Health Department, Federal Ministry of Health
- Mr. Steve Onya, CEO/Managing Director, CHI Pharmaceuticals, Ltd.
- Mr. Jonathan Ukwuru, QA/QC Manager, CHI Pharmaceuticals, Ltd.
- Mr. Nnanyereugp Okereke, Head Corporate Planning & Development, May & Baker Nigeria
- Mr. Olayinka Amoo, Group Quality Manager, Fidson Healthcare
- Mr. Chika Udeozor, Depot Manager, Juhel Nigeria
- Ms. Nkeiru Okoro, Executive Director Operation, Emzor Pharmaceutical Industries, Ltd.
- Mr. Prince Nebe, Managing Director, Phamatex Industries
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- PQM administrative staff and editors

ACRONYMS

API	Active Pharmaceutical Ingredient
CHAI	Clinton Health Access Initiative
DQI	Drug Quality and Information Program
EOI	Expression of Interests
GMP	Good Manufacturing Practices
MCH	Maternal and Child Health
NAFDAC	National Agency for Food and Drug Administration and Control
ORS	Oral Rehydration Salt
PQM	Promoting the Quality of Medicines Program
UN	United Nations
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

The United States Agency for International Development Nigeria Mission (USAID/Nigeria) selected the Promoting the Quality of Medicines (PQM) program to support strengthening the capacity of select Nigerian manufacturers that produce zinc sulfate, chlorhexidine, and other maternal and child health (MCH) priority commodities for the United Nations (UN) Commission on Life-Saving Commodities for Women and Children.

In support of the UN Commission's goals, USAID/Nigeria is working to increase the availability of relevant MCH medicines in the country. Toward that end, PQM will provide technical assistance on Good Manufacturing Practices (GMP) and quality assurance to local medicines manufacturers, to include zinc sulfate, chlorhexidine digluconate, and other commodities in collaboration with the National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria.

At the request of USAID Nigeria, PQM issued solicitations to Nigerian manufacturers requesting that they submit expressions of interest (EOIs) regarding the manufacture of zinc sulfate dispersible tablets and oral rehydration salts (ORS). Responses identified CHI Pharmaceuticals, Ltd. as the only company currently manufacturing the products of interest, with six other companies (Emzor, Swiss Pharma, Phamatex, May & Baker, Fidson, and Juhel) expressing interest in manufacturing the products.

Purpose of Trip

The purpose of the trip was to:

- Conduct a pre-procurement GMP assessment of zinc sulfate manufacturing activities at CHI Pharmaceuticals
- Visit other Nigerian manufacturers to evaluate the status of their zinc manufacturing activities and discuss PQM technical assistance described in the request for EOIs.
- Meet with USAID/Nigeria, Ministry of Health–NAFDAC, Family Health Department, and Clinton Health Access Initiative (CHAI) to provide an update on discussions with manufacturers.

Source of Funding

This trip was funded by USAID Nigeria - MCH.

Overview of Activities

PQM GMP Assessment of CHI Pharmaceuticals

Item	Description
Date	June 24-25, 2013
Specific Objectives	Perform pre-procurement GMP assessment of CHI Pharmaceuticals
CHI Key Personnel	Mr. Steve Onya, Chief Executive Officer/Managing Director Mr. Laure Yakubu, Production Manager Mr. Jonathan Ni, Quality Control Manager Mr. Wagalagave Hanmant, Engineering Manager
Agenda	See <i>Annex 1</i> for the CHI GMP assessment agenda

Areas Evaluated	<ul style="list-style-type: none"> • Quality assurance • GMP for pharmaceutical products • Sanitation and hygiene • Qualification and validation • Complaints • Product Recalls • Contract production and analysis • Self-inspection • Personnel 	<ul style="list-style-type: none"> • Training • Personal hygiene • Premises • Materials • Utilities • Documentation • Good Practices in Production • Good Practices in Quality Control
Key Findings	The PQM assessment audit revealed that CHI pharmaceutical has the systems in place, as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture finished zinc sulfate pharmaceutical products. However, the audit also revealed that CHI had some minor observations regarding GMP compliance.	
Conclusions	Based on the documents reviewed, personnel met, and the manufacturing premises audited, CHI Pharmaceutical in its current status complies with the GMP requirements to manufacture zinc sulfate tablets. The observations mentioned above should be addressed in a corrective and preventive actions (CAPA) plan within six months. <i>NOTE: A full, confidential report of PQM's assessment has been sent directly to CHI</i>	
Next Steps	<ul style="list-style-type: none"> • CHI will complete their CAPA plan by November 20, 2013. • CHI will start a long-term stability study by September 30, 2013. • CHI will start compiling their dossier as per PQM recommendations. 	

Meetings with Other Nigerian manufacturers submitting EOIs – Lagos, Nigeria, June 26-27, 2013

Dr. Evans met with six Nigerian companies to further discuss PQM technical assistance described in the request for EOIs and identify the manufacturers' status regarding the manufacture of zinc sulfate tablets and ORS. Highlights of the individual meetings are given below:

Company	Meeting Highlights
Emzor	<p>Zinc sulfate tablets and ORS</p> <ul style="list-style-type: none"> • New facility under construction, scheduled to be completed in 2014 • Has developed a formulation • Requested market analysis/forecasting information to help make informed decisions regarding production • PQM will provide zinc sulfate active pharmaceutical ingredient (API) manufacturers' contact information to the company <p>Chlorhexidine gluconate gel</p> <ul style="list-style-type: none"> • Currently not producing gels and would need to make capital investment • Requested advice on the equipment needed to manufacture, for budget purposes • Requested forecasting and demand information as well as assistance with sourcing the API

Phamatex	<ul style="list-style-type: none"> • A short tour of new manufacturing facility in Lagos (Ikeja area) was provided. The facility is near completion. Once construction is completed and equipment installed, the company indicated the facility will meet all WHO GMP requirements including validated air-handling and water systems • Currently does not have a formulation for zinc sulfate tablets • Requested assistance in procuring reference standards
Swiss Pharma Nigeria, Ltd.	<ul style="list-style-type: none"> • Zinc product currently in development • A short tour of the facility was provided; facility has ISO 9001 accreditation • Requested clarification on the packaging
Juhel	<ul style="list-style-type: none"> • No longer interested in manufacturing zinc sulfate tablets or ORS
May & Baker Nigeria, PLC	<ul style="list-style-type: none"> • Developed a formulation for zinc sulfate tablets but requested assistance from PQM to ensure it meets the required standard • Will provide a timeline for manufacturing the products • Requested names of reputable zinc sulfate API manufacturers • New GMP-compliant manufacturing facility in Ota recently completed
Fidson Healthcare, PLC	<ul style="list-style-type: none"> • Marketing of zinc/ORS products on hold until packaging issue (co-packaging versus zinc and ORS in separate packaging) resolved • New GMP-compliant manufacturing facility in Ota under construction
Next Steps	<ul style="list-style-type: none"> • PQM will develop individual plans for technical assistance for each company

Meetings with CHAI, NAFDAC, USAID/Nigeria, and the Family Health Department – Abuja, Nigeria, June 28, 2013

Dr. Evans traveled to Abuja to meet with CHAI, NAFDAC, USAID/Nigeria, and the Family Health Department in the Ministry of Health to provide updates on the CHI Pharmaceuticals GMP assessment and the meetings with zinc sulfate tablet and ORS manufacturers. Highlights of the meetings follow:

Meeting with CHAI

- A meeting with Mr. Jason Houdek and Mr. George Fisher of CHAI was convened to update them on PQM's zinc activities in Nigeria.
- Dr. Evans indicated that many manufacturers requested demand/forecasting data for zinc/ORS. These companies' contact information will be provided to CHAI so they can address the requests.
- CHAI and PQM discussed engaging the UNICEF supply division to determine if UNICEF would recognize zinc manufacturers recommended by PQM based on GMP assessments and quality control testing of products.

Meeting with NAFDAC

- A meeting was held with senior members of NAFDAC at the Abuja office. Dr. Paul Orhii, the Director General, was travelling and did not participate. NAFDAC personnel attending the meeting included Mrs. Hauwa Keri, Mrs. Adeline Osakwe, Dr. Ibrahim Ali, Mrs. Fori Tatama, Mr. Kalat Musa, and Mr. Kenneth Onu.
- Mrs. Keri, Director of Establishment Inspection, updated the attendees on the collaboration with PQM regarding MCH medicines manufacturing.

- Dr. Evans explained the type of technical assistance that PQM will be providing to manufacturers with emphasis on pre-procurement assessments for USAID.
- NAFDAC requested PQM training on reviewing safety reports and strategies for implementing effective surveillance systems to monitor medicine products.

Meeting with USAID/Nigeria

- Dr. Evans met with Dr. Joseph Monehin (MCH), Ms. Gertrude Odezugo (MCH), and Ms. Abideni Okechukwu (Malaria) at USAID/Nigeria and debriefed them on the GMP assessment performed at CHI, the meetings with zinc sulfate and ORS manufacturers, and details of PQM activities to increase the capacity of NAFDAC.
- Dr. Monehin emphasized keeping the USAID/Nigeria zinc coordinator aware of all relevant PQM activities.
- USAID/Nigeria may be interested in PQM recommending a chlorhexidine gel manufacturer based on a GMP assessment and quality control testing. Further details of the possible activity will need to be explored.

Meeting with Federal Minister of Health – Family Health Department

- Dr. Evans met with Dr. Wapada I. Balami, Director – Family Health Department in the Ministry of Health, and his staff to discuss PQM activities in Nigeria related to MCH. An update of PQM’s role in UN Commission activities was also provided to the group.

Next Steps

- PQM will begin following up with CHI Pharmaceuticals on its CAPA plan
- PQM will follow up with CHI Pharmaceuticals regarding the status of ORS manufacturing
- PQM will begin working with the other companies to develop company-specific roadmaps to manufacture zinc sulfate tablets and ORS according to GMPs
- PQM and CHAI will contact UNICEF supply division by July 12 to inquire about the possibility of PQM-recommended manufacturers being included on the UNICEF list of selected vendors

Conclusion

PQM’s GMP assessment of CHI Pharmaceuticals went well, and the CAPA plan to address observations should be completed within six months. The other companies that Dr. Evans met were very receptive to receiving PQM technical assistance to increase local manufacturing of quality-assured zinc sulfate tablets and ORS. In addition, the meetings held with Nigerian partners were fruitful and helped increase communication and collaboration efforts.

Day 1 Oral Dosage Form Facility	
Morning 09:30	<u>Opening meeting with key personnel</u> <ul style="list-style-type: none"> • Introductions of all personnel • Confirmation of proposed inspection plan/schedule
10:30-13:00	Facility Tour : <ul style="list-style-type: none"> • Raw Material and Packaging Material Warehouse. • Utilities (HVAC, Water, Compressed Air) • Manufacturing Areas • Finished Products Warehouse • QC and Microbiology Laboratories • Stability Chambers and retain samples
13:00-14:00	Lunch break
14:00-16:00	Document Review
	<u>Quality Management System review:</u> <ul style="list-style-type: none"> • Personnel Policies: Organization charts, Job descriptions, Training, Health and Hygiene • List of products/Production planning/Batch numbering system and batch register • SOP and document preparation, review and control • List of SOPs/SOP Index • Deviations/Change control/OOS + related SOP • Reprocessing/Reworking policy + SOPs • Finished product release procedure • Self inspection (SOP, Plans, reports) • Complaints handling system • Product recall system • Product Master Files, production flow diagrams and specifications key raw materials and FPP for the product in focus • Validation Master Plan • Equipments Qualification • Pest Control • Batch Records • Maintenance Program • Calibration Program • Supplier Qualification • Internal Audits • Change Control • Recalls from the Market • Complaints Managements • Deviation Managements • Annual product Review for the products in focus 2010 & 2011
16:00	Summary of observations for the day

Day 2	
9:30:AM	Document Review
	<p>Review of Plant Layout and Utilities (HVAC, Dust control, Water Purification and Compressed air systems):</p> <ul style="list-style-type: none"> • Block layout, area classification, AHU distribution and material and personnel flow. <p>1. HVAC and Dust Control system:</p> <ul style="list-style-type: none"> • Qualification/Requalification/Monitoring the HVAC + Dust Control System • Inspection of the HVAC + Dust extraction technical area <p>2. Water purification system:</p> <ul style="list-style-type: none"> • PW system drawings and summary of specifications and capacities • Qualification/Requalification/Monitoring the PW system (Sampling and trend analysis) • Inspection of Water Generation and Purification System installations <p>3. Compressed air system Qualification/Requalification/Monitoring the Compressed Air systems</p>
12:00-13:00	Lunch
13:00-16:30	<p>4. Equipment qualification and preventive maintenance:</p> <ul style="list-style-type: none"> • Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment) • Calibration • Preventive maintenance schedules and records <p>5. Validation</p> <ul style="list-style-type: none"> • Validation Master Plan (including status and planned) • Process validation and revalidation for the product in focus • Cleaning validation <p>6. Review of BMRs</p> <ul style="list-style-type: none"> • SOP on batch review and batch release <p>Review of BMRs for selected batches</p>
16:30-17:00	Summary of observations for the day and Closing meeting with company representatives