

**Technical Assistance in Dossier Preparation, Good Manufacturing Practices for Manufacturers of Zinc Sulfate Formulations, and Presentation of USP DQI Capabilities to Tanzania Food and Drug Authority (TFDA)**

**Tanzania**

**June 1-5, 2009**

---

***Trip Report***

**Patrick Lukulay, Ph.D.  
Director**

**Edwin Toledo, ASQ-CQA  
Program Manager/GMP Specialist**

**U.S. Pharmacopeia  
Drug Quality and Information Program**  
12601 Twinbrook Parkway  
Rockville, MD 20852 USA  
Tel: (+1) 301-816-8160  
Fax: (+1) 301-816-8374  
Email: [uspdqi@usp.org](mailto:uspdqi@usp.org)

**Cooperative Agreement #** HRN-A-00-00-00017-00  
**Health Program Element:** P.E. 3.1.2 TB  
**Grantee:** United States Pharmacopeia Drug Quality and Information (USP DQI) Program  
**Author(s) Name:** E. Toledo, Patrick Lukulay  
**Language:** English  
**Date of Publication:** June 30, 2009



This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement number HRN-A-00-00-00017-00. The contents are the responsibility of the U. S. Pharmacopeia Drug Quality and Information Program and do not necessarily reflect the views of the United States Government.

## **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 staff traveled to Tanzania at the request of USAID to meet with TFDA officials to discuss potential areas of USAID support to TFDA to strengthen quality assurance systems in the country. DQI staff also debriefed TFDA about their technical assistance to zinc sulfate manufacturers in Tanzania and described progress made by one of the companies in meeting WHO requirements for prequalification of their zinc sulfate tablets.

The DQI Good Manufacturing Practices (GMP) specialist conducted a visit to Shelys Pharmaceuticals LTD and provided technical guidance on compiling dossiers for submission to the World Health Organization (WHO) Prequalification Programme as part of the WHO Zinc Expression of Interest (EOI). DQI staff provided guidance in addressing responses to the Pharmaceutical Inspection Convention (PIC) as part of European GMP certification and reviewed GMP corrective actions provided by Zenufa Laboratories.

## **Recommended Citation**

Toledo, E., and Lukulay, P. 2009. *Technical Assistance in Dossier Preparation, Good Manufacturing Practices for Manufacturers of Zinc Sulfate Formulations, and Presentation of USP DQI Capabilities to Tanzania Food and Drug Authority (TFDA)*, Tanzania, June 1-5, 2009. Submitted to the U.S. Agency for International Development by the United States Pharmacopeia Drug Quality and Information Program. Rockville, Maryland: United States Pharmacopeia.

## **Key Words**

Shelys Pharmaceuticals Limited (SPL), Zenufa Laboratories Limited (ZLL), Good Manufacturing Practices, Dossier, Standard Operating Procedures, zinc sulfate, UNICEF, Prequalification, Tanzania Food and Drugs Authority.

## Table of Contents

<a href="#"><u>Acknowledgements</u></a> .....	3
<a href="#"><u>Acronyms</u></a> .....	4
<a href="#"><u>Purpose of Trip</u></a> .....	5
<a href="#"><u>Sources of Funding</u></a> .....	5
<a href="#"><u>Section 1: USP, USAID, TFDA Meeting</u></a> .....	6
<a href="#"><u>Section 2: USP DQI Technical Assistance to Zinc Sulfate Manufacturers</u></a> .....	8
<a href="#"><u>Annex 1: Visit Agenda</u></a> .....	10
<a href="#"><u>Annex 2: WHO Dossier Outline</u></a> .....	11
<a href="#"><u>Annex 3: Workplan for PMI</u></a> .....	14
<a href="#"><u>Annex 4: Workplan for PEPFAR</u></a> .....	18
<a href="#"><u>Annex 5: DQI TFDA presentation</u></a> .....	22

## **Acknowledgements**

The writers of this report would like to express their sincere thanks to Mr. Ashok Gupta, Manager Regulatory Affairs and Formulation, Shelys Pharmaceutical Limited; Dr. Kishor Athayle; Mr. Bongo Mgeni, Academy for Educational Development (AED) Tanzania; and Mr. Christian Winger, Deputy Director Point-of-Use Water Disinfection and Zinc Treatment (POUZN) project, AED, for their assistance in this assessment.

Thanks also go to all administrative staff of the DQI Program for their diligent assistance in logistics arrangements and the preparation of the training materials.

DQI would like also to thank the USAID Mission staff, especially Dr. Charles Llewellyn, Population and Health officer; Dr. Raz Stevenson, Quality of Care and Services Delivery Specialist; and Mr. Keith Hummel, Commodities and Logistics Advisor (PEPFAR) as well as Ms. Emily Wainright, Ms. Malia Boggs, Ms. Veerle Coignez, and Mr. Anthony Boni at USAID headquarters in Washington, D.C., for their support and advice.

## Acronyms

ACT	Artemisinin-based Combination Therapy
ADDO	Accredited Drug Dispensing Outlet
AED	Academy for Educational Development
AHU	Air Handling Unit
AMFm	Affordable Medicines Facility for Malaria
BMR	Batch Manufacturing Records
CAP	Corrective Action Plan
DT	Dispersible Tablets
GMP	Good Manufacturing Practices
HVAC	Heating, ventilation, and air conditioning
MOH	Ministry of Health
MSD	Medical Stores Department
ORS	Oral Rehydration Salts
OOS	Out-of-Specifications
POUZN	Point-Of-Use Water Disinfection and Zinc Treatment
QA	Quality Assurance
QC	Quality Control
PIC	Pharmaceutical Inspection Convention
PLC	Programmable Logical Controller
RM	Raw Material
SCMS	Supply Chain Management System
SPL	Shelys Pharmaceutical Limited
SOP	Standard Operating Procedure
TA	Technical Assistance
TFDA	Tanzania Food and Drugs Authority
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

## **Purpose of Trip**

The purpose of the trip was two fold: first, to meet with TFDA to discuss potential areas of collaboration between TFDA, DQI, and USAID; and second, to provide technical assistance to zinc sulfate manufacturers in dossier preparation and GMP compliance.

### TFDA meeting

Accompany USAID Mission staff to TFDA to

1. Discuss possible assistance to TFDA to strengthen their regulatory and quality assurance systems, discuss the quality of zinc sulfate produced in Tanzania, and provide an update on Shelys Pharmaceutical Limited's (SPL) progress toward WHO prequalification.
2. Discuss potential technical assistance to local pharmaceuticals companies in Tanzania to assure the production of good quality opportunistic infectious disease drugs for HIV/AIDS patients.
3. Brief TFDA about technical assistance provided by DQI to other drug regulatory authorities in developing countries. See *Annex 1* for visit agenda.

### Visit to zinc sulfate manufacturers

1. Review SPL zinc sulfate tablet dossier for completeness, consistency, and credibility prior to submission to WHO prequalification group.
2. Provide assistance for Pharmaceutical Inspection Convention scheme (PICs) queries and verify corrective action plans.

## **Source of Funding**

This trip was supported by Core funding for Maternal and Child Health and Common Agenda.

This trip report is divided into two sections. The first section describes a meeting between USAID, USP DQI and Tanzania Food and Drug Authority staff to discuss potential USP DQI assistance to TFDA to strengthen drug quality assurance systems in Tanzania. The second section describes the technical assistance provided by DQI GMP specialist to zinc sulfate manufacturers in Tanzania for compliance with GMP.

---

## Section 1: USP, USAID TFDA Meeting

---

### Background

Recently, USAID/Tanzania requested that the DQI team accompany them to TFDA to discuss a number of issues related to USAID's potential assistance to strengthen TFDA in their regulatory and quality assurance functions. USAID/Tanzania also requested that DQI discuss their technical assistance to Shelys and Zenufa Pharmaceuticals as part of building in-country capacity to provide drugs of assured quality to the Tanzanian people. While DQI has assisted Shelys to comply with good manufacturing practices for the production of zinc sulfate for childhood diarrhea, USAID/Tanzania expressed interest in providing similar assistance to other viable manufacturers for medicines used for opportunistic infections in HIV/AIDS patients.

#### Meeting at USAID: June 2, 2009

Charles Llewellyn (USAID), Keith Hummel (USAID), Michael Hope (USAID/Washington), Jessica Kafuko (USAID) Christy Best (SCMS) Bongo Mgeni (POUZN-AED), Patrick Lukulay (USP DQI), and Edwin Toledo (USP DQI)

The meeting was convened to plan for the meeting at TFDA. After the introductions, Mr. Hummel discussed the objectives of the meeting at TFDA and set expectations for the meeting. The DQI team discussed their work to date with Shelys and indicated that they were in the country to follow up on the progress that Shelys has made toward preparing the zinc dossier for WHO prequalification. The USAID expressed interest in working with DQI to provide similar assistance to Shelys and other local companies for drugs used for opportunistic infectious diseases in HIV/AIDS, including Co-trimoxazole and Vitamin B complex. Participants at the meeting agreed that any assistance would be preceded by an Expressions of Interest (EoI) organized by the USAID Mission in function of its health priority programs. In this way companies are selected in a transparent and objective manner. During the meeting the head of the HIV/AIDS team, Elise Jensen, joined the meeting and welcomed the team to Tanzania. She expressed her appreciation for the progress that the USAID team has made in meeting their objectives to provide life saving drugs and building better health systems and also thanked the partners for their collaboration. She indicated that certain challenges still remain but that systematic progress is being made to meet them.

#### Meeting at TFDA: June 2, 2009

Keith Hummel (USAID), Charles Llewellyn (USAID), Michael Hope (USAID/Washington), Mr. Silo, TFDA Acting director Medicines and Cosmetics), Mr Chikulizu (TFDA director product evaluation and registration) Mr. Alfonso (TFDA manager Inspection department), Mr Yona- (TFDA Manager QC department) Patrick Lukulay (USP DQI), Edwin Toledo (USP DQI) and Bongo Mgeni (POUZN AED)

After introductions, Charles and Keith thanked the TFDA staff for meeting with the visiting team and explained the objectives of the meeting. The TFDA acting director of medicines and cosmetics, Mr. Silo, apologized that the director general was not in attendance. Mr. Silo

announced that zinc sulfate has been granted OTC status in Tanzania. Charles thanked Mr. Silo and inquired about when they can start social marketing activities. Mr. Silo responded that the official letter will be issued by the Ministry of Health very soon. Charles went on to talk about USAID plans to expand ADDO like facilities in Tanzania and inquired about AMFm application plans by TFDA.

The meeting was then turned over to the DQI team. The DQI director, Patrick Lukulay, made a presentation about the technical capabilities of DQI and their accomplishments in supporting drug regulatory authorities in other African countries. He highlighted potential areas where DQI could support TFDA in the exercise of their regulatory functions. He also discussed the Quality of Antimalarials in Sub-Saharan Africa (QAMSA) study, in which Tanzania is participating. At the end of the presentation Mr. Silo expressed keen interest in TFDA working with DQI to strengthen post-market surveillance and training of their GMP inspectors in conducting GMP inspections of pharmaceutical companies.

Before departing Tanzania, the DQI director donated the latest copy of USP NF monographs (four books and supplement) to TFDA.

#### Meeting at MSH/SPS Office in Tanzania: June 3, 2009

Dr. Romwald Mbwasí (SPS senior technical advisor), Dr. Suleiman Kimata (SPS senior Program Associate), Michael Gabra (SPS Regional technical advisor)

The DQI director called on SPS colleagues in their office in Dar es Salaam and discussed the objectives of their mission to Tanzania and then debriefed them about the trip to TFDA and USAID/Tanzania. The DQI director expressed his desire to work closely with SPS in Tanzania if and when they are required by USAID/Tanzania to work on drug quality issues with TFDA and local manufacturers. The SPS colleagues briefed the DQI director about their work in Tanzania and expressed their desire to collaborate with DQI as much as possible to effect meaningful impact on the pharmaceutical systems in Tanzania.

#### **Conclusion and potential opportunities for DQI's technical assistance to TFDA**

On this trip, DQI identified key areas where USAID assistance would be needed to strengthen TFDA in the exercise of its regulatory functions as well as to assist local manufacturers in providing quality-assured medicines for the Tanzanian people. Given limited resources and competing priorities, DQI would like to propose key priority areas where USAID/Tanzania can focus assistance to produce maximum impact:

1. Work with TFDA to develop a national post-market surveillance of the quality of antimalarial, HIV/AIDS, and TB medicines. The collection sites will include public (central medical store) and private facilities (pharmacies, ADDOs and illegal outlets)
2. Technical assistance to local manufacturers to assure the quality of drugs for opportunistic infections for HIV/AIDS patients including Co-trimoxazole and Vitamin B complex. This may include an expression of interest in order to select companies to receive technical assistance.
3. GMP training of TFDA inspectorate to build their capacity for sustained GMP inspections of manufacturers

4. Develop or strengthen the pharmacovigilance system to monitor the safety of antimalarials and HIV/AIDS drugs. This is particularly important as new fixed dose drugs are being introduced in the country

DQI has taken the liberty to prepare work plans for the USAID/Tanzania Mission's consideration as a guide for future planning. DQI fully recognizes that not all activities may be conducted at once and that implementation will depend on the availability of funds and priorities set forth by the Mission. Refer to *Annex 4* and *Annex 5* for the proposed work plans for PMI and PEPFAR, respectively.

---

## Section 2: USP DQI Technical Assistance to Zinc Sulfate Manufacturers

---

### 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. Treatment of acute diarrhea with oral rehydration solution has become widespread, resulting in reduced mortality from dehydrating diarrheas but no decrease in the duration of episodes or their consequences, such as malnutrition. Adherence to recommendations regarding fluid therapy in children with diarrhea is poor because caregivers are focused on reducing the duration of illness, often leading them to use antibiotics and other treatments of no proven value.

Two well-documented determinants of diarrhea duration are low weight-for-age and decreased cell-mediated immunity. A common determinant of both factors is zinc deficiency, thought to be prevalent in children in developing countries. Zinc supplementation has been shown to reduce the duration and severity of childhood diarrhea in randomized controlled trials.

DQI conducted a visit to Shelys Pharmaceuticals Ltd. (SPL) and Zenufa Laboratories Ltd (ZLL) in Tanzania to assess their GMP progress in the manufacturing process for zinc sulfate tablets and oral solutions toward WHO prequalification status.

### Overview of Activities

#### *Monday, June 1, 2009*

**Meeting with Shelys Pharmaceutical Limited:** E. Toledo visited SPL and performed a facility walkthrough in preparation for UNICEF/WHO visit and found Shelys in an adequate state of compliance with WHO GMP guidelines. Mr. Toledo also started the review process of their zinc sulfate dispersible tablets dossier for WHO prequalification.

#### *Wednesday, June 3 2009*

Mr. Toledo met with Mr. Ashok Gupta, Manager Regulatory and Formulation Development, to continue reviewing the zinc dispersible tablets dossier for completeness, consistency, and credibility. SPL had completed most of the dossier documentation and will submit it by the end of June 2009 in response to WHO's first EoI for zinc products. (See *Annex 2* for WHO Dossier outline).

### ***Thursday, June 4, 2009***

Mr. Toledo visited ZLL and verified Corrective Action Plan recommendations put in place. The corrective actions were found to be at an acceptable level of compliance with WHO GMP requirements. Mr. Toledo also collected samples of zinc sulfate oral solution to be tested at USP's laboratory for compliance with the established monograph. ZLL is waiting for TFDA approval of zinc sulfate oral solution registration to launch.

### ***Friday, June 5, 2009***

Mr. Toledo visited SPL to assess ORS manufacturing activities as requested by UNICEF. SPL's ORS manufacturing facility has been designed to maintain temperature and RH as NMT 25degC and NMT 50% respectively. A blender with capacity of 100 kg blending is available in the ORS blending area. Three form-fill-seal sachet machines, each having capacity of about 20,000 sachets per shift, are available in the filling area. Monthly production on single shift basis is about 1.5 million sachets, and they can run the machines in two shifts, if required, and produce about 3 million sachets per month. SPL's ORS formulation is of reduced osmolarity and packing material specifications aluminum foil is as per UNICEF specifications with 70 micron to 80 micron thickness. SPL is the local supplier of ORS for Tanzania Medical Stores Department, a department of the Ministry of Health, furnishing quality drugs and medical equipment at accessible prices, made available through approved government and non-government agencies throughout Tanzania.

### **Conclusion**

USP DQI objectives of the trip were met: SPL's zinc dossier was properly reviewed and compiled and is in compliance with WHO guidelines. ZLL's corrective actions were evaluated and found in an adequate state of compliance with WHO GMP guidelines.

### **Next Steps**

- Ensure that SPL submits their dossier by June 2009
- Perform compendial testing on ZLL zinc oral solution
- Follow up with ZLL on any assistance for dossier compilation

### Annex 1: Visit Agenda of USP DQI Staff June 1 - 5, 2009

<b>Date</b>	<b>Time</b>	<b>Place</b>	<b>Contact</b>
<b>June 1</b> (Monday)	9:00am to 5:00pm	Shelys	Ashok Gupta
<b>June 2</b> (Tuesday)	8:00 am-9:00am	USAID	Keith Humme Charles Llewellyn
<b>June 2</b> (Tuesday)	10:00-12:00	TFDA	Hiiti B. Silo
<b>June3</b> (Wednesday)	9:00am-5:00pm	Shelys	Ashok Gupta
<b>June 4</b> (Thursday)	10:30am-3:30pm	Zenufa	Krishor Athalye
<b>June 5</b> (Friday )	9:30am to 5:30pm	Shelys	Ashok Gupta

## Annex 2: WHO Dossier Outline

### Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs)

For More Information on dossier Submission Documents please go to: <http://healthtech.who.int/pq/>

**APPLICANT:**

**DRUG PRODUCT NAME:**

**DOSAGE FORM:**

**DATE OF SUBMISSION:**

<b>Section 1. CHARACTERISTICS OF THE FPP</b>	
<b>1.1</b>	<b>Details of the product</b> 1.1.1 Name, dosage form and strength 1.1.2 Approved generic name(s) of the product 1.1.3 Visual description of the FPP 1.1.4 Visual description of the packaging
<b>1.2</b>	Visual description of the packaging
<b>1.3</b>	Regulatory situation in other countries

<b>Section 2. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]</b>	
<b>2.1</b>	<b>Nomenclature</b> 2.1.1 International Nonproprietary Name (INN) 2.1.2 Compendial name if relevant 2.1.3 Chemical name(s) 2.1.4 Company or laboratory code, if applicable 2.1.5 Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN) 2.1.6 Chemical Abstracts Service (CAS) registry number
<b>2.2</b>	<b>Properties of API(s)</b> 2.2.1 API not described in BP, PhInt, JP, PhEur, or USP 2.2.2 API described in BP, PhInt, JP, PhEur, or USP 2.2.3 Information from literature
<b>2.3</b>	Site(s) of manufacture

<b>2.4</b>	2.4 Route(s) of synthesis 2.4.1 API not described in BP, PhInt, JP, PhEur, or USP 2.4.2 Specifications of raw materials and intermediates used in the synthesis 2.4.3 API described in BP, PhInt, JP, PhEur, or USP
<b>2.5</b>	<b>Specifications</b> 2.5.1 API not described in BP, PhInt, JP, PhEur, or USP Provide justification for the API specification. 2.5.2 API described in BP, PhInt, JP, PhEur, or USP
<b>2.6</b>	<b>Container closure system</b> Description of the container closure system(s), including the identity of materials of construction of each primary packaging component, and their specifications.
<b>2.7</b>	2.7 Stability testing 2.7.1 Stress testing (forced degradation) 2.7.2 Regulatory stability testing

<b>Section 3. FINISHED PHARMACEUTICAL PRODUCT(S) [FPP(s)]</b>	
3.1	Manufacturing and marketing authorization
3.2	<b>Pharmaceutical development</b> 3.2.1 Company research and development 3.2.2 Information from literature
3.3	Formulation
<b>3.4</b>	Sites of manufacture
<b>3.5</b>	Manufacturing process
<b>3.6</b>	Manufacturing Process Controls of Critical Steps and Intermediates
<b>3.7</b>	<b>Process Validation and Evaluation</b> 3.7.1 New (for t3.7.2 Established (for the generic manufacturer) FPPs he generic manufacturer) FPPs
<b>3.8</b>	<b>Specifications for excipients</b> 3.8.1 Excipients not described in PhInt, JP, BP, PhEur, or USP 3.8.2 Excipients described in PhInt, JP, BP, PhEur, or USP

<b>3.9</b>	<b>Control of the FPP</b> 3.9.1 Specifications for the finished pharmaceutical product 3.9.2 Analytical procedures 3.9.3 Validation of analytical procedures 3.9.4 Batch analysis
<b>3.10</b>	3.10 Container/closure system(s) and other packaging
<b>3.11</b>	<b>Stability testing</b> 3.11.1 Stability-indicating quality parameters 3.11.2 Photostability Testing 3.11.3 Selection of Batches 3.11.4 Container Closure System 3.11.5 Testing Frequency 3.11.6 Storage Conditions 3.11.7 General case 3.11.8 Finished products packaged in impermeable containers 3.11.9 Finished products packaged in semi-permeable containers 3.11.10 Evaluation 3.11.11 Extrapolation of data 3.11.12 Core Storage Statements
<b>3.12</b>	<b>Container labeling</b>  3.12.1 Outer packaging or, where there is no outer packaging, on the immediate packaging 3.12.2 Blisters and strips 3.13 Product information for health professionals 3.14 Patient information and package leaflet

<b>Section 4. INTERCHANGEABILITY</b>	
<b>4.1</b>	Bio-equivalence study report
<b>4.2</b>	Summary of pharmacology, toxicology and efficacy of the product

### **Annex 3: USP DQI PROPOSAL FOR PMI TANZANIA**

#### **Introduction:**

Malaria is endemic across nearly all of mainland Tanzania with 93% of the population living in areas where *Plasmodium falciparum* is transmitted. Malaria accounts for 18% of National Diseases Burden in Tanzania. Health facilities report malaria as the leading cause of outpatient and inpatient health care visits and the primary cause of deaths among children.

In June 2005, the United States Government selected the United Republic of Tanzania (Tanzania) as one of the first of three countries to be included in the PMI. The population of Tanzania constitutes the largest number of persons at risk for malaria among all 15 PMI countries: approximately 40 million individuals of which 38.6 million are in the mainland and 1.3 million in Zanzibar.

The most recent data for malaria interventions in Tanzania comes from the preliminary report of the Tanzania HIV/AIDS and Malaria Indicator Survey (2007-2008) (THMIS). According to this survey, malaria control has improved since 2005. The percentage of fevers confirmed as malaria dropped from 25% in April 2005 to less than 1% of those tested in health facilities in April 2007. In Zanzibar, malaria indicators have shown marked improvement.

In a recent visit to Tanzania (June 2009), the Director of United States Pharmacopeia Drug Quality and Information (USP DQI) met with the USAID Mission and Tanzanian Food and Drug Administration. Both USAID and TFDA are interested in addressing and improving the drug quality assurance systems in Tanzania.

In this context, USP DQI proposes to the following activities for USAID/Tanzania and PMI consideration:

#### **Activities 1& 2. Establishing a drug quality monitoring program**

USP DQI's approach is to first conduct an assessment of Tanzania's capabilities in drug quality control and drug quality assurance. USP DQI team will travel to Tanzania to meet and interview key stakeholders such as (USAID, MoH, WHO, TFDA, malaria control program, HIV/AIDS control program, NGOs, Academia etc.), following a desk review of data about pharmaceutical sector.

USP DQI team will organize a micro-planning workshop with all stake holders to participate in the design of a post-marketing surveillance. Together the participants will select four sentinel sites in Mainland Tanzania and one site in Zanzibar, based on commonly agreed selection criteria. The participants will also discuss the medicines to be included in the program, the number of samples to be collected each round and all detailed logistics needed to carry the program activity. In the first year of the program, only one round of sampling and testing will be carried out. A round consists of sampling and inspecting drug packages and testing the samples using basic tests. The confirmatory tests of samples will be tested in the quality control lab of

TFDA using international pharmacopeia. DQI will train the staff of the QC lab of TFDA on key analytical methods to comply with international standards.

### **Activity 3**

USP DQI will purchase a total of seven Minilabs<sup>®</sup> (one for each site and two for the central lab for training) and organize a training workshop on the use of basic tests to monitor the quality of antimalarials at the sentinel sites level. Based on DQI experience in several other countries, the sentinel site teams are usually made of at least three persons. The role and responsibilities of each team will be defined clearly at the workshop. The workshop participants will design the components of the program including budget and timeline. USP DQI will provide the participants with all the necessary tools, procedures, guidelines to carry all operations of the program. DQI has continued to shape and improve its basic tests approaches learning from similar programs installed in Asia, Latin America, and Africa since 2002.

### **Activity 4**

After receiving the Minilabs<sup>®</sup>, equipment, training, and all the tools needed for sampling and testing antimalarial drugs in the field, the sentinel site teams will collect samples according to DQI procedures and guidelines and test them using basic tests as per DQI training. The sentinel site level is considered level one of quality control. All samples collected at level one should undergo a physical and visual inspection, simple disintegration, and thin layer chromatography. The results will be sent on to the TRDA lab for second level quality control.

### **Activity 5**

A rapid training of the QC lab of TFDA will be coordinated and lead by DQI. This training is necessary because DQI has to make sure that the lab is capable of conducting all confirmatory tests within the program. USP DQI staff will share with TFDA QC lab staff their know-how and will encourage them to comply with standards and deadlines. The training will cover at least three analytical methods according to international pharmacopeia. The analytical methods will be identified based on the drug selected during the micro-planning workshop.

After the training, the staff of the QC lab of TFDA will conduct the confirmatory testing and draft the final drug quality report.

### **Activity 6**

Based on the data of the first completed round of drug quality monitoring program, DQI will share the final report with key stakeholders and will make sure to recommend to TFDA what enforcement actions need to be taken.

DQI gained valuable experience from similar active programs in over 15 countries around the world. Such programs have shown great success in other countries and will certainly have a positive impact in assuring the quality of antimalarial in Tanzania.

**PROPOSAL FOR PMI TANZANIA**

<b>Activities</b>	<b>Descriptions</b>	<b>Deliverables</b>	<b>Timeline</b>	<b>Budget</b>
<p><b>Establish a post marketing surveillance program for Tanzania.</b></p> <p>1- Assess Tanzania's QA/QC capacities</p> <p>2- Lead a Micro-planning workshop to establish a Drug Quality Monitoring (DQM) program</p>	<p>Conduct an assessment of drug quality assurance and quality control capabilities in Tanzania.</p> <p>Review existing data and meet with key stakeholders:</p> <ul style="list-style-type: none"> <li>- TFDA (QC lab, drug registration, drug safety and drug information)</li> <li>- Malaria and HIV control programs</li> <li>- MOH, Academia, NGOs, WHO and others</li> </ul> <p>Lead a micro-planning workshop with all stakeholders in the country to establish a drug quality monitoring program at peripheral level</p> <ul style="list-style-type: none"> <li>- Select five sentinel sites</li> <li>- Identify country partners to be involved in the DQM program</li> <li>- Establish sentinel site teams and select the medicines to be collected and tested</li> <li>- Plan for budget, material, training and other needed resources</li> </ul>	<ul style="list-style-type: none"> <li>- Assessment report finalized and shared</li> <li>- Gaps and the strengths of Drug Quality Assurance and Quality Control systems identified</li> <li>- Areas where technical assistance is needed identified</li> <li>- Actions to be taken to strengthen quality assurance systems in Tanzania prioritized</li> <li>- The program plan is finalized</li> <li>- All program components discussed</li> <li>- Resources needed identified</li> </ul>	<b>Q1</b>	<b>\$ 60,000</b>
<p>3- Equip and train sentinel sites teams</p>	<ul style="list-style-type: none"> <li>- Procure one Minilab to each sentinel site and two Minilabs to central level for training (TFDA)</li> <li>- Train sentinel sites teams on basic tests using Minilabs</li> </ul>	<ul style="list-style-type: none"> <li>- Sentinel sites staff trained</li> <li>- Staff provided with Minilabs, procedures and guidelines to carry all field and lab operations</li> </ul>	<b>Q2</b>	<b>\$ 100,000</b>

4- Conduct Drug Quality Monitoring at five sentinel sites	<ul style="list-style-type: none"> <li>- Sample selected medicines according to DQI program</li> <li>- Test all samples collected using basic tests</li> </ul>	<ul style="list-style-type: none"> <li>- Sampling and basic tests report completed by five sentinel sites</li> </ul>	<b>Q2 – Q3</b>	<b>\$ 100,000</b>
5- Conduct confirmatory testing in TFDA QC lab	<ul style="list-style-type: none"> <li>- Train TFDA QC lab on selected analytical methods to test antimalarials drugs present in Tanzanian market</li> <li>- Conduct confirmatory testing of samples collected in five sentinel sites using pharmacopeial methods</li> </ul>	<ul style="list-style-type: none"> <li>- QC lab of TFDA trained on pharmacopeial analytical methods.</li> <li>- Confirmatory testing of all sentinel sites samples completed by TFDA QC lab</li> </ul>	<b>Q3 –Q4</b>	<b>\$ 50,000</b>
6- Promote enforcement actions to be taken by TFDA	<ul style="list-style-type: none"> <li>- Use the DQM data to promote appropriate regulatory enforcement</li> </ul>	<ul style="list-style-type: none"> <li>- Appropriate enforcement recommended to TFDA</li> </ul>		<b>\$ 5,000</b>
<b>ESTIMATED BUDGET</b>				<b>\$ 255,000</b>

## **Annex 5: PROPOSAL FOR PEPFAR TANZANIA** **(for one-year funding)**

### **Introduction**

Tanzania has a population of about 40 million; 1,400,000 are living with AIDS. The prevalence of HIV/AIDS in Tanzania is estimated at 6.2%. AIDS alone caused 96,000 deaths in 2007, making it the first cause of death in the country. The control of HIV/AIDS in Tanzania is complex because of the high prevalence of other major diseases such as malaria and tuberculosis.

Most of ARVs are imported and paid for by MoH and many foreign aid programs such as USAID, Global fund, UNAID and others. Tanzanian Pharmaceutical manufacturers generally do not comply with international Good manufacturing Practices (GMP), but some of them, have benefited from international collaborations and will be able to qualify for WHO GMP if they get technical assistance.

Recently, the USAID mission had expressed keen interest to have USP DQI work closely with TFDA. In a recent visit to Tanzania (June 2009), USP DQI Director met with USAID mission and discussed technical assistance USP DQI can offer to TFDA to help them with all GMP issues.

The USAID mission also requested DQI to discuss their technical assistance to Shelys and Zenufa pharmaceuticals as part of building in-country capacity to provide drugs of assured quality to the Tanzania people. Whilst DQI has assisted Shelys to comply with good manufacturing practices for the production of zinc sulfate for childhood diarrhea, the USAID mission expressed interest in providing a similar assistance to not only Shelys but other viable manufacturers for drugs used for opportunistic infections in HIV/AIDS patients. Training of TFDA GMP auditors is essential if standards are to be established and maintained, basic formal education alone would be limited in scope and intensity. Well trained TFDA inspectors in GMP, will ultimately help local manufacturers meet international standards of quality.

In this work plan, based on the TFDA and USAID mission requests, USP DQI proposes to provide technical assistance to strengthen the capacities of both TFDA auditors and inspectors and local Tanzanian pharmaceutical manufacturers. In addition, USP DQI proposes to assist TFDA and MoH in strengthening the Tanzanian Pharmacovigilance program in collaboration with WHO. USP DQI has carried out similar work in many other countries supported by USAID.

### **Assessment of Quality Assurance Capabilities of TFDA**

USP DQI will conduct a thorough assessment of TFDA practices and procedures. The aim of such assessment is to review and strengthen the systems in place to assure the safety, efficacy and quality of medicines. The assessment will also cover the manufacturers, wholesalers, importers and distributors of medicines. Together with TFDA inspectors, USP DQI assessors will determine the major gaps in the compliance with international norms (GMP, GLP, GDP, GSP) and will make clear recommendations to address the gaps in the whole pharmaceutical sector in Tanzania. Such an assessment is key to prioritize the actions to be taken to address the gaps in the systems.

### **Training of TFDA inspectors on GMP**

USP DQI will conduct up to three separate trainings of TFDA on all aspects of GMP. This gradual approach to training inspectors will enable them to effectively enforce the drug regulations and also assist the local manufacturers, wholesalers and distributors of medicines. If required, the inspectors will also be able to travel abroad and conduct GMP audits of their suppliers to make sure that the products they purchase are manufactured according to GMP. This will help assure the quality of medicines before they get into the supply and distribution chain.

### **Assist local pharmaceutical manufacturers**

For many years Tanzanian TFDA and MoH have encouraged local manufacturers to comply with GMP. Many of them have collaborated with international partners and this resulted in producing local, affordable and of good quality medicines (eg. TPI with Artesunate, Shelys with zinc sulfate etc.). After assessment of selected manufacturers and in collaboration with TFDA, USP DQI will provide an implementation plan to each manufacturer and will follow up and monitor their progress and provide them with technical assistance they need to meet international standards. Based on experience and taking into consideration that the manufacturers will not be at the same level, it can be expected that more than one year of technical support will be required. The commitment of local partners and the support of the government is key to achieve success in this field.

### **Assist TFDA strengthen its pharmacovigilance program**

TFDA, with the support of CDC and MSH/RPM Plus, has initiated PV activities. However, to date, few ADR reports are being collected, and the quality of ADR reports is not always good. USP DQI proposes to work with TFDA and MSH to strengthen PV into a self-sustaining national program, including the central PV office in Dar es Salaam as well as the four regional centers.

USP DQI and WHO PV experts can provide technical assistance to TFDA and assist with training and the increasing need to report ADRs to the international center in Uppsala, Sweden. USP DQI can assist TFDA to expand the program as necessary and train health professionals and medicines manufacturers to increase ADR reporting and improve the quality of ADR reports.

**PROPOSAL FOR PEPFAR TANZANIA**

<b>Activities</b>	<b>Descriptions</b>	<b>Deliverables</b>	<b>Timeline</b>	<b>Budget</b>
<b>Assessment of Quality Assurance Capabilities of TFDA and Drug Manufacturers</b>	<ul style="list-style-type: none"> <li>➤ Conduct a thorough assessment of drug quality assurance capacities in Tanzania.</li> <li>➤ Review in details the procedures and practices of TFDA (drug registration, inspection, pharmacovigilance, drug information and quality control)</li> <li>➤ In collaboration with TFDA, audit selected local manufacturers, wholesalers and importers of drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Assessment report</li> <li>• Audit report of visited manufacturers, wholesalers and importers of medicines in Tanzania</li> <li>• Recommendations on how to address GMP in Tanzania</li> </ul>	<b>Q1</b>	<b>\$ 40,000</b>
<b>Training of TFDA inspectors on GMP</b>	<ul style="list-style-type: none"> <li>➤ Conduct up to three training of TFDA inspectors to cover all aspects of GMP</li> <li>➤ Review and improve all TFDA procedures and practices about GMP audits</li> <li>➤ Establish a clear guide for TFDA GMP inspection</li> </ul>	<ul style="list-style-type: none"> <li>• All TFDA inspectors are well trained on all aspects of GMP and GMP audits</li> <li>• Practices and procedures improved</li> <li>• Guideline for GMP inspections established</li> </ul>	<b>Q1 - Q3</b>	<b>\$ 150,000</b>
<b>Assist local manufacturer to comply with GMP</b>	<ul style="list-style-type: none"> <li>➤ Assist selected local manufacturers of opportunistic infectious diseases by conducting audits, providing TA on how to address non compliance, and monitoring and evaluating progress</li> <li>➤ Support manufacturers ready to apply for WHO prequalification for</li> </ul>	<ul style="list-style-type: none"> <li>• Audit reports and plans for corrective actions</li> <li>• Plan for WHO prequalification</li> <li>• Possible WHO prequalification for one company for one product</li> </ul>	<b>Q2 - Q4</b>	<b>\$ 150,000</b>

	any product of interest			
<b>Strengthen the PV program in Tanzania</b>	<ul style="list-style-type: none"> <li>➤ Review the existing PV program and identify gaps.</li> <li>➤ Organize a national PV workshop to get feedback of all stakeholders</li> <li>➤ Collaborate with WHO and Uppsala PV center on drafting a national PV plan</li> <li>➤ Train trainers on ADR reporting according to international PV system</li> </ul>	<ul style="list-style-type: none"> <li>• PV review report made and shared</li> <li>• A National PV plan established</li> <li>• Trainers on ADR reporting according to international PV system trained</li> <li>• Implementation of national PV plan initiated</li> </ul>	<b>Q1 - Q4</b>	<b>\$ 200,000</b>
<b>ESTIMATED BUDGET</b>				<b>\$ 540,000</b>



U.S. PHARMACOPEIA  
DRUG QUALITY AND  
INFORMATION PROGRAM

Tanzania Food and Drug Administration  
Dar es Salaam, Tanzania ♦ June 2, 2009

## USP Drug Quality and Information Program (USP DQI)

A supporting mechanism for PMI,  
PEPFAR and other USG Initiatives

Patrick Lukulay, Ph.D., Director  
United States Drug Quality and  
Information Program



## Presentation Outline

- ♦ What is USP DQI?
- ♦ Overview of DQI's Technical Capabilities
- ♦ DQI's Work in Tanzania
- ♦ Current Initiatives





## United States Pharmacopeia (USP)

USP Drug Quality and Information Program

- ◆ Founded in 1820, non-profit organization establishes officially recognized standards for medicines quality
- ◆ Only nongovernmental pharmacopeia in the world
- ◆ Over 500 staff and four laboratories in the U.S., India, China, and Brazil
- ◆ Over 600 volunteers on USP Expert Committees



## USP Drug Quality and Information Program

USP Drug Quality and Information Program

- ◆ Cooperative Agreement between USP and USAID
  - ◆ October 2000–September 2010
  - ◆ **Objectives:**
    - ▶ Develop or strengthen medicines quality assurance systems in developing countries
    - ▶ Increase availability and use of unbiased drug information
- ▶ [www.uspdqi.org](http://www.uspdqi.org)





## Where USP DQI Currently Works

USP Drug Quality and Information Program

- ◆ **Africa**
  - ▶ Benin, Ethiopia, Ghana, Liberia, Madagascar, Mali, Senegal, and Uganda
- ◆ **Southeast Asia**
  - ▶ Cambodia, Laos, Philippines, Thailand and Vietnam
- ◆ **Latin America**
  - ▶ Bolivia, Brazil, Colombia, Ecuador, Guyana, Paraguay, Peru, and Suriname
- ◆ **Europe/Eurasia**
  - ▶ Russia



## USP DQI Priority Disease Program Areas

USP Drug Quality and Information Program

- ◆ **Malaria**
  - ▶ Benin, Ethiopia, Ghana, Madagascar, Mali, Senegal, Uganda, as well as countries in Latin America and Southeast Asia
- ◆ **Tuberculosis**
  - ▶ India, Philippines, Russia, Senegal, and Southeast Asia
- ◆ **HIV/AIDS**
  - ▶ Senegal, Southeast Asia
- ◆ **Antibiotics**
  - ▶ Bolivia, Paraguay, Peru, and Southeast Asia
- ◆ **Maternal and Child Health (MCH)**
  - ▶ Bangladesh, Nepal, Tanzania



## Targets for USP DQI Technical Assistance

USP Drug Quality and Information Program

### Medicines Regulatory Authority

- ◆ Establish in-country medicines quality monitoring program
- ◆ Provide TA in drug registration
- ◆ Establish Drug Information Centers
- ◆ Provide TA in dossier evaluation for BA/BE
- ◆ Establish PV program

### Manufacturer

- ◆ GMP inspection
- ◆ Technical assistance
- ◆ Capacitate to WHO prequalification
- ◆ Capacitate to UNICEF tender list



## Targets for USP DQI Technical Assistance

USP Drug Quality and Information Program

### National Medicines Quality Control Lab

- ◆ Conduct training in lab techniques for quality control
- ◆ Provide training in methods and validation
- ◆ Advise on procurement of reference standards and equipment

### Technical Resource For Global Initiatives

- ◆ Serve as technical resource for international orgs (WHO, UNICEF)
- ◆ Conduct multi-country surveys
- ◆ Develop monographs for key drugs (zinc sulfate, oseltamivir)



## Case study: Medicine Quality Monitoring in Ghana

USP Drug Quality and Information Program



### Sentinel Sites

- ▶ Bolgatanga
- ▶ Kumasi
- ▶ Ho
- ▶ Accra
- ▶ Tarkwa

Sites were selected by stakeholders based on the following criteria:

- ▶ Epidemiological
- ▶ Geographical
- ▶ Administrative
- ▶ Areas known for traffic in fake drugs
- ▶ Border provinces



## Basic Tests Using GPHF Minilab®

USP Drug Quality and Information Program



Visual Inspection



Disintegration Test



Color Reactions  
(not used by DQI)



Thin Layer Chromatography



## Why Postmarketing Surveillance?

USP Drug Quality and Information Program

### ◆ **Verify Product Stability**

- ▶ Storage and distribution conditions may impact product quality
- ▶ Inherent instability in certain batches produced—not captured during QC for batch
  - ▶ Antib-4 (four-ingredient FDC for TB) failed accelerated stability test in South Africa — withdrawn (2008)



## Why Postmarketing Surveillance?

USP Drug Quality and Information Program

### ◆ **Safeguard against counterfeits**

- ▶ Fake Cotecxin (Operation Mamba) and Metakelfin

### ◆ **Safeguard against rogue manufacturers**

- ▶ Change manufacturing processes and ingredients without informing regulators
- ▶ Rambaxy investigated by US FDA for using unapproved API to make HIV/AIDS medicine





## Work in Tanzania

USP Drug Quality and Information Program

- ◆ Quality, mfg specs developed with WHO/UNICEF
  - ▶ Rodael/Nutriset, Square Pharmaceuticals, Nepal zinc producers
- ◆ GMP assessment and dossier preparation
  - ▶ toward WHO prequalification
    - Shelys and Zanufi companies
- ◆ GMP assessment of Tanzania Pharma Enterprise
- ◆ Workshop on drug quality control
  - ▶ 14 countries participated
- ◆ QAMSA launched in 2007
  - ▶ 9 countries trained and participating



## Current Initiatives

USP Drug Quality and Information Program

- ◆ Provide TA to national laboratories toward ISO 17025 accreditation and WHO Prequalification (Ethiopia, Ghana)
- ◆ Develop monographs (public standards) for key antimalarial (AS+MQ) and anti-TB medicines (Prothionamide and Levofloxacin)
- ◆ Provide TA to manufacturers of 2nd-line anti-TB medicines toward WHO prequalification (Lupin and Svizera)





## Potential Areas of Collaboration

USP Drug Quality and Information Program

- ◆ Develop regional secondary reference standards
- ◆ Develop a network of quality control laboratories to promote south-south collaboration
- ◆ Evaluate new technologies for counterfeit detection



## New Advances in Counterfeit Detection

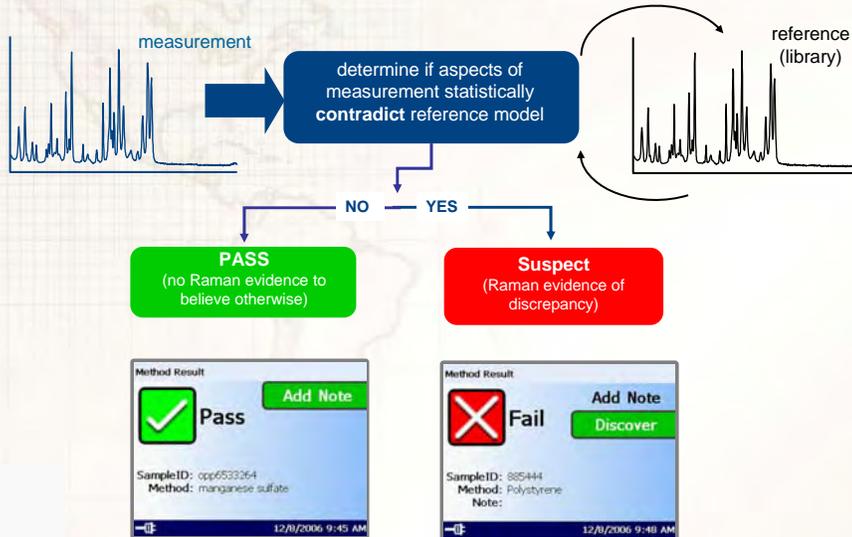
USP Drug Quality and Information Program





## TruScan™ System Logic

USP Drug Quality and Information Program



## Conclusion

USP Drug Quality and Information Program

### USP DQI promotes international public health through —

- ◆ Education and training of regulators, QC laboratories, and manufacturers
- ◆ Evaluation of new technologies for counterfeit detection
- ◆ Raising awareness of import role drug quality plays in public health
- ◆ Development of unbiased public standards for medicines for USAID priority diseases





U.S. PHARMACOPEIA  
DRUG QUALITY AND  
INFORMATION PROGRAM

# Thank You

**Contact:** [phl@usp.org](mailto:phl@usp.org)  
+1 301-816-8166

*This presentation is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement number HRN-A-00-00-00017-00. The contents are the responsibility of the U.S. Pharmacopoeia Drug Quality and Information Program and do not necessarily reflect the views of the United States Government.*



U.S. PHARMACOPEIA  
DRUG QUALITY AND  
INFORMATION PROGRAM

# Questions?

