

World Health Organization Medicines Prequalification in a New Decade

Copenhagen, Denmark
July 26-27, 2010

Trip Report

Patrick H. Lukulay, Ph.D.
Director

Promoting the Quality of Medicines Program

Implemented by U.S. Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: (+1) 301-816-8166
Fax: (+1) 301-816-8374
Email: pqm@usp.org

Cooperative Agreement # GHS-A-00-09-00003-00
Grantee: Promoting the Quality of Medicines (PQM) Program
Author(s) Name: PQM Staff
Language: English
Date of Publication: September 3, 2010



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 No. GHS-A-00-09-00003-00 through the President's Malaria Initiative (PMI). The contents are the responsibility of the Promoting the Quality of Medicines Program, implemented by the U. S. Pharmacopeia, and do not necessarily reflect the views of USAID, PMI, or the United States Government.

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 leadership 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.

Abstract

At the invitation of the World Health Organization (WHO), Dr. Lukulay travelled to Copenhagen, Denmark to attend a WHO meeting with manufacturers and to discuss PQM's technical assistance to manufacturers of second-line anti-tuberculosis (TB) medicines.

In separate meetings, Dr. Lukulay encouraged manufacturers to participate in the prequalification program and to request PQM assistance toward prequalification of their second-line anti-TB medicines.

Recommended Citation

Lukulay, Patrick. 2010. *World Health Organization Medicines Prequalification in a New Decade*. Submitted to the U.S. Agency for International Development by the Promoting the Quality of Medicines Program. Rockville, Maryland: United States Pharmacopeia.

Key Words

WHO prequalification, second-line anti-TB medicines, Good Manufacturing Practices

Table of Contents

<u>Acknowledgements</u>	4
<u>Acronyms</u>	5
<u>Conference Theme</u>	6
<u>Purpose of Conference</u>	6
<u>Source of Funding</u>	6
<u>Conference Highlights</u>	6
<u>Annex 1: Conference Agenda</u>	8
<u>Annex 2: PQM presentation</u>	10

ACKNOWLEDGEMENTS

I would like to thank:

Anthony Gould, the manager of the WHO prequalification program, and his staff for their support of the WHO/PQM partnership and for inviting me to speak at the meeting

Susan Bacheller, of the USAID TB team, for her continued support of PQM in facilitating the prequalification of second-line anti-TB medicines

Anthony Boni, the PQM Agreement Officer's Technical Representative at USAID/Washington, for his guidance and leadership

PQM's editorial team for their diligent editorial services

ACRONYMS

API	Active Pharmaceutical Ingredient
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
PQM	Promoting the Quality of Medicines Program
QAMSA	Quality of Antimalarials in Sub-Saharan Africa
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Conference Theme

WHO Medicines Prequalification in a New Decade

Purpose of Conference

- Brief manufacturers about new developments and requirements for the prequalification of medicines
- Obtain concerns from manufacturers about the prequalification process
- Inform manufacturers about technical assistance available to assist them in the prequalification process

Source of Funding

Dr. Lukulay's trip was funded by Core TB funds through USAID/Washington.

Conference Highlights

The conference agenda can be found in Annex 1, and Dr. Lukulay's presentation is included in Annex 2.

The meeting was opened by Dr. Lembit Rago, the coordinator of the WHO prequalification program. Dr. Rago gave the history of the prequalification program and highlighted the progress that has been made as well as challenges that remain to be addressed. He emphasized that the prequalification program is a voluntary program that requires the support of manufacturers. Without that support, there would be no prequalification program.

Since the inception of the program, a total of 237 products have been prequalified in 16 countries. In 2009, 84 dossiers were submitted for evaluation, and 53 were accepted for further review.

Dr. Rago spoke highly of the *Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda* (QAMSA) and indicated that the results showed that products which were prequalified showed an insignificant failure rate compared to products which were not prequalified.

The requirements for prequalification have changed and new guidance will be in effect by October. These changes include:

- The number of batches required to demonstrate product stability for both complicated and uncomplicated dosage forms will change.
- WHO will require manufacturers to apply for "Requalification" every five years. WHO will review documentation and may conduct an audit to verify that products which have been prequalified continue to be produced under current Good Manufacturing Practices ("cGMP" or "GMP").
- Dossier will be submitted in the form of Common Technical Document structure, with the Electronic Summary: Pharmaceutical Quality Information Form replaced with Quality Overall Summary.
- The current requirement to have three batches of pilot scale for stability will be reduced to having not less than two batches of at least pilot scale, or in the case of an uncomplicated Finished Pharmaceutical Product (FPP) not less than one batch of at least

pilot scale, and a second batch which may be smaller (e.g. for solid oral dosage forms 25,000 or 50,000 tablets or capsules).

- The process validation report for primary batches is no longer required.
- In the case of sterile active pharmaceutical ingredients (APIs), sterilization of the API is generally regarded by the WHO Prequalification Programme and the licensing authorities as part of finished product manufacture. Therefore data on the sterilization process of the API, including validation data, should be submitted by the applicant to WHO for inclusion in the FPP dossier.

Manufacturers asked WHO to publish a list of prequalified API manufacturers. WHO does not publish such a list but is discussing the idea internally. However, WHO does have a list of manufacturers that have been inspected and found to be operating under GMP.

A survey sponsored by the Prequalification Programme showed that manufacturers are interested in becoming more aware of resources to assist them during the prequalification process.

Applicants place a premium on feedback, communications and problem resolution during the prequalification process.



Dr. Patrick Lukulay with the Ukrainian delegation



PQP

QUALITY MEDICINES FOR EVERYONE

PREQUALIFICATION OF
MEDICINES PROGRAMME
A UNITED NATIONS PROGRAMME
MANAGED BY WHO



Meeting with Manufacturers WHO Medicines Prequalification in a New Decade

Copenhagen, Denmark, 26 - 27 July 2010
Conference Hall 1, WHO Regional Office for Europe, Scherfigsvej 8, 2100

Proposed Meeting Agenda:

DAY 1		
		Moderator: Lembit Rägo
9:00	Opening and welcome	Lembit Rägo
Topic: Common dossier deficiencies and how to address them		
9:15	Dossier issues - quality	Lynda Paleshnuik
9:45	Dossier issues - bioequivalence	John Gordon
10:05	Comparator issues (including illustrative examples of how PQP has identified acceptable comparators)	Jan Welink
10:25	Coffee break	
Topic: Update on new or revised procedures and guidelines, including re-qualification		
10:45	BCS based biowaivers - experience since start	John Gordon
11:05	Notes on BE assessment in PQ, including bioanalytical methodologies	Jan Welink
11:35	Product information in the WHOPAR	Regine Lehnert
11:50	APIMF procedure	Antony Fake
12:05	Requalification	Rutendo Kuwana
12:20	Variations	Hua Yin
12:30	Panel discussion on dossier assessment	
13:00	Lunch	
		Moderator: Tony Gould
Topic: Common GMP deficiencies and how to address them		
14:00	Examples of critical and major observations: - APIs and CROs - FPPs	Andre van Zyl Iveta Streipa
15:30	Coffee break	

Topic: Update on new or revised WHO GMP guidelines		
15:45	Sterile, Product Quality Review	Iveta Streipa
16:05	Microbiology laboratories, Transfer of Technology	Deus Mubangizi
Topic: Capacity building and technical assistance		
16:25	PQP support to manufacturers of needed medicines	Milan Smid
16:45	Panel discussion on GMP	

DAY 2		
Moderator: Mark Kays		
9.00	Introduction to PQP survey of manufacturers	Tony Gould
9:15	Report on the results of the survey of manufacturers	Mark Kays
9:45 (15 minutes each)	Manufacturers experiences with WHO medicine PQP - IPCA, India - Sanofi-Aventis, France - Cipla, India	Kavita Sehwan Valerie Faillat-Proux Katgeri Venkatesh
10:30	Discussion on survey of manufacturers	
11:00	Coffee break	
Moderator: Tony Gould		
11.30 (15 minutes each)	Procurement experiences with manufacturers and WHO medicines PQP - Global Fund - GDF - UNFPA - UNICEF - UNITAID	Sophie Logez Paloma Marroquín Lerga Agnes Chidanyika Francisco Blanco Lorenzo Witherspoon
13:00	Lunch	
14:00	USP, Promoting the Quality of Medicines Program - Program activities and experiences	Patrick Lukulay
14:30	Panel discussion on the Prequalification of Medicines Programme	
16:00	Close	
16:00 -	PQP staff and experts will be available for discussion with new manufacturers interested in prequalification	

Note: The final agenda will be posted on the Prequalification of Medicines Programme website - <http://www.who.int/prequal> .



Meeting with Manufacturers
WHO Medicines Prequalification in a New Decade
Copenhagen, Denmark ♦ July 26-27, 2010

PQM Technical Assistance in GMP for Pharmaceutical Manufacturers

Patrick Lukulay, Ph.D.
Director

Promoting the Quality of Medicines Program



USAID
FROM THE AMERICAN PEOPLE



The PQM Program

Promoting the Quality of Medicines Program

USAID-funded mechanism for promoting medicines quality globally

- ◆ Strengthen quality assurance and quality control systems for medicines regulatory authorities
- ◆ Conduct training and education in QC procedures for national QC laboratories
- ◆ *Technical assistance in GMP compliance for manufacturers*
- ◆ Advocate for the importance of medicines quality globally



Multidrug-Resistant (MDR) TB

Promoting the Quality of Medicines Program

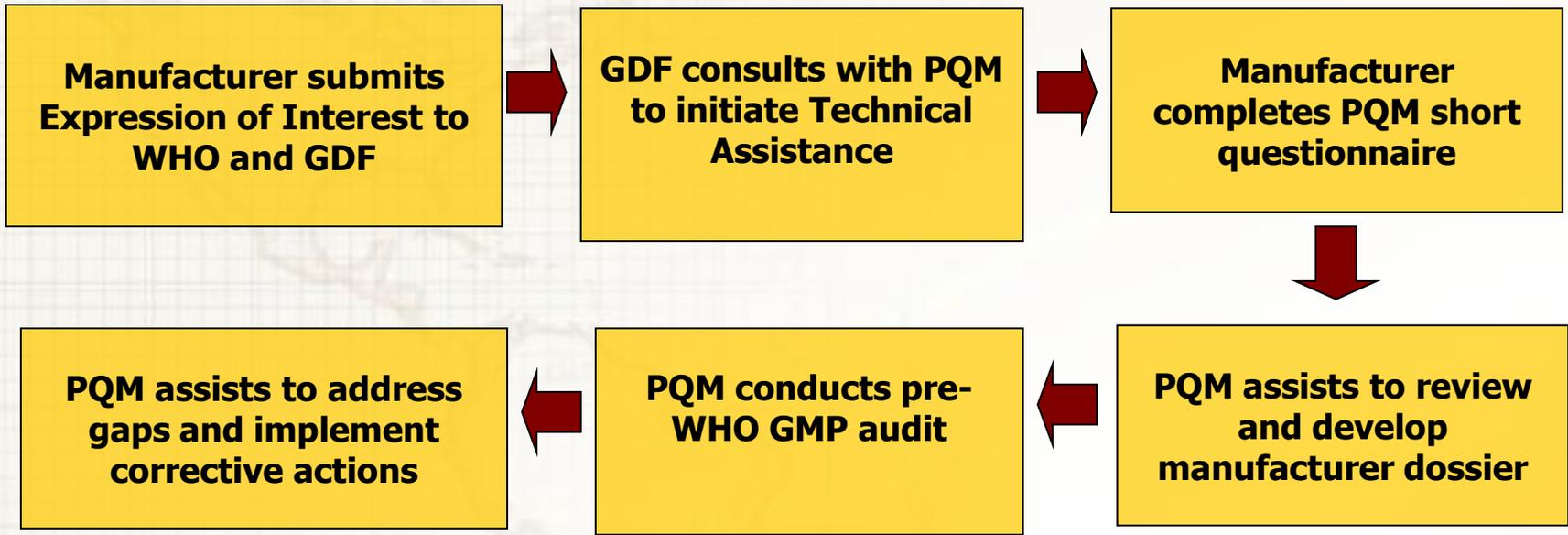
Barriers to large-scale effective treatment

- ◆ Limited supply of quality-assured second-line anti-TB medicines
 - ▶ Increase pool of quality-assured anti-TB medicines
 - ▶ Increase demand for quality-assured anti-TB medicines
 - ▶ Build local capacity for Good Manufacturing Practices with deep global reach



Technical Assistance Workflow

Promoting the Quality of Medicines Program



PQM does not approve your application but facilitates the approval by WHO Prequalification Team

Strengthening the quality of the dossier expedites the approval process



Selection of Manufacturers

Promoting the Quality of Medicines Program

The screenshot shows a web browser window displaying the USP website. The page title is "Technical Assistance toward WHO Prequalification". The main content area includes a header with the USP logo and "U.S. PHARMACOPEIA". Below the header, there is a navigation menu with categories like "OUT USP", "P-NF", "DD CHEMICALS CODEX", "NDING & NON-US STANDARDS", "REFERENCE STANDARDS", "P-VERIFIED", "UCATION", "ALTHCARE QUALITY & SAFETY", and "P IN DEVELOPING COUNTRIES". The main content area features a sub-header "Technical Assistance toward WHO Prequalification" and a paragraph stating: "USP DQI is assisting the Global Drug Facility (GDF) in its efforts to increase affordable price. To expedite the process of prequalification with the World Health Organization (WHO), USP DQI will provide technical assistance to interested companies on the pre-qualification process (EQIs)."

Currently there are not enough WHO-prequalified second-line TB medicines multidrug-resistant TB. In order to ensure good-quality products, United Nations non-governmental organizations mandate that only medicines prequalified by procurement. Subsequently, a number of companies have applied to WHO for pre-qualification.

The Expression of Interest that must be submitted to WHO for consideration product in specific order as presented in the "Information for Applicants" see manufacturers to:

- ▶ Prepare their product dossier for submission to the WHO Prequalification team;
- ▶ Facilitate discussions with WHO to remedy incomplete dossiers or
- ▶ Guide them onsite in complying with the principles and guidelines

Manufacturers that wish to receive technical assistance from USP DQI in this team on the following products:

- ▶ Capreomycin 1 g powder for injection, vial
- ▶ Cycloserine 250 mg capsule
- ▶ Kanamycin 1 g powder for injection, vial
- ▶ Levofloxacin 250 mg tablet
- ▶ Moxifloxacin 400 mg tablet
- ▶ Para-Aminosalicylic Acid (PASER) 4 g granules
- ▶ Para-Aminosalicylic Sodium 60% 100 g granules

- ◆ Obtain list of priority second-line anti-TB meds from GDF and TB Drug Management Sub-Working Group (SWG)
- ◆ Identify and select potential manufacturers with GDF based on response using pre-defined questionnaire
- ◆ Establish regular communication with manufacturers selected



Dossier Review

Promoting the Quality of Medicines Program



- ◆ Receive dossier from manufacturer prior to WHO pre-Q submission
- ◆ Assist to translate dossier into English if necessary
- ◆ Screen dossier for completeness based on PQ guidelines (stability, validation, API source, etc)
- ◆ Address gaps with manufacturers prior to submission
- ◆ Work with manufacturers to respond to WHO inquiries
- ◆ Inform GDF of progress made by manufacturer



GMP Assessment

Promoting the Quality of Medicines Program



- ◆ Conduct on-site GMP inspection to prepare manufacturer for prequalification audit
- ◆ Validate integrity of data submitted
- ◆ Collect samples
- ◆ Conduct full pharmacopeial monograph analysis and reporting



- ◆ Maintain up-to-date info on WHO requirements and deadlines
- ◆ Communicate info to manufacturers, dedicate PQM staff to respond
- ◆ Provide periodic updates to GDF regarding status of dossier preparation





PQM Experiences

Promoting the Quality of Medicines Program



India

- ◆ Assisted mfr submit dossier for Capreomycin Injectable - WHO accepted dossier on 1st submission
 - ▶ API DMF critical and can hold up application
- ◆ Assistance to others in progress

Russia

- ◆ Conducted symposium for Russian and Ukrainian manufacturers on Prequalification process
- ◆ Translated documents for a Russian manufacturer for kanamycin 1 g



Brazil

- ◆ Conducted workshop to promote prequalification in collaboration with GDF and WHO



Philippines

- ◆ Conducted GMP audit of a Levofloxacin manufacturer and assisted to compile dossier





Barriers to Manufacturer Interest

Promoting the Quality of Medicines Program

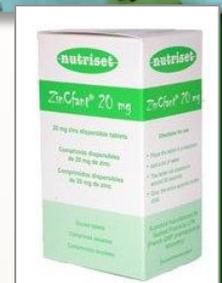
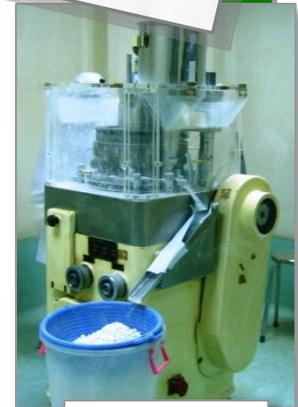
- ◆ Not familiar with processes and procedures for prequalification
 - ▶ Help available through PQM TA
- ◆ Lack of demand because local markets do not demand prequalification
 - ▶ Think globally — look at global markets
- ◆ May require capital investment with no guaranteed return on investment
 - ▶ Ensures quality and helps build reputation



Zinc Sulfate Success Story

Promoting the Quality of Medicines Program

- ◆ DQI provides TA to Rodael/Nutriset to produce zinc tablets of pharmacopeial and GMP standards
 - ▶ **Apr 2005:** UNICEF audits zinc tablet production; manufacturer does not meet WHO GMP
 - ▶ **Nov 2005:** DQI assesses, recommends changes, and provides TA on mfg, stability, QA issues
 - ▶ **Apr 2006:** DQI prepares Rodael for UNICEF audit
 - ▶ **May 2006:** Rodael passes UNICEF audit, first qualified mfr of zinc sulfate for global supply





Zinc Sulfate Success Story

Promoting the Quality of Medicines Program

- ◆ **May 2006:** DQI works with Square Pharmaceuticals, Bangladesh manufacturer of zinc sulfate
- ◆ **May 2008:** Square becomes second UNICEF qualified manufacturer for zinc sulfate



USAID
FROM THE AMERICAN PEOPLE



Conclusions

Promoting the Quality of Medicines Program

- ◆ One barrier to large-scale treatment of MDR-TB
 - ▶ Address by increasing number of quality-assured second-line anti-TB medicines
- ◆ Effective TA to manufacturers
 - ▶ Available to local and multinational companies
- ◆ PQM positioned to assist manufacturers to obtain WHO prequalification —
 - ▶ Dossier preparation and guidance toward prequalification
 - ▶ GMP assessment to prepare manufacturers for audit inspection
 - ▶ Quality control of products in USP lab



Promoting the Quality of Medicines Program

Questions?



USAID
FROM THE AMERICAN PEOPLE



Promoting the Quality of Medicines Program

Thank You

phl@usp.org
301-816-8166

<http://www.usp.org/worldwide/dqi/WHOQualificationRequest.html>

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 GHS-A-00-09-00003-00. The contents are the responsibility of the Promoting the Quality of Medicines Program and do not necessarily reflect the views of USAID or the United States Government.



USAID
FROM THE AMERICAN PEOPLE