

# **PQM Good Manufacturing Practices Assessment: Akrikhin Pharmaceuticals**

**Moscow, Russia  
April 23-24, 2012**

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## ***Trip Report***

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## **Promoting the Quality of Medicines**

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**PROMOTING THE QUALITY OF MEDICINES**

## Executive Summary

On April 23-24, 2012, PQM assessed the pharmaceutical manufacturing and laboratory capabilities of Akrikhin Pharmaceuticals Company in Moscow, Russia regarding compliance with the World Health Organization's current Good Manufacturing Practices (WHO cGMPs) main principles for pharmaceutical products. Akrikhin Pharmaceuticals Co. is interested in obtaining WHO Prequalification for Prothionamide 250mg tablets.

This assessment was performed using the general scheme of the systems approach for assessing the manufacture of pharmaceuticals, and included coverage of the following systems:

1. **Quality System**, which includes the overall compliance assessment, with Good Manufacturing Practices, internal procedures and specifications.
2. **Facilities and Equipment System**, which includes the activities of the facility, that they provide an appropriate environment and resources needed in the manufacture of pharmaceutical products.
3. **Materials System**, which includes the measure and activities used to control the raw materials, in-process materials, and product containers and closures, as well as, the validation of computerized inventory control processes, storage, and distribution controls.
4. **Production System**, which includes the measures and activities used to control the manufacture of pharmaceuticals, in-process sampling and testing, and process validation.
5. **Packaging and Labeling System**, which includes the controls used in the packaging and labeling of finished goods.
6. **Laboratory Control System**, which includes the activities and controls used related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the firm's stability program.

The objective in using this assessment approach was to provide the most comprehensive GMP coverage to a facility and products in a short period of time and to determine whether the manufacturer has the systems in place to operate in a state of control and in compliance with WHO cGMPs for the manufacture of finished pharmaceuticals.

The assessment revealed that Akrikhin Pharmaceuticals Co. had no critical observations and that they have the capability and necessary systems in place to maintain control and operate in compliance with WHO cGMPs.

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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.

## ACKNOWLEDGEMENTS

We would like to thank:

- Mr. Jan Slob, President, Akrikhin Pharmaceuticals Company
- Mr. Maxim Chikov, Vice President, Operations, Akrikhin Pharmaceuticals Company
- Mr. Ivan Tyulyaev, First Vice President, Akrikhin Pharmaceuticals Company
- Ms. Tatyana Kozelskaya, Chief of Quality Assurance Department, Akrikhin Pharmaceuticals Company
- Mr. William Slater, Ms. Suzanne Hoza, Dr. Nikita Afanasiev, and Dr. Marina Kulikova, USAID/Russia
- Mr. Anthony Boni and Dr. Maria Miralles at USAID Headquarters in Washington, D.C.
- PQM administrative staff and editors

## ACRONYMS

API	Active Pharmaceutical Ingredient
BA/BE	Bioavailability/Bioequivalence
DMF	Drug Master File
DQI	Drug Quality and Information Program
GMP	Good Manufacturing Practices
PQ	Prequalification
PQM	Promoting the Quality of Medicines Program
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

## Background

Tuberculosis (TB) is a global concern, and PQM has actively contributed to the USAID strategic objective of “increased use of effective interventions to reduce the threat of infectious diseases, including tuberculosis” (P.E.1.2 -TB). PQM assists countries to implement anti-TB medicine quality monitoring, and in 2008, began providing technical assistance to interested companies on the preparation of medicine dossiers they submit to the World Health Organization (WHO) with their "Expressions of Interest" for the WHO Prequalification (PQ) Programme.

## Purpose of Trip

The purpose of the trip was to:

- Establish a working relationship with Akrikhin Pharmaceuticals Company management
- Assess Akrikhin’s overall compliance with WHO Good Manufacturing Practices (GMP)
- Provide assistance in compiling dossiers for Prothionamide tablets for submission to the WHO Prequalification Programme.

## Source(s) of Funding

This trip was funded by USAID core funding for Tuberculosis.

## Overview of Activities

The following summarizes the pre-assessment of Akrikhin Pharmaceutical Company’s manufacturing facility conducted by PQM. The assessment was conducted to assess the firm’s capabilities and future potential in terms of compliance with WHO current Good Manufacturing Practices (WHO cGMPs) main principles for pharmaceutical products. This pre-assessment was performed using the general scheme of the systems approach for auditing the manufacture of pharmaceuticals and included coverage of the areas listed in the table below.



Item	Description
Institution Evaluated	Akrikhin Pharmaceuticals Co: 29, Kirov Str., Staraya Kupavna, Noginsky District, Moscow Region, 142450, Russian Federation
Specific Objectives	<ul style="list-style-type: none"><li>• Assess overall compliance with WHO cGMP standards</li><li>• Provide assistance in compiling dossiers for Prothionamide tablets for submission to the WHO Prequalification Programme</li></ul>
Auditors/ Evaluators	Kennedy Chibwe, David Vanscoy, Oksana Dmitrenok, Natalia Morozova
Key Personnel: Quality Assurance and Lab Management	<ul style="list-style-type: none"><li>• Mr. Jan Slob, President</li><li>• Dr. Ivan Tyulyaev, First Vice President</li><li>• Mr. Maxim Chikov, Vice President Operations</li><li>• Mr. Rustam Ixanov, Vice President, Strategic Development</li></ul>

	<ul style="list-style-type: none"> <li>• Ms. Tatyana Kozelskaya, Chief, Quality Assurance Department</li> <li>• Ms. Marina Lavrova, Quality Director</li> <li>• Mr. Vladimir Griban, Production Director</li> <li>• Mr. Nikolay Yurchenko, Regulatory and Medical Affairs Director</li> </ul>
Agenda	See <i>Annex 1</i> for a detailed audit agenda
Areas Evaluated	Manufacturing facility, Warehouse facility, and Laboratory facility
Key Findings	<ul style="list-style-type: none"> <li>• Manufacturing resource planning system needs to be fully validated.</li> <li>• Temperature monitoring of active pharmaceutical ingredient (API) storage and reference standards storage should be enhanced.</li> </ul> <p>PQM presented the findings of the visit on the final day to key Akrikhin personnel. A complete confidential report of the visit observations, findings, and recommendations will be sent to the company separately.</p>
Conclusion	Based on the areas inspected, Akrikhin Pharmaceuticals has all of the required systems to successfully participate in the WHO PQ Programme for Prothionamide tablets.
Next Steps	<ul style="list-style-type: none"> <li>• Initiate new bioavailability/bioequivalence (BA/BE) study at a WHO-approved facility</li> <li>• Initiate long-term stability testing at 30+/- 2°C, 75+/- 5% RH</li> <li>• Contact API supplier for updated drug master file (DMF)</li> <li>• Begin compilation of dossier</li> </ul>

#### Meeting with USAID/Russia, Office of Health, April 25, 2012

Participants: Office of Health, USAID/Russia (Mr. William Slater, Director; Ms. Suzanne Hoza, Project Officer; and Dr. Marina Kulikova, Project Management Specialist, TB control program) and the PQM team (Dr. Kennedy Chibwe, Oksana Dmitrenok, and Ms. Natalia Morozova)

The PQM team briefed USAID/Russia on the purpose of this PQM trip, updated them on the progress of PQM activities in Russia, and discussed future projects.

The following summarizes the discussions:

- Dr. Chibwe thanked Mr. Slater and staff for their continued support of PQM.
- Mr. Slater stated that he was happy with PQM's activities in Russia, mentioning that the positive relationships that USP has with Roszdravnadzor and the Russia Ministry of Health are appreciated.
- Dr. Chibwe highlighted the activities conducted on this particular trip, including four presentations at the International Conference in Moscow, auditing Akrikhin, and additional audits of Rostov and Kazan Labs (see *Annex 2* for a summary of activities). [NOTE: the additional activities mentioned here are covered in detail in separate trip reports]
- Dr. Chibwe informed USAID that Akrikhin may need support for the BA/BE studies. Mr. Slater stated that USAID/Russia will gladly look into this.

## Visit Agenda

Date	Time	Place	Contact
Monday April 23, 2012	9:30 AM–6:00 PM	GMP Assessment, Akrikhin Pharmaceuticals Co.	Tatyana Kozelskaya Chief of Quality Assurance Dept
Tuesday, April 24, 2012	9:30AM-5:30PM	GMP Assessment, Akrikhin Pharmaceuticals Co.	Tatyana Kozelskaya Chief of Quality Assurance Dept

## Audit Agenda

Site:	<b>AKRIKHIN Pharmaceuticals Co. (OJSC “AKRIKHIN”)</b>
Address:	“AKRIKHIN Pharmaceuticals Co”: 29, Kirov Str., Staraya Kupavna, Noginsky District, Moscow Region, 142450, Russian Federation
Contact Persons	Mr. Ivan Tyulyaev, mob. +79857840101; tel: +74957029510 e-mail: <a href="mailto:i.tyulyaev@akrikhin.ru">i.tyulyaev@akrikhin.ru</a> Mrs. Tatyana Kozelskaya mob. +79163118482; e-mail: <a href="mailto:t.kozelskaya@akrikhin.ru">t.kozelskaya@akrikhin.ru</a>
Date:	April 23 & 24, 2012
Products	Prothionamide, coated tablets, 250 mg, the drug has Marketing Authorization in the territory of Russia.
<b>Day 1: Monday April 23, 2012</b>	
Morning 0930 AM	Opening meeting with key personnel <ul style="list-style-type: none"> <li>• Introductions of all personnel</li> <li>• Stated purpose of Visit &amp; Review of Agenda</li> </ul>
1000 AM	<ul style="list-style-type: none"> <li>• Presentation of Akrikhin followed by Discussions</li> <li>• Presentation &amp; Discussions by PQM</li> <li>• Timeline of activities; BA/BE Studies status – CTD compilations; status of stability; validation activities, process validation; status of API DMF</li> </ul>
1300 PM	Lunch Break
1430 PM	Tour of Warehouse and Manufacturing Area
1630 PM	Summary of Day 1 – Action Items
<b>Day 2: Tuesday April 24, 2012</b>	
0930 AM	Review of Day 1 and any follow-up completion from Day 1
1000 AM	Tour of Manufacturing Area (continued from Day 1, if necessary) and Quality Control Laboratory
1230 PM	Lunch Break
1400 PM	Documentation Review
1600 PM	Wrap Up, Next Steps and Action Items

## 2012 Commonwealth of Independent States Activities Report

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1. **March 19 – 23, Moscow, Russia**  
 PQM training course  
*Basic tests and selection of samples for monitoring of anti TB medicine quality using Minilabs in Russian TB clinics* (theory and practice)  
 Presentations and training:
  - *Global Pharma Health Fund Minilabs<sup>®</sup>* by Richard Jaehnke
  - *Minilab<sup>®</sup> Training* by Lukas Roth and Sanford Bradby
  - *Medicines Quality Monitoring in TB clinics in Russia and Study Protocol* by Kirill Burimski, Oksana Dmitrenok, and Lukas Roth
  
2. **March – August, Moscow, Russia**  
 Translation of WHO Prequalification materials into Russian
  
3. **April 17 – 18, Rostov-on-Don, Russia**  
 Follow up visit/Second audit of Roszdravnadzor Medicines Quality Control Laboratory by Ofelia Villalva Rojas and Kirill Burimski
  
4. **April 19 – 20, Moscow, Russia**  
 International Conference  
*Quality of Medicines and Medical Products*  
 Presentations:
  - *Raman Spectroscopy for Monitoring Medicines Quality* by Fred Long
  - *PQM Technical Assistance for participation in WHO Prequalification Program* by Kennedy Chibwe (core funding)
  - *Report on the 1<sup>st</sup> audit (September 2011) of Roszdravnadzor Rostov-on-Don laboratory* by Ofelia Villalva Rojas
  - *Modification of Pharmacopeial Monographs* by Natalia Kouznetsova, USP (USP funding)
  
5. **April 23 – 24, Moscow Region, Russia**  
 WHO prequalification  
 Visit to AKRIKHIN Pharmaceuticals Co. by Kennedy Chibwe, David Vanscoy, Oksana Dmitrenok, and Natalia Morozova (core funding)
  - Meeting with Akrikhin management and discussion of issues regarding registration, standards, BA/BE studies, pharmacovigilance, etc.  
 Visit to the production site (solid finished products)
  - Visit to the warehouses and Quality Control lab.

6. ***April 23 – 27, Kazan, Russia***  
First audit of Roszdravnadzor Medicines Quality Control Laboratory by Ofelia Villalva Rojas, David Andrews, and Kirill Burimski
  
7. ***June 11 – 13, Rockville, MD, USA***  
Visit of Roszdravnadzor delegation to USP – not sponsored by USAID
  - Acting Director Dr. Elena Telnova
  - Seven directors of Roszdravnadzor regional offices to USP
  
8. ***June 25 – 29, Rockville, MD, USA***  
Visit of six Roszdravnadzor Medicines Quality Control Laboratory managers to USP.  
Some topics:
  - USAID-USP PQM Program
  - International Quality Standards ISO 17025 and WHO's GLP
  - Regulation of Compounded Preparations
  - Spectral Libraries Database
  - Tour of USP laboratories
  - Potential visit to an FDA laboratory
  
9. ***July – October, St. Petersburg, Krasnoyarsk, Russia***  
Pharmacopeial Education courses for Roszdravnadzor laboratory staff  
July, St. Petersburg – Analytical
  - Basic approaches to sample preparation
  - Validation of analytical methods
  - Identification of residual organic solvents by Gas Chromatography
  - Atomic absorption spectroscopy in drug tests
 September, St. Petersburg – Microbiology
  - Definition of bacterial endotoxins in injectables and medicine substances
  - Test for microbiological contamination
  - Microbiological assay of antibiotics
  - Cleaning and disinfection of microbiology laboratory
 September-October, Krasnoyarsk – Pharmacology
  - Drugs toxicity in post-registration Medicines Quality Control. Pharmacopeial and other methods
  - Histamine-like and depressor substances, identifying in medicines
  - Pre-clinical medicines studies
  
10. ***July – August, Russia and Ukraine***  
Tentative PQM visits to manufacturers of second line antituberculosis medicines.