

# USP DQI Good Manufacturing Practices Assessment and Dossier Technical Assistance

Russia

August 3-7, 2009

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## *Trip Report*

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## **About USP DQI**

The United States Pharmacopeia Drug Quality and Information (USP DQI) Program, funded by the U.S. Agency for International Development (USAID) under 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**

The DQI team (Dr. Kirill Burimski and Mr. Edwin Toledo) conducted a visit to Kurgan Joint-Stock Company of Medical Preparations and Articles (Sintez JSC), in Kurgan, Russia to perform a baseline GMP assessment in manufacturing kanamycin powder for injection and levofloxacin tablets and to provide assistance in compiling dossiers for submission to the World Health Organization (WHO) Prequalification Programme.

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## **Key Words**

Kurgan Joint-Stock Company of Medical Preparations and Articles (Sintez JSC), Good Manufacturing Practices, validation, Standard Operating Procedures, kanamycin powder for injection, levofloxacin tablets dossier, Prequalification.

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USP DQI would like also thank Dr. Nikita Afanasiev, Senior Infectious Diseases Advisor, USAID/Russia, and Ms. Veerle Coignez and Mr. Anthony Boni from USAID Headquarters in Washington, D.C., for their support and advice.

## Acronyms

CAP	Corrective Action Plan
DMF	Drug Master File
DOTS	Directly-Observed Treatment, Short-course
DUR	Drug Utilization Review
EOI	Expression of Interest
FDC	Fixed Dose Combination
GDF	Global Drug Facility
GLC	Green Light Committee
GMP	Good Manufacturing Practices
OOS	Out of Specifications
QA	Quality Assurance
QC	Quality Control
ROSZDRAVNADZOR	Federal Service on Surveillance in Healthcare and Social Development of Russian Federation
Sintez JSC	Kurgan Joint-Stock Company of Medical Preparations and Articles
UNOPS	United Nations Office for Project Services
USAID	United States Agency for International Development
USP DQI	United States Pharmacopeia Drug Quality and Information Program
WHO	World Health Organization

## **Background**

Tuberculosis, a global concern for many decades, is now compounded by the development of multidrug-resistant tuberculosis (MDR-TB) – strains of tuberculosis that are resistant to both isoniazid and rifampicin. The situation has been exacerbated by the emergence of extensively drug resistant tuberculosis (XDR-TB), which is described as resistance to isoniazid, rifampicin, and two or more of the six classes of second-line anti-tuberculosis drugs.

In 2007, USAID asked USP DQI to assist the Global Drug Facility (GDF) and the Green Light Committee (GLC) to increase the number of manufacturers of good quality second-line anti-TB drugs that are WHO prequalified. In response, USP DQI assisted GDF and GLC to design a questionnaire to include with requests to manufacturers to submit Expressions of Interest (EOI) in the WHO prequalification process. These facilitate the evaluation of manufacturers of priority second-line anti-TB drugs (capreomycin, kanamycin, and para-amino salicylic acid) that may be eligible for and interested in becoming WHO prequalified. Through these collaborative efforts, the manufacturers selected will receive technical assistance to improve their GMP compliance.

In March 2009, the director of USP DQI attended the GDF Super Team meeting in Rio de Janeiro, Brazil and presented the services USP DQI provides to manufacturers to help them prepare registration dossiers for the consideration of the WHO prequalification program. During the meeting, the director met with Mr. Yuri Petrov, head of production development for SIA International (Moscow, Russia) who showed interest in having USP DQI visit Sintez JSC to evaluate their GMP compliance and dossier for kanamycin and levofloxacin in preparation for WHO prequalification.

## **Purpose of Trip**

The DQI team visited Sintez JSC to assess their compliance with GMP standards and provide assistance in compiling dossiers in the manufacturing of kanamycin powder for injection and levofloxacin tablets for submission to the WHO Prequalification Programme. Meetings were held with USAID/Russia and the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (ROSZDRAVNADZOR) to debrief officials.

## **Source of Funding**

This trip was supported by USAID core funds for Tuberculosis.

## **Overview of Activities**

### ***Monday, August 3, 2009***

**Meeting with USAID/Russia Mission:** The USP DQI team, including USP DQI Russian Project Consultant Dr. Oksana Dmitrenok, met with Dr. Nikita Afanasiev, Senior Infectious Diseases Advisor. The team informed Dr. Afanasiev about implementation and future plans for the USP DQI projects funded by USAID/Russia, including (1) assessing the impact of the Infectious Diseases Textbook and the Distance Learning Program on prescribing patterns of antimicrobial medicines in selected health facilities in Russia and (2) improving the quality of anti-TBs and other medicines by establishing a routine low-cost mechanism of drug quality monitoring and reporting. As for the first activity, ten health care facilities in Russia participated in the Drug Utilization Review (DUR) with focus on use of antimicrobial medicines. More than 1,400 Case Report Forms were received and entered into a specially developed database. As for the second

activity, the Minilabs<sup>®</sup> have not arrived in Russia yet as it takes a great deal of time and effort to prepare for customs clearance. A broker company to facilitate customs clearance was recommended by USAID/Russia partners and was contacted by USP DQI; the documents that are necessary to submit to customs are being collected. Partners have decided to postpone the Minilab<sup>®</sup> training workshop, which was initially planned for September, until October or November 2009.

Later that day, all mentioned above met at the USAID/Russia office with Cheril Kamin, Director, Office of Health; Nina Khurieva, TB Project Manager Specialist, Office of Health; and Kate Weber, Foreign Officer, to discuss the details of the trip. The USP DQI team provided details of the technical assistance USP DQI is providing to Sintez JSC on kanamycin and levofloxacin dossiers and GMP compliance (see *Annex 1* for the Assessment Agenda). USP DQI staff also informed USAID colleagues about a major conference on Harmonization and Standardization of Regulatory Requirements that will be held at the end of November in Moscow. USAID staff asked for more details about the conference, as they become available.

**Next steps:**

1. USP DQI team will send this trip report to Dr. Afanasiev.
2. USP DQI team will provide information on the Harmonization and Standardization of Regulatory Requirements conference to USAID/Russia staff.

**Meeting with Valentina Kosenko:** Later that day, Mr. Toledo and Dr. Burimski met with Dr. Valentina Kosenko, Director of the Department of State Control of Medicinal and Disability Rehabilitation products at ROSZDRAVNADZOR to discuss the technical assistance that USP DQI is providing to second-line anti-TB manufacturers and to explore possible collaboration in the identification of more manufacturers as possible candidates. Dr. Kosenko was interested and might be able to help identify manufacturers willing to pursue WHO prequalification. She is also interested in having USP DQI participate in the Harmonization and Standardization of Regulatory Requirements conference, which is being organized by ROSZDRAVNADZOR.

**Next steps:**

1. USP DQI team will send this trip report to Dr. Kosenko.
2. USP DQI will discuss the possibility of presenting the program at the Harmonization and Standardization of Regulatory Requirements Conference.

***Monday, August 3, 2009***

The team traveled from Moscow to Kurgan.

***Tuesday - Thursday, August 4-6, 2009***

The team visited the Sintez JSC manufacturing site and met with several representatives of the company – Vitaly Pshenichnikov, Executive Director; Mr. Sergey Ivchenko, Technical Director and Chief Engineer; Ms. Margarita Kamenskaya, Quality Assurance Director; Ms. Lubov Pshenichnikova, Drug Quality Director; Ms. Natalia Smelova, Interpreter; and Mr. Nikolay Uliakov, Leading Economist; as well as Ms. Madina Sottaeva, Chief GMP Specialist, SIA International, to evaluate the status of Sintez JSC compliance with GMP standards in manufacturing kanamycin powder for injection and levofloxacin tablets and to provide assistance in dossier compilation toward WHO prequalification. The USP DQI GMP evaluation covered

the air handling unit, water purification system, compressed air system, starting materials stores, production rooms, packaging area, QC laboratory, and kanamycin and levofloxacin formulation (see *Annex 2* for findings report).

***Friday, August 7, 2009***

The team traveled from Kurgan to Moscow and debriefed USAID/Russia by phone.

**Conclusion**

Based on the areas inspected, and the corrective actions programs in place as part of USP DQI recommendations, Sintez JCS is operating at an acceptable level of GMP compliance for local kanamycin powder for injection and levofloxacin tablets manufacturing, as recognized by local regulatory authorities. The company is willing to submit expressions of interest for kanamycin and levofloxacin products evaluation in response to the invitation from the WHO Prequalification Program.

**Next steps:**

1. USP DQI will establish a Corrective Action Plan for Sintez JSC GMP deficiencies.
2. Sintez JSC will provide USP DQI with all necessary information for dossier preparation, in English.
3. Sintez JSC will request the Drug Master File for kanamycin active ingredient from the Chinese supplier.
4. Sintez JSC will prepare a dossier for WHO prequalification of kanamycin and levofloxacin.

## **Audit Agenda**

August 4-6, 2009

**Products:** kanamycin powder for injection and levofloxacin tablets

### **I. Introduction**

- Introduce personnel (all)
- Purpose of the visit
- Review of compliance report
- Discussion of WHO prequalification process for kanamycin and levofloxacin

### **II. Warehouse, Plant, and Laboratory Tour**

### **III. Compliance Report Documentation Review**

1. Site Master File
  - Amendments, if applicable
  - Annual Report
2. Drug Registration and dossier

### **IV. Quality Systems**

1. Master Batch Record Control and Review
2. Release Process
3. SOPs and Documentation Practices
4. Records and Sample Retention (Reserve sample program)
5. Change Control
6. Customer Notification Procedures
7. Training (GMP and job-specific)
8. Complaint System
9. Internal/External Audit Program
10. Investigation reports (will be selected during the audit)
11. Stability Program: procedure, Protocol and Summary of data
12. Rejects: Investigation
13. Quarantine product
14. General Manufacturing Procedures

## Sintez JSC Audit Findings

The inspection involved the following key personnel from Sintez/SIA:

Executive Director	Vitaly Pshenichnikov
Technical Director	Sergey Ivchenko
Quality Assurance Director	Margarita Kamenskaya
Drug Quality Director	Lubov Pshenichnikova
Interpreter	Natalia Smelova
Chief GMP Specialist	Madina Sottaeva

General information for Sintez JSC:

Name of manufacturer	Sintez JSC
Physical and postal address	7 Constitusii Prospect, Kurgan, Russia 640008
Telephone number	(3522) 481246
Fax number	(3522) 449125
Summary of activities of manufacturer	Manufacturing of products in the following dosage forms: Injectables, Dry syrup, Tablets, Capsules, Liquids, Medical devices
Scope of Assessment	Assessment of the manufacturing of kanamycin powder for injection and levofloxacin tablets with special emphasis on dossier, validation/qualification of manufacturing process, equipment and utilities
Date of Assessment	August 4-6, 2009
Program	PE 3.1.2 TB

## Summary

Kurgan Joint-Stock Company of Medical Preparations and Articles (“Sintez” or “Sintez JSC”) with initial name “Kurgan Plant of Medical Preparations” has been operating since September 1958. Sintez JSC is one of the largest pharmaceutical enterprises in Russia and is located in an industrial area in the south-western suburbs of Kurgan. Total area of the enterprise is 67.602ha. The injectable drug filling site is situated in Workshop No.7 (Building 103), on the 3<sup>rd</sup> floor, and the tablet and capsule production is situated in Workshop No.6 (Building 2) on the first floor. The company has more than 4,000 employees with 120 people dedicated to Quality Service. This was the first time the company had been inspected by a USP DQI team. The objective of the inspection was to verify compliance with WHO GMP, in the framework of the Prequalification Programme on priority essential medicines, specifically in regard to the manufacture of kanamycin powder for injection and levofloxacin tablets.

The inspection covered all areas of activity related to the manufacture of the dosage forms: Quality assurance; Facilities, i.e., HVAC, compressed air, water system, and electrical power back-up system; Storage areas; Sampling and dispensing areas; Filling, sealing, primary and secondary packaging; and Quality control and microbiological laboratories.

<b>Sintez JSC GMP Status</b>	
<b>Quality assurance</b>	A quality assurance system was implemented and maintained. The QA and QC units were independent from production. QA personnel were involved in all production and QC activities.
<b>Good manufacturing practices for pharmaceutical products</b>	Good manufacturing practices were implemented and maintained. Manufacturing processes were clearly defined and reviewed. Manufacturing steps were recorded in Batch Manufacturing Documentation. Necessary resources were provided. Instructions and procedures were written in clear and unambiguous language.
<b>Sanitation and Hygiene</b>	The site's sanitation and hygiene program covered personnel, equipment, materials and premises. The sanitation and hygiene measures in place at the time of the inspection were generally found to be sufficient to assure the prevention of contamination of the premises and product.
<b>Qualification and validation</b>	The key elements of a qualification and validation program were defined and documented in the Validation Master Plan. Generally, validations were considered to be appropriately performed. For cleaning validation, a matrix had been set up. This matrix was based on the assessment of the solubility and the toxicity of the active pharmaceutical ingredient in order to select some of the more toxic and the less soluble active substances as the worst case products (product chosen). <b>However, process validation for kanamycin and levofloxacin needs to be completed.</b>
<b>Complaints</b>	Complaints and other information concerning potentially defective products were reviewed according to a written procedure and corrective/preventive actions were taken.
<b>Product Recalls</b>	Recalls were handled in accordance with a written procedure. The recall procedure was regularly reviewed and updated.
<b>Contract production and analysis</b>	No manufacturing was contracted out.
<b>Self-Inspection</b>	Self-inspection was performed in accordance with a written procedure. The procedure included questionnaires on GMP requirements and all essential GMP items were covered. After completion of each self inspection, a report was drawn up and necessary CAPAs were initiated. The self inspection schedule was available for inspection. Self inspections were carried out every 6 months. The self inspection team was properly trained. Self inspection observations were classified and self inspection trends were evaluated.
<b>Personnel</b>	The personnel met during the audit were experienced, skillful and conscientious. An organization chart was available. Key personnel responsibilities were specified in job descriptions. The production and quality control responsibilities were independent and in line with GMP requirements.
<b>Training</b>	Training issues were covered in written SOPs. The company provides training at the time of recruitment, specific training relevant to area of deployment, and regular SOP training. Training comprehension was assessed by discussions and observation of performed activities.
<b>Personal Hygiene</b>	Personnel were trained in personal hygiene procedures and facilities were provided in the form of changing rooms, protective garments, and disinfectants. The facilities were generally adequate and the procedures were well enforced. <b>However, personnel working on kanamycin manufacturing should use face masks in zones A and B.</b>

<b>Premises</b>	Buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance, and production operations. Facilities were designed to minimize potential contamination; the production area had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. There was also sufficient space for the movement of materials and personnel. There were separate personnel and material entrances. Temperature, relative humidity, and pressure differentials were regularly monitored and recorded. In general, the buildings were well-maintained and clean. <b>However, the API warehouse at workshop #6 needs to be fixed to correct some deficiencies in the structure in order to avoid dust and pests entering the building.</b>
<b>Equipment</b>	Equipment calibration schedule was established on an annual basis and the calibration was performed accordingly.
<b>Materials</b>	The procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials was available. Incoming goods and finished products were quarantined until tested and released by QC. <b>However, warehouses visited did not have a material location system as part of material management and temperature mapping study. Vendor qualification program needs to be established for all raw material vendors.</b>
<b>Documentation</b>	There was a procedure for preparation, review, approval and authorization of SOPs. For products reviewed, there was a master formula, specification of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results.
<b>Good Practices in Production</b>	Production operations were carried out following clearly defined procedures. Operations on different products were not carried out simultaneously or consecutively in the same room. During processing, materials, bulk containers, major items of equipment, and the rooms and used packaging lines were labeled and indicated the products being processed, their strength and the batch number. Access to the production premises was restricted. All doors leading to the production areas were appropriately interlocked. An environmental monitoring program was established and followed. Aseptic processing was monitored continuously by exposing settle plates. Settle plates were exposed for four hours; this exposure time had been validated. Contact plates were used for monitoring surfaces. Non viable particles were monitored according to a written procedure. An appropriate operator monitoring system was in place. Line clearance was performed and recorded before processing operations were started.
<b>Good Practices in Quality Control</b>	In general, good practices in Quality Control were implemented and maintained. The quality control functions were independent of other departments. Adequate facilities, trained personnel and approved procedures were available for all relevant activities. Batches of products were released for sale or supply only after certification by the authorized person or designated persons. Sufficient samples of starting materials and products were retained to permit future examination of the product. Quality control personnel had access to production areas. Each “out of specification” (OOS) was appropriately evaluated and investigated in accordance with a written procedure.
<b>Stability Program</b>	The full range of validated stability cabinets was available and all were constantly monitored for temperature and relative humidity. ICH guidelines were followed using an approved protocol. The protocol detailed the number of samples to take to ensure that full testing over three years was possible. Long-term study intervals were 0, 3, 6, 9, 18, 24 & 36 Months. Accelerated storage was for 6 months at 40°C and 75% RH. Data for testing at each time interval was recorded along with the product specification. Long-term study intervals were 0, 3, 6, 9, 18, 24 & 36 Months. No matters of concern were noted.