

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Quality Control Laboratory

Part 1: General information

Name of the QC Laboratory	Testing centre of drug products quality expert evaluation of the Federal Governmental Budget Organization “Scientific Centre on Expertise of Medical Application Products” of The Ministry of Health and Social Development of The Russian Federation		
Physical address	Schukinskaya street 6, Moscow 117246, Russia		
Date of inspection	24 to 27 January 2011		
Type of inspection	Prequalification of Medicines Programme		
Type(s) of testing included in the inspection	Quality control of starting materials and products (Chemistry and microbiology).		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Physico – Chemical analysis	pH, density, refractive index, optical rotation, water content, conductivity, residual solvents, limit tests, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass, content)	pH, refractometry, refractive index, optical rotation, viscosity, melting point, distilling range, loss on drying, water content, heavy metals, residual solvents and limit tests.
	Identification	HPLC (UV-Vis, PDA, RI, detection), GC (FID, ECD, TCD), TLC, UV-VIS spectrophotometry, IR, basic tests	HPLC (UV-Vis, PDA, RI, detection), LC/MS, GC (FID, ECD, TCD), TLC, UV-VIS spectrophotometry, IR, basic tests

Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Assay, impurities and related substances	HPLC (UV-Vis, PDA, RI detection), GC (FID, ECD, TCD), UV-Vis spectrophotometry, FTIR, volumetric titrations	HPLC (UV-Vis, PDA, RI, detection), LC/MS, GC (FID, ECD, TCD), UV-Vis spectrophotometry, FTIR, volumetric titrations
	Biological tests	Sterility test, microbial limit tests, microbial assay of antibiotics	Sterility test, microbial limit tests, microbial assay of antibiotics

Part 2: Summary

General information about the laboratory and site

In total the laboratory “Scientific centre for Expertise of medicinal products” has 12 laboratories.

- Laboratory of control and regulations - sector GLC;
- Laboratory of chemical-pharmaceutical preparations No 1;
- Laboratory of phyto preparations and homeopathic medications;
- laboratory of vitamins, hormones and synthetic analogues;
- Pharmacological laboratory;
- Animal house;
- Microbiology laboratory;
- Laboratory of radiopharmaceutical preparation and in-vitro diagnostic
- Laboratory of biotechnological preparations;
- Laboratory of nanomedications, preparations for cell and gene therapy.

The above mentioned laboratories were located at Nauchny Proezd, 14-a, Moscow

Only the following two laboratories located at Shukinaskaya Street, 6, Moscow were subjected to inspection under the WHO prequalification program.

- Laboratory of chemical-pharmaceutical preparations No. 2
- Laboratory of antibiotics

The bulk of inspection time was spent in the chemical laboratory No. 2.

The main function of the two laboratories is to test products, API and excipients as part of product registration using test procedures submitted by either applicants or directly by manufacturers. Reference materials with certificate of analysis (CoA) were also supplied along with documentation. In some cases, HPLC columns were also supplied to facilitate testing.

History of WHO and/or regulatory agency inspections

The laboratories have not been previously inspected by WHO. The laboratory is accredited to ISO 17025 standard and the accreditation certificate is valid until 2014. The Centre has also been accredited by EDQM to ISO 17025.

Focus of the inspection

The inspection focussed on the quality management system, physico-chemical and microbiological activities of the laboratories.

Inspected Areas

The following areas of the WHO good practices for the pharmaceutical quality control laboratories were covered in this inspection:

- 2.1 Quality system
- 2.2 Control of documents
- 2.3 Records
- 2.4 Data-processing equipment
- 2.5 Personnel
- 2.6 Premises
- 2.7 Equipment, instruments and other devices
- 2.8 Reagents
- 2.9 Reference substances and reference materials
- 2.10 Calibration, verification of performance and qualification of equipment, instruments and other devices
- 2.11 Traceability
- 2.12 Incoming samples
- 2.13 Analytical sheet
- 2.14 Validation of analytical procedures
- 2.15 Testing
- 2.16 Evaluation of results
- 2.17 Certificate of analysis
- 2.18 Retained samples
- 2.19 Safety

2.1. Quality system

The organization of the laboratory was defined in an organization chart. The laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in their job descriptions. There were two supervisors and four group leaders to provide adequate supervision to laboratory experts and technical specialist.

A signature register of all employees was also available.

Records were kept for all incoming samples using standard operating procedures. The laboratory had a central registry dealing with registration and distribution of samples. Records of incoming samples were appropriately logged in a register. Samples were inspected on receipt and appropriately stored until testing started.

Procedures and documents (SOPs) were approved and available for the laboratory employees to perform different procedures and tasks. Reference to some of the SOP reviewed during the audit is given in the following sections of the report.

2.2. Control of documentation

An SOP for document control was available for review during the audit. The document and its application were considered to be satisfactory. A three year review period was assigned to each document. However, if required, documents were reviewed before the due date.

In the Antibiotics Microbiology Laboratory there were a number of documents that were in draft format. This was partly due to the fact that the Laboratory had recently been restructured and documents were still being transferred to a new system.

2.3. Records

Analytical data were recorded in analyst books and were fully traceable to samples, instruments, test procedures and reference standards. Records related to laboratory activities such as instrument qualification, calibration, raw data, test results and reports were appropriately stored in a chronological order. LIMS was not used in the laboratory; hard copies were the official version of records.

2.4. Data-processing equipment

HPLCs, GC, UV and IR instruments were linked to computers operated by their respective software. All raw data generated by these instruments were stored as hard copies and electronically on a server.

2.5. Personnel

An organization chart showing the hierarchical arrangements, responsibilities and reporting lines in the laboratory was available.

Current job descriptions were available. Documents were signed and dated by the relevant employees.

The following job responsibility cards were reviewed and found to be satisfactory:

- Head of Laboratory
- Laboratory supervisor
- Head of group (Line supervisor)

For each laboratory staff, a folder containing the following information was available:

- Competency list
- Starting date
- Qualifications
- Training

Interactions with staff during the inspection showed that most staff members had been with the laboratory for a considerable time because of low staff turnover. This enhanced staff competency in different analytical techniques and instruments and performing different tests.

Training to new recruits was imparted by a system of mentoring in that new starters worked with experienced staff until they became competent in performing a particular task. This was confirmed by reviewing training records.

The chemical laboratory participated in the proficiency testing scheme on assay of cefoxitin sodium by HPLC under the auspices of OMCL. The laboratory performed well in this study.

The Antibiotics Microbiology Laboratory had also participated in collaborative studies for the microbiological standardization of WHO Antibiotic Reference Preparations and the results had been accepted and included in the calculations to assign potency to the Reference Preparations.

2.6. Premises

The laboratory premises were spacious, well maintained, clean, and tidy and provided adequate room for laboratory activities. The laboratory environment was appropriate for performing different tests. Separate small laboratories were dedicated to different analyses such as HPLC, GC and physical tests (dissolution and disintegration).

Laboratory glassware was washed manually. All glassware with the exception of volumetric glassware was dried in ovens kept at 100°C. The clean glassware was appropriately stored in cupboards in the wash up room and also distributed to other work areas for easy access to analysts. The whole process of glassware washing, handling and storing was performed very competently.

Laboratory had appropriate storage facilities for reference standards, reagents and solvents. Acids and bases were appropriately separated and inflammable solvents were stored in cupboards suitable for this purpose. Only limited quantities of these materials were kept in the main laboratory.

The Antibiotics Microbiology Laboratory was also spacious, clean, tidy and well maintained. Access to the area was restricted to authorized personnel. Personnel were required to wear dedicated outer garments, shoes and head covering. The sterility testing area was supplied with HEPA filtered air and was accessed via an airlock/change room. Pressure differentials of not less than 20 KPA were maintained between the testing room, airlock and uncontrolled area. Pressures were measured with manometers mounted in the corridor adjacent to the testing area. The pressures were manually recorded daily and monitored randomly during the day; however there were no alarms present to indicate any fault with the air supply to the sterility testing area.

Sterility testing and other microbiological testing was carried out in Biological Safety Cabinets which were regularly calibrated by an external organization. The sterility testing area was cleaned according to the written SOP. Disinfectants were prepared according to Work Instruction. Environmental monitoring consisted of settle plates exposed in the Biological Safety Cabinet and on a bench in the testing area. Results of environmental monitoring were recorded on a form. Limits were included on the form. Operator gloves were monitored after each sterility testing session. Results from 2010 showed that no organisms were recovered from environmental monitoring during 2010.

2.7. Equipment, instruments and other devices

As stated previously, the laboratory was well equipped to perform almost all pharmacopoeial tests for finished dosage forms. All analytical instruments, equipment and other measuring equipment had been purchased from suppliers of world repute. Calibration of instruments was carried out annually by the State Agency. Additionally, major instruments such as HPLC, UV and IR were calibrated in-house every three months.

Critical incubators were fitted with temperature measuring devices and temperatures were measured daily with thermometers.

2.8. Reagents

As stated previously, all laboratory reagents were purchased from reputable suppliers.

All reagents, chemicals and solvents were appropriately stored. This function of the laboratory was controlled by one person and the stocks were regularly monitored. All purchased materials were inspected on receipt and then logged into a database. The date opened was recorded on the label of each container.

Titrimetric determinations were rarely performed in the laboratory. If required, ready-made volumetric solutions were used and the unused stock was discarded immediately after the determination was complete. On rare occasions when the solution was stored, it was standardized before use. The solutions were labeled and stored appropriately.

Water was supplied by a Millipore system for HPLC systems. For general use, water was purified by distillation. The laboratory was serviced by two distillation units. A similar arrangement was in place in the Antibiotic Laboratory. Samples of Water purified by the two methods were tested monthly according to the Russian Pharmacopoeial monographs.

In the Antibiotics Microbiology Laboratory culture media were prepared in-house. Dried media were stored and labeled appropriately with opening date and expiry date. Media were prepared according to the manufacturer's instructions and plates were poured in a dedicated Biological Safety Cabinet. Media were labeled appropriately and included a batch number and expiry date. Expiry was according to the requirements of the Russian Pharmacopoeia.

2.9. Reference substances and reference materials

All reference and impurity standards required for analysis were supplied by either applicants or manufacturers. Each reference material was supplied with certificate of analysis. On receipt, reference materials were stored at appropriate storage conditions till required by analysts.

In the Antibiotics Microbiology Laboratory the microbiological culture collection was very well organized. Cultures were obtained from a commercial source and also from the Russian collection of microorganisms. All cultures used were within 5 passages from the original type strain. Organisms were checked with a gram stain.

Reference preparations from the Russian Standards Collection were used for antibiotic assay. These were calibrated against WHO Reference Preparations and recalibrated every two years. They were stored in sealed vials. Storage was appropriate.

2.10. Calibration, verification of performance and qualification of equipment, instruments and other devices

Equipment items were uniquely identified and log books were available for instruments. There were two approaches to calibrating instruments. The main calibration programme was run by the State Agency. This was done annually. Then there was in-house calibration programme. Under this plan, the instruments were calibrated every three months.

Labels indicating equipment calibration status were affixed to all equipment and instruments.

pH meters were verified with standard buffer solutions before use. A number of analytical balances were available. These were verified daily using a single mass. In addition, all balances were calibrated by the State Agency annually.

In the Antibiotics Microbiology Laboratory refrigerators and incubators had been subjected to temperature mapping on commissioning. Temperatures of refrigerators and incubators were manually recorded daily.

2.11. Traceability

Test results were traceable to analyst, analytical instruments, equipment, reagents, reference substances and test procedures.

2.12. Incoming samples

As explained in Section 2.1 “Quality system”, records were kept for all incoming samples using the standard operating procedures. The laboratory had a central registry dealing with registration and distribution of the samples. Records of incoming samples were properly kept by logging in a register. A sample laboratory sheet with tests to be performed and limits was generated for each sample at the time of logging. Samples were inspected on receipt and appropriately stored until testing started.

A repository of client methods was also maintained.

2.13. Analytical worksheet

Analysts recorded tests performed, raw data, calculations and results in books. Sufficient details were recorded in books to establish traceability. This was confirmed by auditing a number of samples.

2.14. Validation of analytical procedures

The laboratories did not develop or validate analytical procedures because as stated earlier only manufacturers methods were used.

Validation of the Sterility Test procedure for antibiotic preparations was conducted each time a product was tested unless the formulation had been previously tested. The Sterility Test Procedure followed the Russian Pharmacopoeia method.

2.15. Testing

The samples were tested in accordance with the work plan.

Test results were recorded in analysts' books as discussed earlier and print outs from instruments were stored with sample information and CoA. System suitability criteria were fulfilled when defined in the method.

In the Antibiotics Microbiology Laboratory biological assays were carried out according to the requirements of the Russian Pharmacopoeia. Either petri dishes or large plates were used. Results were analyzed statistically to determine the validity of assays. Results were calculated using password protected spreadsheets; spreadsheets were validated according to EDQM requirements.

Testing of non-sterile dosage forms was also conducted according to the Russian Pharmacopoeia. Very few organisms were ever detected during testing. Purified water was also tested according to the Russian Pharmacopoeia method.

Sterility testing using the membrane filtration method was observed. Operators were appropriately gowned and appeared competent. Sterility testing was carried out according to the Russian Pharmacopoeia method.

2.16. Evaluation of test results

Test results were duly reviewed by group heads and supervisors. The review included completeness and accuracy of results. Before accepting it was confirmed that test results met the relevant specifications.

Out of specification results (OOS) of chemical testing were investigated according to written SOP. This was based on EDQM guideline (PA/PH/OMCL 07 28 DEF CORR). The process was also summarized in a flow chart. The final decision as to whether pass or fail the sample was derived based on reviewing all test results generated. The SOP and its application to OOS investigations were considered satisfactory.

2.17. Certificate of analysis

A number of certificates of analysis (CoA) were reviewed. The reviewed CoA were satisfactory and included all necessary details.

2.18. Retained samples

Retained samples were appropriately stored. The samples were kept for 6 months. Considering the purpose of testing, this was considered satisfactory.

2.19. Safety

Laboratory personnel wear appropriately attired with protective clothing while working in the laboratory and safety instructions were followed.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, «Testing centre

of drug products quality expert evaluation» Laboratory of chemical-pharmaceutical preparations No 2 and Laboratory of antibiotics, located at Shukinaskaya street, 6, Moscow was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.