

WHO PUBLIC INSPECTION REPORT**(WHOPIR)****Quality Control Laboratory****Part 1: General information about the inspection**

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| Name of laboratory | Ministry of Health of Ukraine State Administration for Drug Control and Medical Devices, Central Laboratory for Quality Control of Medicines |
| Physical address | 10G Kudryavskaya street, Kiev 04053 Ukraine |
| Postal address | As above |
| Telephone number | +380 442725498 |
| Fax number | +380 442725798 |
| Summary of all the activities performed by the laboratory | The laboratory was involved in: <ul style="list-style-type: none"> • Conventional chemical analysis • Instrumental analysis • Microbiological analysis • Biological testing (contracted out) |
| Scope of inspection | Prequalification inspection of QC laboratory |
| Focus of inspection | <ul style="list-style-type: none"> • Quality system of the Quality Control Laboratory • Conventional chemical analysis • Spectrophotometric analysis (IR, UV, AAS) • Chromatographic methods (HPLC, GC, TLC) • Dissolution and Disintegration testing |
| Date of inspection | 15 and 16 December, 2009 |
| Programme | Prequalification of Medicines Programme |

Part 2: Summary

The Central Laboratory for Quality Control of Medicines was re-inspected by the inspectors on 15th and 16th, December 2009.

General information about the company and the site

The Central Laboratory for Quality Control of Medicines had the Accreditation Certificate of Ukrainian GMP Inspectorate (authorized body on accreditation of pharmaceutical

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manufactures and pharmaceutical control laboratories) No. 01/2 of April 12, 2007 (valid till April 12, 2010).

The Central Laboratory for Quality Control of Medicines was established in 1998.

The Central Laboratory for Quality Control of Medicines was performing the following analysis:

| Type of Analysis | Finished products | Active pharmaceutical Ingredients |
|---|-----------------------------|-----------------------------------|
| Physical / Chemical analysis | pH | pH |
| | Friability | Acid value |
| | Disintegration time | Iodine value |
| | Density | Limit Tests |
| | Dissolution | Apparent Volume |
| | Dimensions | Clarity & Colour of solutions |
| | Limit Tests | Solubility |
| | Apparent Volume | Acid neutralizing capacity |
| | Colour of solutions | Residue on Evaporation |
| | Uniformity of content | Insoluble matter |
| | Uniformity of weight | Heavy metals |
| | Minimum fill | Acidity/Alkalinity |
| | Water content (K. Fischer) | Non volatile matter |
| | Determination of nitrogen | Water content (K. Fischer) |
| | Refractive index | Refractive index |
| | Viscosity | Viscosity |
| | | Distillation range |
| | | Loss on drying |
| | | Determination of nitrogen |
| | Identification | FTIR |
| Identification reactions | | Identification reactions |
| TLC | | TLC |
| HPLC | | HPLC |
| GC | | GC |
| UV-vis Spectrophotometry | | UV-vis Spectrophotometry |
| Basic tests | | Basic tests |
| Assay, impurities and related substances | HPLC(UV-VIS, refractometer) | HPLC(UV-VIS, refractometer) |
| | GC (FID) | GC (FID) |
| | AAS | AAS |
| | UV-vis Spectrophotometry | UV Spectrophotometry |
| | FTIR | FTIR |
| | Volumetric Titrations | Volumetric Titrations |
| Microbiological | Microbial limit tests | Microbial limit tests |

| | | |
|---|--------------------------------------|--------------------------------------|
| analysis | | |
| | Bacterial Endotoxins | Bacterial Endotoxins |
| | Sterility tests | Sterility tests |
| | Microbiological assay of antibiotics | Microbiological assay of antibiotics |
| Biological analysis (contracted out) | Abnormal toxicity (contracted out) | Abnormal toxicity (contracted out) |
| | Pyrogens (contracted out) | Pyrogens (contracted out) |

History of WHO or regulatory agencies inspections

The Central Laboratory for Quality Control of Medicines was previously inspected by the WHO on 28 and 29 October, 2008.

Focus of the inspection

This inspection focused on:

- implementation of corrective actions from the previous inspection
- evaluation and investigation of out of specification (OOS) results
- dealing with reference materials
- specific equipment and tests such as:
 - HPLC
 - UV
 - IR
 - AAS
 - Dissolution
 - Disintegration
 - Analytical balances

2.1. ORGANIZATION AND MANAGEMENT

The organization of the Central Laboratory for Quality Control of Medicines 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 job descriptions. The laboratory had a central registry. Records were kept for all incoming samples. The laboratory followed Ukraine Pharmacopeia, USP, BP and EP monographs and tests methods.

2.2 QUALITY SYSTEM

The Quality Manual was available and was based on ISO 9001 standard. The Quality Manual was periodically reviewed (not less than once per year). A new edition of the Quality Manual was issued every three years. The Quality Manual was accessible to all of the staff.

The quality system was systematically reviewed by internal audits

A complaint SOP was available. Till the date of inspection the laboratory did not receive any complaints.

Generally, observations from the previous inspection were satisfactorily addressed and corrective actions implemented.

2.3 CONTROL OF DOCUMENTATION

There were 2 levels of the documents - external documents (for example legislation) and internal documents. The internal documents included the following:

- Quality Manual,
- SOP's,
- Work instructions,
- Analytical log books for the chemical laboratory and analytical forms for the microbiological laboratory,
- Analytical work sheets.

There were procedures in place to generate, review and approve records and analytical reports as well as procedures for the issuance of certificates of analysis.

2.4 RECORDS

Training records, analytical reports and sample logs were available. The records included the identity of the personnel involved in the preparation and testing of the samples. Samples were not collected by the laboratory staff. Usually samples were collected by the inspection services and wholesalers. The institution which collected the samples was identified in the LIMS and traceable from the work orders, analytical work sheets and certificates of analysis.

2.5 DATA PROCESSING EQUIPMENT

The HPLC systems, GC, UV, AAS and IR equipment were linked to the computers operated by their respective software.

2.6 PERSONNEL

The personnel met during the inspection were experienced, skilled and conscientious. An organization chart was showing the arrangements, responsibilities and reporting lines in the laboratory.

A training program for individual employees was available. The training and training evaluation were documented in the individual training files.

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

An analyst competency list was available.

2.7 PREMISES

The Central Laboratory for Quality Control of Medicines premises was well maintained and clean. The laboratory had suitable testing equipment.

Samples, retained samples, reference standards were stored in a separate archive room. Reagents were stored in a separate room close to the laboratory. Flammable liquids, hazardous substances and precursors were stored in metal cupboards.

2.8 EQUIPMENT, INSTRUMENTS AND OTHER DEVICES

Generally observations from the last inspection were satisfactorily addressed and corrective actions implemented. Operational SOPs were available for all equipment.

2.9 SPECIFICATION ARCHIVE

Obsolete document copies were stored in an archive room. Master copies of documents were stored in the quality assurance department.

2.10 REAGENTS

The preparation of reagents was performed according to Pharmacopoeia methods. Liquid volumetric solutions were appropriately labelled. Volumetric solutions were standardized according to the relevant Pharmacopoeia methods. Reagents were appropriately labelled.

2.11 REFERENCE MATERIALS

Official reference standards and working standards were used for the analysis.

2.12 CALIBRATION, VALIDATION AND VERIFICATION OF THE EQUIPMENT, INSTRUMENTS AND OTHER DEVICES

Equipment was calibrated by the state metrological service. Labels indicating equipment calibration status (of calibration and due day) were affixed to all equipment and instruments.

pH meters were verified with standard buffer solutions at least once a day.

2.13 TRACEABILITY

Traceability of results was assured by:

- Keeping proper records of observations
- Verifying observations, calculations and results

- Using primary reference standards
- Regularly calibrating instruments and equipment
- Performing system suitability tests as specified in relevant compendia monographs

2.14 INCOMING SAMPLES

Incoming samples and corresponding documents which were submitted for analysis were registered by the secretary in the samples registration book and by the registration manager in the LIMS. Incoming samples were allocated to the designated technicians. A unique registration number was allocated to the samples.

2.15 ANALYTICAL WORKSHEET

Data generated and results obtained were compiled in LIMS. Analytical work sheets in LIMS were generated by the analyst who performed the test. The analytical records were checked, signed and dated by the analyst, then checked and signed by the technical manager or the head of the department. Certificates of analysis were generated by the LIMS according to the specifications. The certificates were approved by the director.

2.16 TESTING

Values obtained from the tests were entered on the analytical records and graphical data were attached.

Sterility and total microbial count tests were verified for every product where appropriate.

2.17 EVALUATION OF TEST RESULTS

The test results were reviewed and approved. The SOP dealing with OOS was available for inspection.

2.18 RETAIN SAMPLES

Retain samples were kept for a predefined duration - at least 6 months if testing results were within the specifications and at least 12 months if testing results were OOS.

2.19 SAFETY

Personnel at the laboratory had to wear protective clothing. Safety instructions were followed.

Part 3: Conclusion

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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, The Central Laboratory for Quality Control of Medicines, 10G Kudryavskaya Street, Kiev 04053, Ukraine was considered to be operating at an acceptable level of compliance with WHO Good practices for national pharmaceutical 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.