# Prequalification Team
## WHO PUBLIC INSPECTION REPORT
### Quality Control Laboratory

## Part 1: General information

<table>
<thead>
<tr>
<th>Name of the QC Laboratory</th>
<th>State Drug Administration of Ukraine, State Enterprise “Central Laboratory for Quality Control of Medicines and Medical Products”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical address</td>
<td>10 G Kudryavska street, Kyiv 04053 Ukraine</td>
</tr>
<tr>
<td>Date of inspection</td>
<td>10 - 11 May 2016</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Routine inspection</td>
</tr>
<tr>
<td>Type(s) of testing included in the inspection</td>
<td>Physical / Chemical analysis</td>
</tr>
<tr>
<td></td>
<td>Microbiological analysis, sterility test</td>
</tr>
</tbody>
</table>

## Summary of the testing activities performed by the Laboratory

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical / Chemical analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>Friability</td>
<td>Acid value</td>
<td></td>
</tr>
<tr>
<td>Disintegration time</td>
<td>Iodine value</td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td>Limit Tests</td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td>Apparent Volume</td>
<td></td>
</tr>
<tr>
<td>Dimensions</td>
<td>Clarity &amp; Colour of solutions</td>
<td></td>
</tr>
<tr>
<td>Limit Tests</td>
<td>Solubility</td>
<td></td>
</tr>
<tr>
<td>Apparent Volume</td>
<td>Acid neutralizing capacity</td>
<td></td>
</tr>
<tr>
<td>Colour of solutions</td>
<td>Residue on Evaporation</td>
<td></td>
</tr>
<tr>
<td>Uniformity of content</td>
<td>Insoluble matter</td>
<td></td>
</tr>
<tr>
<td>Uniformity of weight</td>
<td>Heavy metals</td>
<td></td>
</tr>
<tr>
<td>Minimum fill</td>
<td>Acidity/Alkalinity</td>
<td></td>
</tr>
<tr>
<td>Water content (K. Fischer)</td>
<td>Non volatile matter</td>
<td></td>
</tr>
<tr>
<td>Determination of nitrogen</td>
<td>Water content (K. Fischer)</td>
<td></td>
</tr>
<tr>
<td>Refractive index</td>
<td>Refractive index</td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>Viscosity</td>
<td></td>
</tr>
<tr>
<td>Refractive index</td>
<td>Distillation range</td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>Loss on drying</td>
<td></td>
</tr>
<tr>
<td>Distillation range</td>
<td>Determination of nitrogen</td>
<td></td>
</tr>
</tbody>
</table>

## Identification

<table>
<thead>
<tr>
<th>FTIR</th>
<th>FTIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification reactions</td>
<td>Identification reactions</td>
</tr>
<tr>
<td>TLC</td>
<td>TLC</td>
</tr>
<tr>
<td>HPLC</td>
<td>HPLC</td>
</tr>
<tr>
<td>GC</td>
<td>GC</td>
</tr>
</tbody>
</table>

WHOPIR:
State Enterprise “Central Laboratory for Quality Control of Medicines and Medical Products
Ukraine 10-11 May, 2016
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 analysis**  
Microbial limit tests | Microbial limit tests  
Bacterial Endotoxins | Bacterial Endotoxins  
Sterility tests | Sterility tests  
Microbiological assay of antibiotics | Microbiological assay of antibiotics  

**Part 2: Summary**
State Enterprise “Central Laboratory for Quality Control of Medicines and Medical Products” was inspected on above mentioned dates.

**General information about the company and the site**
Central Laboratory for Quality Control of Medicines and Medical Products was established in 1998. In 2004 it became a state enterprise.

The Laboratory had obtained a national attestation covering a number of tests. (It was explained to inspectors that the former accreditation had been replaced with attestation in the particular field of testing of medicinal products).

The Laboratory performed tests on human medicines upon the request of SAUMP (State Administration of Ukraine on Medicinal Products).

The Laboratory is the full member of GEON - General European OMCL Network (OMCL – official medicines control laboratories), which operates under the Council of Europe, EDQM (European Directorate for the Quality of Medicines and HealthCare). The Laboratory participates in some EDQM testing projects (injections, powders for injection, etc.).

The Laboratory participates in National proficiency testing schemes (PTS) from 2000, in EDQM PTS from 2012, in other EDQM programs: marketing surveillance studies (MSS) and collaborative studies for candidates of chemical reference standards.

The Laboratory participates in revision of EDQM guidelines:
- Qualification of pH meter
- Revision of EDQM guideline qualification of HPLC
  and revision of PhEur monograph for potentiometric determination of pH.
**History of WHO or regulatory agencies inspections**

State Enterprise “Central Laboratory for Quality Control of Medicines and Medical Products” was inspected by the WHO:

- 28 - 29 October 2008
- 15 - 16 December 2009
- 4 - 5 February 2013

The Laboratory had passed a second EDQM audit and achieved EDQM attestation for ISO EN 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:

- Organization and management
- Quality management system
- Control of documentation
- Records
- Data-processing equipment
- Personnel
- Equipment, instruments and other devices
- Reagents
- Calibration, verification of performance and qualification of equipment, instruments and other devices
- Traceability
- Incoming samples
- Analytical worksheet
- Validation of analytical procedures
- Testing
- Evaluation of test results
- Certificate of analysis
- Retained samples
- Safety

**2.1. Organization and management**

In general the laboratory had managerial and technical personnel to identify the occurrence of departures from the quality management system. No significant changes had occurred since the previous WHO inspection. The Quality Assurance (QA) department stated that they are orientated to ISO EN 17025 and EDQM guidelines. Organogram was presented as part of the Quality manual.
2.2. Quality management system
In general the laboratory had established, implemented and maintained a quality management system and authorized written SOPs. Documentation system was operated by LIMS. Hybrid documentation was maintained, some data were available only electronically (e.g. distribution of samples, reagent management, management of reference substances) but majority of records and reports were printed and kept on paper. Back-up procedures of electronic data were briefly described.

The activities of the laboratory were periodically audited to verify compliance with the requirements of the quality management system. Corrective and preventive actions were applied and reported to the management. Internal audits were carried out according to the monthly schedule for different areas. Last internal audit was carried out from 18-19 April, 2016. Internal audits were carried out according to the check lists. After audit, report was written and if required corrective actions and preventive actions were proposed.

Management review (QMS review) was carried out once in a year. In 2016 MR was planned to be performed twice per year (June and December). The last MR according the ISO 17015 was carried out 11 January 2016. QMS performance summary assessment for 2015 was discussed.

The Laboratory participates in proficiency testing schemes of EDQM; the results demonstrated to inspectors were satisfactory. The laboratory was participating in WHO proficiency testing from 2010 till 2013.

After the last EDQM inspection laboratory introduced customer satisfaction questionnaire; questionnaire was approved on 1 April 2016.

Complaint SOP and registers for 2013-2015 were discussed. According to the SOP complaints should be trended. There were no complaints registered.

2.3. Control of documentation
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. A master list identifying the current version status and distribution of documents was available.

The SOP for change control entitled improvements of Quality Management system. It described how information was collected about non-conformities, deviations (only in the QMS and not in the sample analysis/testing), change control, complaints, and how preventive and corrective actions were planned and executed. The respective forms were available for:
- Notification of change/deviation/ nonconformity etc.
- Analysis of notification for the problem
- Change Control form
- Corrective action and preventive action CAPA (Control Task) form
The SOP for Risk Assessment was discussed. The SOP required using probability, severity and detection to determine the risk number.

The SOP showed the following risk numbers:

- 1 - 150 = very small level of risk
- 151 - 250 = small level of risk
- 251 - 500 = medium level of risk
- 501 - 750 = high level of risk
- 751 - 1000 = very high level of risk

Until the date of inspection, risk assessment was applied to qualitative risk assessments.

### 2.4. 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. Original observations, including calculations and derived data, calibration, validation and verification records and final results were retained. 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. A signature register of all employees was available.

### 2.5. Data-processing equipment

The HPLC systems, GC, UV, AAS and IR equipment were linked to the computers operated by their respective software. Electronic data were backed up at regular intervals.

### 2.6. Personnel

The laboratory had sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions. An organization chart showing the hierarchical arrangements, responsibilities and reporting lines in the laboratory was available. Current job descriptions were maintained.

General Job descriptions were seen for following people:

- Head of Quality Assurance (QA) department also Qualified Person
- The Deputy Director of Microbiological and Immuno-biological Control laboratory

Conflict of interest declarations were signed every year, in reference with Quality Manual, for protection of trade secrets and confidential information. According to the SOP, the form for declaration of interest obtained from the government schedule in the regulations was used. Completed conflict of interest forms were available.

Laboratory personnel participated in different external trainings. Internal training was not discussed during this inspection.
2.7 Premises

The QA department of the Laboratory had moved its office rooms to another house adjacent to the building where testing was conducted.

Test samples, retained samples and 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 with ducting to the outside of the building.

2.8 Equipment, Instruments and other devices

In general equipment, instruments and other devices were designed, constructed, adapted, calibrated, qualified, verified and maintained as required by the operations to be carried out. Instruments were calibrated externally and internally at defined intervals. A calibration and preventive maintenance schedule was available.

La Calhene flexible isolator was used for sterility testing, the isolator had been operational for several years, peracetic acid vapor was used as a vaporized decontaminant. The isolator was qualified every after six months and the last qualification had been done on 6 May 2016.

A bio-safety cabinet Class II was used for re-culturing and testing of non-sterile products.

2.9 Contracts

The laboratory did not have any contracts for any laboratory testing work as no testing was outsourced to outside laboratories.

2.10 Reagents

Reagents, chemicals and solvents were appropriately stored and were of appropriate quality. Reagents were received along with certificates of analysis (CoA). Upon receiving, reagents were inspected visually. The date of receipt and opening was recorded on the label of each container. The appropriate grades of water were used for specific tests.

2.11 Reference substances and reference materials

Reference and impurity standards required for analysis were supplied by manufacturers and purchased by laboratory. Reference materials were supplied with certificate of analysis. On receipt, reference materials were stored at appropriate storage conditions till required by analysts. The register for reference substances including working standards was maintained.

2.12 Calibration, verification of performance and qualification of equipment, instruments and other devices

Equipment items were uniquely identified and log books were available for instruments. Qualification schedule and procedures were in place.
Equipment in the microbiology laboratory was qualified by outsourced companies (sterility test isolator and transfer box, including validation of de-contamination cycles, autoclave, including validation of sterilization cycles, bio-safety cabinet).

Independent state metrology body had regularly conducted external calibrations. The Laboratory also had its in-house calibration and verification schedules and procedures (e.g. balances, temperature sensors).

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

pH meters were verified with standard buffer solutions daily. A number of analytical balances were available. These were verified daily and qualified/calibrated with regular intervals.

The Laboratory reported to inspectors about corrective actions implemented in qualification of equipment for disintegration testing, dissolution testing, IR, UV, Karl Fisher and AAS.

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

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 and was traceable through all the operations. The samples received were visually inspected by laboratory staff to ensure that the labelling conforms to the information contained in the test request.

2.15 **Analytical worksheet**
Data generated and results obtained were compiled into 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.

Validated excel sheets were used for assay (chemical and microbiological) calculations.
2.16 Validation of analytical procedures
Validation of analytical procedures was performed according to the ICH guidelines. The following parameters were validated:

- Accuracy
- Specificity
- Range
- Robustness
- Repeatability
- Linearity

The validation protocol for caffeine, acetophenamine and chlorphiramine maleate for XX tablets was reviewed. The test procedure (also called SOP) following the above validation was verified and HPLC set parameters were found to be consistent with those indicated in the validation report.

2.17 Testing
Physical / Chemical analysis laboratory
On spot-checks, testing was conducted as per approved methods and with qualified equipment; system suitability tests where applicable had been performed as prescribed.

Microbiology laboratory
Media preparation, documentation and testing protocols were appropriately organised. Identification of microorganisms was done by selective media, gram staining, and biochemical tests.

2.18 Evaluation of test results
Test results were reviewed and evaluated after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation took into consideration the results of all the tests.

Out of specification (OOS) results were investigated, an SOP was in place for OOS procedures. The procedure for OOS was discussed.

OOS investigation protocols for sterility tests, microbiological purity, LAL, physical chemical assay, visual test (appearance) were discussed. Each protocol had a checklist and section for repeat analysis. OOS flow charts were available.

2.19 Certificate of analysis
Certificates of analysis (CoA) were generated by LIMS based on data entered in LIMS by analysts. CoA was prepared for each batch of a substance or product and contained required information. The certificates were approved by the Director.
2.20 Retained samples
Sufficient amount of retained samples were stored to allow at least two re-analyses. The retained samples were kept in their original pack.

2.21 Safety
Material safety data sheets were available. Smoking, eating and drinking in the laboratory was prohibited. A special dining room was provided for staff. Personnel were wearing protective clothing. Emergency overhead water shower and eye wash bottles were provided in the chemical laboratory.

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, as well as the corrective actions taken the State Drug Administration of Ukraine, State Enterprise “Central Laboratory for Quality Control of Medicines and Medical Products”, located at 10 G Kudryavska street Kyiv 04053 Ukraine, 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 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.