WHO PUBLIC INSPECTION REPORT
Quality Control Laboratory

Part 1: General information

<table>
<thead>
<tr>
<th>Name of the QC Laboratory</th>
<th>The State Expert Center Ministry of Health of Ukraine</th>
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</thead>
<tbody>
<tr>
<td>Physical address</td>
<td>14, Ezhena Pottier St., Kyiv, Ukraine</td>
</tr>
<tr>
<td>Date of inspection</td>
<td>12 – 13 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 Microbiological analysis</td>
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</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>pH</td>
<td>pH</td>
</tr>
<tr>
<td></td>
<td>Friability</td>
<td>Acid value</td>
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<tr>
<td></td>
<td>Disintegration time</td>
<td>Iodine value</td>
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<td></td>
<td>Tablet hardness</td>
<td>Peroxide value</td>
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<tr>
<td></td>
<td>Density</td>
<td>Ester value</td>
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<tr>
<td></td>
<td>Dissolution</td>
<td>Hydroxyl value</td>
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<tr>
<td></td>
<td>Dimensions</td>
<td>Saponification value</td>
</tr>
<tr>
<td></td>
<td>Limit Tests</td>
<td>Unsaponifiable matter</td>
</tr>
<tr>
<td></td>
<td>Delivered Volume</td>
<td>Nitrogen by sulphuric acid digestion</td>
</tr>
<tr>
<td></td>
<td>Clarity &amp; Colour of solutions</td>
<td>Water semi-micro determination</td>
</tr>
<tr>
<td></td>
<td>Uniformity of content</td>
<td>Clarity &amp; Colour of solutions</td>
</tr>
<tr>
<td></td>
<td>Uniformity of weight</td>
<td>Limit Tests</td>
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<tr>
<td></td>
<td>Minimum fill</td>
<td>Solubility</td>
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<tr>
<td></td>
<td>Acid value</td>
<td>Density</td>
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<tr>
<td></td>
<td>Iodine value</td>
<td>Acid neutralizing capacity</td>
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<td></td>
<td>Peroxide value</td>
<td>Residue on Evaporation</td>
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<tr>
<td></td>
<td>Ester value</td>
<td>Heavy metals</td>
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<tr>
<td></td>
<td>Anisidine value</td>
<td>Anisidine value</td>
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<tr>
<td></td>
<td>Hydroxyl value</td>
<td>Acidity/Alkalinity</td>
</tr>
<tr>
<td></td>
<td>Saponification value</td>
<td>Refractive index</td>
</tr>
<tr>
<td></td>
<td>Unsaponifiable matter</td>
<td>Optical rotation</td>
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<tr>
<td></td>
<td>Nitrogen by sulphuric acid digestion</td>
<td>Viscosity (capillary &amp; rotating)</td>
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<tr>
<td></td>
<td>Water semi-micro determination</td>
<td>Melting point</td>
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<td></td>
<td>Residue on Evaporation</td>
<td>Loss on drying</td>
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## Part 2: Summary

The State Expert Center, Ministry of Health of Ukraine was inspected on above mentioned dates.

### General information about the laboratory

The Laboratory was involved in pre-registration control of substances and of finished medicinal products; quality control of finished products designed for clinical trials; conducting trials to confirm compliance of quality of samples of medicinal products submitted for pre-registration control or designed for clinical trials with their specifications, and reproducibility of analytical methods indicated in registration materials; in vitro comparative studies to justify equivalence of medicinal products in oral solid dosage forms for systemic use; run-time arbitration quality analysis of medicinal products; counseling and method assistance to institutions and organizations concerning quality analysis of medicinal products.

The Laboratory is ISO 9001:2008 certified, certificate is valid till 20.06.2017.

<table>
<thead>
<tr>
<th>Heavy metals</th>
<th>Conductivity</th>
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<tbody>
<tr>
<td>Acidity/Alkalinity</td>
<td></td>
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<tr>
<td>Refractive index</td>
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<tr>
<td>Optical rotation</td>
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<tr>
<td>Viscosity (capillary &amp; rotating)</td>
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<tr>
<td>Loss on drying</td>
<td></td>
</tr>
<tr>
<td>Conductivity</td>
<td></td>
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</tbody>
</table>

### Identification

| FT IR spectrophotometry | FT IR spectrophotometry |
| TLC | TLC |
| HPLC | HPLC |
| GC | GC |
| UV-VIS Spectrophotometry | UV-VIS Spectrophotometry |
| Atomic absorption spectrometry | Atomic absorption spectrometry |
| Basic tests | Basic tests |

### Assay, impurities and related substances

| HPLC (UV-VIS, DAD, Fluorescence, Refraction, Conductivity) | HPLC (UV-VIS, DAD, Fluorescence, Refraction, Conductivity) |
| GC (incl. Head-space) | GC (incl. Head-space) |
| UV-VIS Spectrophotometry | UV-VIS Spectrophotometry |
| Atomic absorption spectrometry | Atomic absorption spectrometry |
| Volumetric Titrations | Volumetric Titrations |

### Biological (Microbiological) analysis

| Microbial limit tests | Microbial limit tests |
| Bacterial Endotoxins | Bacterial Endotoxins |
| Sterility tests | Sterility tests |
| Microbiological assay of antibiotics | Microbiological assay of antibiotics |
History of WHO or regulatory agencies inspections
The Laboratory was first inspected by the WHO:
- 9 - 10 December 2008
- 17 - 18 December 2009
- 4-5 February 2013

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.

A current organogram was part of the approved Laboratory information file (LIF), approved by the Head of the Laboratory. The LIF was reviewed every year. Every page of the LIF, including the page for the organogram, was signed by the Head of the Laboratory.
The organogram showed five departments that were directly and independently reporting to the Head of the Laboratory, namely:

- Quality Assurance department. This was independent of all other departments
- Organization department for administrative functions of the Laboratory. It receives and registers pre-marketing authorization samples from applicants from abroad or locally. It also received the number of samples required for analysis and the specific reagents needed
- Department of physical-chemical methods, mainly handling chromatographic techniques of analysis
- Department of Microbiology analysis and assay analysis of antibiotics. The Laboratory performed sterility, microbiological purity, bacterial endotoxins (LAL) and biological assays
- Department of Chemical analysis

2.2. Quality management system
In general the Laboratory had established, implemented and maintained a quality management system and authorized written SOPs.

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. The SOP “Internal audits” was discussed. Planned internal audits were carried out according to the schedule. It was noted that till the date of inspection schedule was followed.

Management review (MR) was carried out once in a year. Last MR was performed on 29 January 2016.

The SOP “Complaints” was discussed. According to the SOP quality assurance department was responsible for complaint management.

The SOP “Change control”, flow chart and forms were discussed. Change register was maintained as Microsoft Excel sheet.

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. An electronic documents master list identifying the current version status and distribution of documents was available.

Generally review of SOPs was performed after every 3 years or if there was a necessity to review the SOP. The SOPs that were soon to be reviewed were highlighted on the SOP list.
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 and reference standards were requested from manufacturers by the Laboratory administrative group, respective documentation was maintained about the request and actual receipt.

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.

Job descriptions (JD):
JD of the Head of Quality Assurance was reviewed. It contained the following sections like: general information, functional tasks and duties of the employee, rights of the employee, responsibilities, qualification requirements, and relations according to the job and confidentiality declaration. It was stamped with the official stamp of the Laboratory and also with stamp showing that it was the original document.

Current JDs for other key personnel were available and were similarly written, approved and signed.

Training of personnel
Plan for conducting of training for the employees for the year 2016 showed the date of the planned training, subject of the training or seminar, name of the person responsible for the training and trainee signature.

The SOP for training entitled “Determination of training trainees for employment in the pharmaceutical laboratory analysis was reviewed. A list of tests and methods that the trainee had to go through was available. A typical training record for a new leading specialist for physical test methods was reviewed and found satisfactory. A competence report for the trainee for the testing using HPLC was also available. After this a list of responsibilities for this particular employee was developed and approved.

A list was available showing the respective departments and the analytical techniques and the personnel responsible for them.
2.7 Premises
The Laboratory was located on the third floor of a larger building. The Laboratory premises were well maintained and clean. The Laboratory environment was appropriate for the tests to be carried out. In general there was sufficient space available to separate different types of analysis.

Microbiological laboratory had separate entrance and was fully separated from chemical laboratory. Appropriate classification was applied to sterility testing facilities; room pressure differentials were monitored by Magnehelic gauges.

The records were kept for three years after which they were transferred to the Expert Center offices. The validity period of the product registration (marketing authorization) in Ukraine is five years. Hence, the associated records are kept for a period of only five years.

2.8 Equipment, Instruments and other devices
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.

A list of persons authorised to use each piece of equipment e.g. the HPLC was displayed near the equipment. The file for authorised persons for two HPLCs number XX and YY were discussed.

2.9 Contracts
No contract laboratories were used.

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 receipt, 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.

Inventory management for the chemicals and reagents was managed by use of both paper stock cards and electronically in a database management in Microsoft Excel sheets. It was done satisfactorily. A label was placed on each bottle or container of a chemical or reagent, showing date of expiry, date of first opening of the closure and name and signature of responsible person. The expiry date was obtained from the certificate of analysis from the manufacturer.

There were two types of water systems, distilled water units and three units of Milli-Q water purification system with terminal filter of 0.22µ. Distilled water was used as
feed water for the Milli-Q units to produce purified water that was used analysis. The Mill-Q purified water was produced and used immediately and was not stored.

2.11 Reference substances and reference materials
Reference and impurity standards required for analysis were supplied by manufacturers. Reference materials were supplied with certificate of analysis. On receipt, reference materials were stored at appropriate storage conditions till required by analysts.

When primary standards were supplied by manufacturers in vials which evidently had been already opened, the Laboratory made respective comments in the receipt records. Chemical reference substances were stored in refrigerators. Temperature monitoring was done using temperature data loggers.

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 all the major equipment and instruments. Qualification schedule and procedures were in place.

The report on qualification of HPLC 1200 2D LC system, performed by Laboratory staff was discussed. Nine parameters were checked during validation: linearity of the detector signal, noise of the baseline of the detector, wavelength accuracy, reproducibility of injection, transfer of trays in the injector, accuracy flow rate, accuracy of mixing of gradient regime, accuracy of column temperature. All raw data and print outs from the analytical balances and chromatograms were attached and countersigned.

The calibration report for the dissolution apparatus Erweka DT 700 was reviewed and was found to be satisfactory. The calibration kit was complete and the calibration status of the measurement devices was still valid.

The calibration status of other measuring equipment was shown on calibration labels, were checked and found to be still valid.

The independent State metrology body had regularly conducted external calibrations. The Laboratory also had its in-house calibration and verification schedules, procedures and trained personnel.

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

pH meters were calibrated with traceable standard buffer solutions before use. A number of analytical balances were available. These were verified daily and calibrated at regular intervals.
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 and compiled in a product/ sample folder. Incoming samples were allocated to the designated technicians.

Upon receiving samples were visually checked. The amount of samples was sufficient for analysis and for sample archive.

Samples were received by personnel in the sample registration unit. Each sample delivery was accompanied with a covering letter from the State Expert Center Ministry of Health of Ukraine, clearly stating the reason for sending the sample and the method of analysis. In some cases samples would be accompanied with the required HPLC column(s), chemical reference standard or chemical reference substance and specific chemicals and reagents.

Each sample received was logged in by allocating it a unique sample identification number, and its details entered in a controlled hard copy sample logbook/ register.

2.15 Analytical worksheet
Three different analytical worksheets were used, for the physical-chemical laboratory, chemical laboratory and for microbiology laboratory. Analytical worksheets / testing forms were prepared and printed by the Administrative group of the Laboratory for every sample after sample registration; analysts filled the forms.

Analytical records (including calculations) were checked by the analyst and then by the Quality assurance group of the Laboratory.

2.16 Validation of analytical procedures
The Laboratory did not perform method validation. The Laboratory was intended to check/ evaluate the methods of the pre-registration samples and the quality of the sample. The test procedures were those that were presented by applicants along with the product registration dossiers. So the Laboratory uses methods presented to it by applicants for pre-registration testing of samples. The Laboratory only performed system suitability tests using the methods provided by applicants.

As to sterility test, it was understood that approbation was performed in case the test method submitted by the manufacturer differed from the pharmacopoeia monograph.

The Laboratory was part of the registration department. The pre-registration test methods were required to be approved by this Laboratory so as to be used later by other laboratories in Ukraine after approval by this Laboratory. Legislation in Ukraine
is changing and pre-registration procedures are no longer required for products that are registered in the European Union, USA and by other stringent regulatory authorities.

If the results were negative, the applicant is required to change/revise the methods or sample.

In case of dispute of results the Laboratory may repeat the tests in the presence of representatives of the applicant and the Analyst who did the initial tests is the one that does the repeat testing. A typical example that was repeated in the presence of the applicant was for visual test for clarity that on 24th Feb 2016 and the process of registration of the affected product is still ongoing.

2.17 Testing

Physical/Chemical analysis laboratory
On spot-checks, testing was conducted as per methods received from the applicants and with qualified equipment; system suitability tests had been performed as prescribed.

Microbiology laboratory
Media preparation and documentation were appropriately organised. Identification of microorganisms was done by selective media, gram staining, and biochemical tests. Strains for growth promotion testing were re-cultured; intermediate passages (for long-term storage) could be kept for 1 year at 2-8 °C.

Proficiency testing schemes/collaborative trials (performance, follow-up)
WHO proficiency testing schemes is not free of charge and is becoming expensive to the Laboratory to participate.

The Laboratory participate in the WHO proficiency testing scheme (PTS), and in FIP-LMCS PTS programme organised by The Laboratory of the Dutch of Pharmacists in the Netherlands, and in the PTS testing scheme for professional testing by the State Expert Pharmacopoeial Center of the Ministry of Health of Ukraine.

Certificate of participation in the PTS for FIP-LMCS for proficiency testing round KNMP 2015 was reviewed. It involved testing of Theophylline Solution 30mg/ml by HPLC, and testing of buffer solutions by pH meter.

The WHO PTS Phase 6 samples were tested in October 2015.

PTS testing organised by the Ukrainian Scientific Pharmacopeia Center for quality of Medicines were reviewed.

PTA results were satisfactory.
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. The SOP “Control of analytical results by QA department” was discussed.

The SOP “Investigation of out of specification results”, flow chart, questionnaire and register were discussed.

2.19. Certificate of analysis
A certificate of analysis was prepared for each sample/product and contained required information. Data for certificates were entered manually (certificates were not automatically generated from LIMS). The certificates were approved by the Head of the Laboratory. If the method submitted by a manufacturer raised concerns, the Laboratory prepared an additional document to the SAUMP.

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. Retained samples were kept in a secure and temperature controlled area in lockable steel cabins with limited access to authorised personnel.

Retained samples were kept for 6 months after testing because the purpose of testing was only for pre-marketing of the product.

2.21. Safety
Smoking, eating and drinking in the laboratory was prohibited. A special dining room was provided for staff. Personnel were wearing protective clothing. Emergency water showers were provided.

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 Expert Center of The Ministry of Health of Ukraine, located at 14 Ezhena Pottier St., Kyiv, 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.