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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
of the Quality Control laboratory

Part 1	**General information**
Laboratory Details	
Name of the laboratory	The State Scientific Research Laboratory for Quality Control of Medicines –The Testing Laboratory
Address of the inspected site	50 Popudrenka str. Kyiv, 02094 Ukraine Fax. + 38(044)559-57-11(00)
Address of corporate office, telephone number and fax number	State Institution "O.M. Marzeiev Institute for public health of the National Academy of Medical Sciences of Ukraine" 02660 Kyiv Str. Popudrenko, 50 Ukraine
Inspection details	
Dates of inspection	12-14 June 2019
Type of inspection	Routine
Introduction	

Brief description of testing activities

Type of analysis	*Finished products*	*Active pharmaceutical ingredients*
Physical/Chemical analysis	Clarity and degree of opalescence of liquids, degree of coloration of liquids, pH, density, osmolality, refractometry, optical rotation, viscosity, conductivity, water content, acid value, iodine value, peroxide value, ester value, hydroxyl value, saponification value, nitrogen determination, heavy metals, loss on drying, limit tests, disintegration, dissolution, uniformity of dosage units (mass, content), friability, tablet hardness, dimensions, particulate contamination (sub-visible/visible particles)	pH, density, refractometry, optical rotation, viscosity, osmolality, conductivity, melting point, water content, acid value, iodine value, peroxide value, ester value, hydroxyl value, saponification value, unsaponifiable matter, nitrogen determination, heavy metals, loss on drying, limit tests

	Identification	HPLC (DAD, RID, UV-Vis, FLD), GC (FID, ECD), TLC, UV-Vis Spectrophotometry, FTIR spectroscopy, basic tests	HPLC (DAD, RID, UV-Vis, FLD), GC (FID, ECD), TLC, UV-Vis Spectrophotometry, FTIR spectroscopy, basic tests
	Assay, impurities and related substances	HPLC (DAD, RID, UV-Vis, FLD), GC (Au/HS (FID, ECD)), UV-Vis Spectrophotometry, FTIR spectroscopy, Water determination, basic tests	HPLC (DAD, RID, UV-Vis, FLD), GC (Au/HS (FID, ECD)), UV-Vis Spectrophotometry, FTIR spectroscopy, Water determination, basic tests
	Microbiological tests	Not applicable	Not applicable
General information	The State Scientific Research Laboratory for Quality Control of Medicines – the testing laboratory was established in 1996 following the merge of the Laboratory of quality control of products, the Laboratory of sanitary microbiology and the Clinic for experimental animals in one entity. The Laboratory forms a part of the State Institution "O.M. Marzeyev Institute for Public Health of the National Academy of Medical Sciences of Ukraine" which has the status of a legal entity with its own legal liability. The Laboratory was authorized to conduct the quality control of medicines according to the methods of testing mentioned in the field of certification/accreditation.		
History	The laboratory was accredited for compliance with the ISO/IEC 17025:2017 by the ILAC member, as well as authorized by the State administration of Ukraine on Medical Products to conduct on behalf of government, quality control testing of medicines. The laboratory's QMS was certified in accordance with ISO 9001:2015 on July 2017. The laboratory was previously inspected by WHO as part of the Pre-qualification of Medicines Program – Inspection of Quality Control Laboratory during September 2015.		
Brief report of inspection activities undertaken – Scope and limitations			
Areas inspected	Management & Quality Management System Documentation and Records, including data processing and archiving Personnel & training Premises and Equipment including Validation, Qualification and Calibration Contracts Method validation and verification Laboratory Practices, including evaluation of test results Safety Reference standards – Reagents - Water		

Restrictions	Prequalification of microbiological testing (Sterility test, microbiological purity, bacterial endotoxin test (BET), microbiological assay) was requested, however the microbiology division was not eligible for inclusion in the list of prequalified tests until a comprehensive re-design following by a re-inspection is performed. The Microbiological laboratory agreed to be excluded from the scope of the inspection.
Out of Scope	Methods of pharmacognosy, Stability testing
Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GC	Gas chromatography or Gas chromatography equipment
GMP	Good manufacturing practices
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
KF	Karl Fisher titration
LIMS	Laboratory information management system
MB	Microbiology
MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometry or spectrophotometer

Part 2	Summary of findings and recommendations

1. Organization and management

The organizational chart of the testing laboratory "State Scientific Research Laboratory for Quality Control of Medicines of State Institution "O.M. Marzeyev Institute for Public Health of the National Academy of Medical Sciences of Ukraine" was provided in Annex 5 of the organization's LIF. The total number of staff accounted to 49 at the time of inspection. The laboratory organization was divided in three sections (Physicochemical, Microbiological and Biological – toxicity and pyrogens) and 13 processes.

The Quality Policy required that any involvement of employees of the Laboratory in any activity which could compromised the competence of the Laboratory, impartiality or objectivity of its activities should be avoided. The laboratory had a policy in place to ensure confidentiality of information contained in marketing authorizations and test reports.

The Laboratory carried out quality control of the following types of test samples:

- finished dosage forms;
- active pharmaceutical ingredients (substances);
- additive agents (excipients);
- medicinal plant raw materials and medicinal plant products;
- dietary supplements;
- materials and containers;
- food products.

The Laboratory carried out quality control of medicines imported to the Ukraine by performing an arbitrative and manufacturer's control, as well as safety testing of dietary supplements, games and toys.

Customers of the Laboratory were categorized as:

- State Service of Ukraine on Medicines and Drugs Control;
- State Expert Centre of the Ministry of Health of Ukraine;
- Other authorized state bodies;
- Legal entities and private individuals.

The deficiencies identified on the organization and management were adequately addressed in the QCL's CAPA plan.

2. Quality management system

A quality manual defining the quality management system was available. The last version of the Quality Manual, approved on 3 April 2019, was reviewed. This document, describing all the aspects of the Quality System, was required to be updated every 3 years.

The Quality Policy formed a basis for determination of the quality objectives that contributed to the improvement of activities of the laboratory, through an efficient review by the senior management.

The laboratory was accredited by the National Accreditation Agency of Ukraine for the conformity with State Standard of Ukraine ISO/IEC 17025:2006 “General requirements for the competence of testing and calibration laboratories” in 2004. The quality management system was implemented in 2007 in conformity with State Standard of Ukraine ISO 9001 “Quality management system”.

The governing documents of the QMS were:
- Quality Manual and Annexes to the Quality Manual
- Quality Procedures
- Standard Operating Procedures

The Quality Manual contained the Quality Policy and the Quality Objectives. The Quality Policy was issued by senior management. SOPs were defined as
- approved method
- work instruction
- procedure, etc.

The laboratory participated in various rounds of Proficiency Testing Programs for laboratories, organized by the State Enterprise “Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines” and “Belarusian State Institute of Metrology" (BelSIM)”. Interlaboratory comparisons were carried out in the laboratory by arrangements with other testing laboratories for quality control of medicines, accredited in accordance with the requirements of DSTU ISO / IEC 17025.

Management review

Management reviews were conducted biannually and a 6-monthly report provided by the Quality Management and the laboratory supervisors was reviewed; covering audit reports, complaints, proficiency test and other topics in accordance with the applicable SOP. The latest reports from 1 Jul 2018 and 29 Dec 2018 were available.

Internal audits

SOP titled as “Conducting internal audits in the laboratory” was provided. The Head of Quality was responsible for planning, controlling the timing of audits and appointing an audit group (including chief auditor and a technical expert). The internal audits were conducted by qualified and trained personnel who had completed the relevant training program. The deficiencies and number of identified inconsistencies as well as the conclusion and assessment of the CAPA were recorded. The audit plan for 2018, 2019 and a randomly selected audit report were reviewed to confirm the adequacy of the audits and related reports.

Complaints:
In case of complaints received by the laboratory (in accordance with the requirements in SOP for Consideration of reviews and proposals, resolving complaints, claims, complaints, customer's dissatisfaction with the activities of the Laboratory or the execution of works) an investigation would take place in accordance with SOP for Control of non-confirming work. All complaints were recorded in a logbook. The last complaint was registered on 17 Jun 2016.

Handling of deviations – CAPA
SOP on Corrective actions was developed to manage the procedure for handling of a corrective action which started with determination of the main causes of the deviation.

The laboratory monitored the results of the introduced corrective actions in order to ensure their effectiveness in accordance with the SOP for Corrective actions. The Results were periodically analyzed by the laboratory senior management to improve functioning of the QMS.

Change Control
Document changes were handled in accordance with the following procedures:

- SOP for Internal documentation control
- SOP for Control of changes in the documentation of the quality management system
- SOP for Procedure for preparing, approval, distribution, and review of Standard Operating Procedures

When document changes were required, the proposals for changes were reviewed by the appropriate personnel, i.e. the document owner/author, the Head of Quality and the Head of the laboratory. Proposed changes in the documents were implemented into the relevant documentation by the responsible person, when approved.

Since 1 Jan 2019, the following changes were introduced:
- Change to the documentation due to the introduction of the new process #12 « Testing for radionuclides », proposed on 18 Mar 2019. The change had not been implemented at the time of the inspection.
- Change to the modification of the quality management of the process #13 « Risk assessment », proposed on 18 Mar 2019. The change had not been implemented at the time of the inspection.

The deficiencies identified on the QMS were adequately addressed in the QCL CAPA plan.

3. Control of documentation

The laboratory had established and maintained a system of procedures to control all documents (preparation, revision, distribution, return, archiving).

A master list identifying the Quality Procedures and SOPs was provided in the LIF with information about the name of SOP, the identification number and reference to ISO 17025:2017 and/or ISO 9001:2015. Each controlled document had a unique identifier, version number, date of approval and reference to the previous version. The documents were released by the quality manager and available at the relevant location. An SOP was in place comprising the authorization for copying and the identification of copies from official and controlled documents.

The approved paper version of the SOPs was entered into a folder that was stored by the QM, and the electronic version was stored in Lotus database. The Employees of the laboratory had access to Lotus database, section "Operating" from their personal computers using an individual password, without having any editorial rights. Copies of the SOPs, depending on the type of activity, were stored in the premises of the laboratory where the tests were conducted. A template for SOP training records for relevant staff and one for distribution list were attached to the master copy of each SOP, completed by required information.

SOP for Procedure of keeping workbooks for physical and chemical testing described the process of recording of the results of tests of medicines, substances, dietary supplements and toys, etc. in the workbooks.

A separate module was integrated in the Lotus database to generate a unique identification number for all controlled documents used for the record of the activities, including the logbooks identification number. The ID number was chronologically generated and printed on each controlled documentation.

The deficiencies identified on the control of documentation were adequately addressed in the QCL CAPA plan.

4. Records

SOP for Preparation of test results and ongoing documents was reviewed. Records of analytical tests, including calculation and derived data, method validations / verifications, instrument use, calibrations and maintenance and sample receipt were available in log books containing consecutively numbered pages. The records were complete and signed, alterations were commented, and references were made to appendices containing the relevant recordings, e.g. chromatograms and spectra. The specifications used were consistent with the information currently held in the dossier.

Records such as chemist notes and logbooks were kept with the respective personnel for 3 years and transferred to the archive for a period of seven years. Access to the archive was restricted to the authorized personnel and the archive door was locked and sealed.

The deficiencies identified on the records were adequately addressed in the QCL CAPA plan.

5. Data processing equipment

Lotus database system was deployed as the laboratory information management system (LIMS), in addition to the computerized systems connected to the equipment and instrument for various laboratory activities and tests. The Laboratory used the Lotus database for preparation of analyst worksheets, certificates of analysis, registration and verification of expiration dates of retain samples, reference samples, chemical reagents, calculation of uncertainty of test results, electronic management of QMS documentation, etc.

Records on hardware configuration and installation were properly kept. The efficacy of the Lotus database system's audit trail and the system's access rights were verified and described by the IT-personnel at the time of inspection. The system's audit trail was an integrated component of the software.
Electronic data was protected from unauthorized access by using passwords for each system.

The electronic data was backed up at appropriate regular intervals in accordance with for Back up procedure. An ongoing automated backup was carried out to store the generated data in LIMS on the servers located in the building under the supervision of the IT-department. A standalone hard-disk was also used to provide additional backup of data on a regular basis.

A daily backup of standalone workstations' generated data was performed by the person responsible for the respective instrument, while a monthly backup was carried out by the IT-personnel.

Concerning spreadsheets (e.g. Excel®), all cells including calculations were locked so that formulas could not accidentally be overwritten. Free access was only given to cells to be filled in with data. The Excel sheets were prepared by the analyst and validated by the IT-department in accordance with the applicable SOP. The sheets were made available in a functional section of Lotus database.

The deficiencies identified on the data processing equipment were adequately addressed in the QCL CAPA plan.

6. Personnel

The laboratory had sufficient personnel with the necessary education, training, technical knowledge and experiences for their assigned functions. Staff undergoing training was assessed on completion of the training. The Laboratory maintained current job descriptions and the training documentation for all personnel involved in tests and/or calibrations, validations and verifications.

Relevant staff was trained on the new and revised SOPs; and a list of attendees for SOP training was attached to the master copy of each SOP. An annual training plan for employees was prepared at the end of each year based on an assessment made by the operational management to upgrade the staff's competency and skills.

Training of staff took place in accordance with SOP on Training.

The deficiencies identified on the training of personnel were adequately addressed.

7. Premises

The laboratory was a part of the State Institution "O.M. Marzeyev Institute for Public Health of the National Academy of Medical Sciences of Ukraine". The premises of the Laboratory were divided in two departments of Physico-chemical testing and Microbiology which were located on two floors.

The Physico-chemical testing laboratory facilities were of suitable size and design to suit the functions and to perform the operations to be conducted in them. Separate storage facilities were maintained for the secure storage of samples, retained samples, reagents, laboratory accessories and reference substances, if necessary under refrigeration (2-8°C) and frozen (-20°C). The environmental conditions of these rooms were monitored and controlled. Gases were stored in a dedicated store, isolated from the main building. The laboratory provided separate rooms for storing flammable substances, fuming and concentrated acids and bases.

Access to the laboratory facilities was restricted to designated personnel.

8. Equipment, instrument and other devices

The equipment, instruments and other devices used for the performance of tests, calibrations, validations and verifications were inspected to verify whether they met the applicable requirements. The required test equipment and instruments for the performance of laboratory activities, including preparation of samples and the processing of and analysis of test and/or calibration of data were available.

The following equipment were randomly selected to verify the adequacy of their calibration/validation certificates:

- Volumetric glassware verification in accordance with the respective SOP
- Temperature mapping of refrigerator no 9
- Disintegration instrument and the respective logbook, stopwatch and thermometer used for the performance verification
- UV-visible spectrophotometer and the integrated software. The periodic performance verification was carried out in accordance with Ukrainian Pharmacopeia.
- The balance room and the balances, including the temperature and humidity monitoring device:
    - 2 analytical balances
    - 1 half micro balance
- Incubator and the related temperature monitoring
- pH meter
- HPLC instrument and the associated Agilent Chemstation chromatography software system. The laboratory had 1 HPLC in operation, 1 out of order and another one just purchased.
- Dissolution test equipment Vankel VK 7000 used for tablets and capsules dissolution testing
- FTIR (Fourier Transform Infrared Spectrophotometer) made by Shimadzu
- Automatic Digital Polarimeter, made by Krüss, for optical rotation testing
- Tablet Friability Tester made by Biobase

The deficiencies identified on the equipment were adequately addressed in the QCL's CAPA plan.

9. Contracts

The process of selection and purchasing of services and supplies was carried out in accordance with SOP for Selection and assessment of service providers, procurement of services and resources effective on 20 Nov 2018, by applying questionnaires and scoring system. A risk assessment was made to determine whether a physical audit was required.

Tests might be subcontracted to a selected subcontractor, i.e. Independent Laboratory Testing Center Etalon in Khmelnitsky; Ukraine in case of:

- Equipment break down
- Atomic absorption spectrometer
- Atomic emission spectrometer

There was a procedure which described the interactions between the laboratory and the subcontractor. The subcontractor was required to be audited once a year. The entire audit documentation performed on 7 Dec 2018, including the auditee's CAPA and related assessment was presented. In the available contract, it was required that a confidentiality application / non-disclosure would be signed by the subcontracted staff performing the tests on the behalf of the laboratory.

10. Reagents

Reagents and other materials were purchased by the laboratory and stored in the cabinets in the chemical laboratory. The inflammable and toxic reagents were separately stored in the fireproof cabinets with restricted access. An analytical balance was placed under an exhaust hood, to be used for weighing of the hazardous reagents. The reagents used were of appropriate quality and correctly labelled. Labels of reagents contained the required information. Expired reagents were retested to be given a new validity based on their characteristic.

Reagent solutions prepared in the laboratory were labelled with the name of the reagent, date of preparations and initials of technician or analyst, expiry date or retest date, as justified and concentration/molarity, if applicable.

The reagents inventory list, as well as their consumption were documented in the Lotus database.

Three types of water were used in the laboratory:

- Purified water
- Distilled water, produced by water destillator
- Deionized water, produced by Millipore apparatus
- Water used for chromatography (HPLC) purposes, purchased from supplier (Merck)

Quality of water produced by the distillatory was regularly tested for conductivity, oxidizer particles, heavy metals and nitrates and microbiological counts and recorded in a logbook together with the respective specification.

The expiry date and stability of the inhouse prepared solutions were justified/determined in accordance with the respective SOP.

The deficiencies identified on the reagents were adequately addressed.

11. Reference substances and reference materials

Reference substances were either purchased from approved vendors or supplied by customers, initially tested, released, and stored in the required condition, in a refrigerator or in a locked cupboard under controlled temperature, and periodically monitored according to the following provisions:

- Instructed by manufacturer
- Verification of USP Reference standards retest date every three months on the USP website, or other relevant websites.

The following information was kept on the labels of reference substances:

- Name and description of the material
- Batch and identification number
- Source
- Date of receipt
- Date the container was first opened
- Expiry date or retest date

The identification number was quoted on the analytical worksheets whenever the reference substance was used. A register of all reference substances was also available in the Lotus database system.

The deficiencies identified on reference standards were adequately addressed in the provided CAPA plan.

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

Each instrument was uniquely identified. Labels indicated the status of the calibration and the date when recalibration was due. Equipment were required to undergo DQ, IQ, OQ, PQ, as well as periodic qualification in accordance with the Ukrainian pharmacopeia.

The balances were checked daily in accordance with internal calibration processes, using suitable test weights. Calibration was performed annually by a suitable service provider, i.e. State Enterprise Center for Standardization Metrology.

Records/logbooks were not consistently kept for the items of equipment with information to identify the device, current location, maintenance carried out, history of damage, malfunction, modification or repair. Usage of the HPLC instrument was not recorded. Nonetheless, the calibration certificates were issued and kept with the instruments.

Calibration certificates and qualification documentation of randomly selected equipment were reviewed and verified. For details refer to section 8 of this report.

The deficiencies related to this section were adequately addressed.

13. Traceability

All calibrations or qualification of instruments were traceable to certified reference materials.

The traceability of samples from receipt, throughout the stages of testing, to the completion of the analytical test report was ensured.

The following records was reviewed to study the traceability of the records.

- Preparation of HCl 1 % used for titration of sample 1233 on 21 May 2019

The deficiencies on the traceability were sufficiently addressed.

14. Incoming samples

The laboratory was not involved in physical sampling. Samples were received from clients in a "Receiving room" before being transferred and stored in the sample storage room. Visual inspection of samples was carried out by the sample custodian to ensure that the labelling conformed with the information contained in the test request. The shipment condition was also registered and verified upon the receipt of the samples.

The test requests were reviewed to ensure that the laboratory had the resources to meet required specifications and that the selected tests/methods were capable to meet the customers' requirements. Consequently, a sample analytical sheet was generated in the Lotus database system upon the verification of resources. Samples were also recorded in a logbook where they were assigned an identification number in a chronological order.

A test request accompanied each sample submitted to the laboratory and contained the following information:

- description of the sample
- specification to be used for testing
- required storage conditions

Samples were stored in a storage room with restricted access, controlled temperature and relative humidity. Both maximum and minimum temperature was recorded daily.

The samples were divided into three portions prior to the submission to the laboratory:
- Immediate testing
- Confirmation of testing, if required
- For retention in case of dispute

The sample room was secured by alarm system and the samples were properly indexed and organized under controlled environmental conditions. The temperature and humidity were digitally monitored throughout the facility.

The samples were sent for testing to the specific unit together with the test request by the responsible person. A list of competency matrix was available in the Lotus database system.

All tests were performed after receipt of test request on a "First in – First out" order. Samples were kept for at least 6 months after the completion of the test and in case of OOS, until the end of the samples' shelf-life.

15. Analytical worksheet

SOP for Procedure for formalizing of analyst worksheets with the use of Lotus Notes program, processing of analyst worksheets and storage thereof described the requirements of formalizing, management and storage of analyst worksheets in the laboratory.

Upon receipt and recording of test samples, the analyst worksheet was electronically prepared in accordance with the requirements and printed on paper.

Analyst worksheet contained the following information:
- date, name of the person performing the tests
- sample name, sample registration number
- serial number
- name of applicant
- name of manufacturer
- date of receipt
- type of control
- reference documentation according to which the test would be conducted
- list of indicators (tests)
- the conditions of sample storage, the duration of the tests, the provision of primary materials, if necessary

Upon completion of testing of the sample, the following information was recorded by the analyst into the analyst worksheet:

- results obtained, including calculations, if necessary
- information about any inaccuracies or changes to the documentation in accordance with Reference documentation, any observations, clarifications, etc.
- test results obtained by subcontract, if available
- conclusion regarding compliance (incompliance) of the sample with the requirements of the Reference documentation based on the tested quality indicators

The completed analytical worksheets were signed by the responsible analyst and verified, approved and signed by the supervisor. For corrections, the old information was deleted by putting a single line through it. Alterations were signed by the person making the corrections and the date for the changes inserted. The reason for the change was given.

At the back of the analyst worksheet, a remark was made regarding the transfer of the remainder of the sample to be archived.

Completed, checked and signed analytical sheets were transmitted by the Researcher for the execution of the Certificate of analysis.

16. **Validation of analytical procedures**

The standardized test methods as referred in the pharmacopeia or other reference documentation were used in the laboratory's activities. Therefore, the laboratory was not involved in the validation of test methods. However, provided that the relevant procedures were submitted, the laboratory might conduct validation of analytical methods.

Appropriate system suitability tests were employed prior to the analytical tests for verification of pharamcopoeial methods and/or validated analytical procedures.

The SOP for Test method verification was reviewed. The verification of the quantitative test methods was carried out by verifying their correctness and precision.

An example of method verification for quantitative identification of Nifuroxazide Hard Capsule 100 mg using UV-spectrophotometry method, performed on 15 Apr 2019, was reviewed. The value to be identified was the quantitative content of Nufuroxazide. Precision, correctness and comparison precision between the sample and the standard solution were required to be verified in accordance with the Ukrainian Pharmacopoeia.

17. Testing

Test procedures were described in detail and allowed analysts to perform the analysis in a reliable manner. Deviations from the test procedures were approved and documented.

18. Evaluation of test results and OOS investigation

Verification of questionable test results (OOS) and implementation of corrective actions regarding management of out-of-specification results and inconsistencies of testing was carried out in accordance with the respective SOP.

In the event of a questionable (OOS) test result, the laboratory conducted duplicate re-testing by different analytical chemists who studied the causes of OOS results and took appropriate measures to eliminate them. During re-testing the mean values obtained by each analytical chemist were separately calculated to provide reliable evidence of the fact that the sample was tested.

Doubtful results were rejected only if an error could clearly be identified.

Randomly selected analytical test reports and OOS investigations were reviewed.

If the investigation was inconclusive, the SOP gave clear guidance on the number of retests allowed (based on statistical principles). Once an error was identified, corrective and preventive measures were recorded and implemented. All individual results (all test data) with acceptance criterial was reported. The repeat of tests was done by a second analyst, sufficiently experienced and competent as the first one.

Analytical test reports were issued by the laboratory based on information recorded in analytical worksheets. When investigative testing was performed, the estimated uncertainty of quantitative results was also given.

The test reports further included the following information:

- the background and the purpose of the testing
- reference to the specifications and methods used
- the results of all tests performed (or numerical result with the SD of all tests performed)
- the statement whether the sample complies with the requirements

19. Certificate of analysis

A certificate of analysis was prepared for each sample/batch of a substance or product and contained series of information, among others:

- The results of the tests performed with the prescribed limits
- A conclusion as to whether the sample was found to be within the limits of the specification
- The date on which the tests were completed

The completed analyst worksheets were transferred to the leaders of processes for the control of correctness of completion in accordance with the requirements implemented in SOP for Procedure for formalizing of analyst worksheets with the use of Lotus Notes program, processing of analyst worksheets and storage upon completion of testing. The Analyst worksheets were reviewed and approved by the Head of Laboratory after completion of the analytical test.

Certificate of analysis was electronically prepared in the Lotus database system and then printed out in accordance with the requirements of SOP for Procedure of presentation (formalization) of test results. The Certificates of analysis were chronologically numbered from '1' to 'n' of the current calendar year in the electronic form and were assigned with an identification number that was printed in the lower right corner of the page.

The Certificate of analysis was approved by signature of the Head of Laboratory and seal of the SI "IPH NAMSU".

An electronic version was kept, together with a paper photocopy of the Certificate of analysis along with analyst worksheets and stored for a period of 10 years.

The samples were required to be tested within a defined deadline. The certificates of analysis were flagged in the database if the deadline was exceeded and a trend assessment would be made to implement corrective actions, if necessary.

20. Retained samples

Refer to section 14 of this report.

21. Safety

Staff was wearing laboratory coats, including eye protection. Special care was taken in handling highly potent, infectious or volatile substances. Highly toxic and/or genotoxic samples were handled in safety cabinets. Safety showers were installed. Rubber suction bulbs were used on manual pipettes. Safety data sheets were available before testing was carried out.

Handling of waste materials was addressed as per SOP for Waste management/recycling obtained during testing and trial; 8 Nov 2018.

Narcotics and precursor disposal was handled in accordance with a separate SOP, in presence of responsible staff.

The deficiencies identified on the safety were sufficiently addressed.

Miscellaneous	
Assessment of the Laboratory Information File	The Laboratory Information File contained specific and factual information about the operations being carried out at the QCL and essential steps for each activity were described and where appropriate, supportive documentation was appended.
Annexes attached	N/A

Part 3	Conclusion – Inspection outcome

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 State Scientific Research Laboratory for Quality Control of Medicines – The Testing Laboratory*** located at ***50 Popudrenka str. Kyiv, 02094; Ukraine***, was considered to be operating at an acceptable level of compliance with WHO GPPQCL Guidelines.

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 manufacturer, 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.

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
   Short name: WHO TRS No. 961, Annex 2
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.
   Short name: WHO GDRMP guidance or ***WHO TRS No. 996, Annex 5***
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

6. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO GMP guidelines*** or ***TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en

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