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

Part 1	**General information**
Laboratory Details	
Name of the Laboratory	Central Laboratory for Quality Control of Medicines and Medical Products (CLQCM)
Address of inspected Laboratory	10 G Kudryavska Street Kyiv 04053 Ukraine
GPS Coordinates	Latitude: 50.458001 Longitude: 30.502243
Dates of inspection	17-20 February 2020
Type of inspection	Routine
Introduction	

Brief description of testing activities

Type of analysis	***Finished products***	***Active pharmaceutical ingredients***
Physical/ Chemical analysis	Appearance, clarity and degree of opalescence of liquids, degree of coloration of liquids, potentiometric determination of pH, relative density, refractive index, optical rotation, viscosity (falling ball method), melting point, volumetric and potentiometric titration, AAS, FTIR, UV-vis, TLC, GC, HPLC, loss on drying, conductivity, determination of nitrogen by sulphuric acid, water content: semi-micro	Appearance, potentiometric determination of pH, relative density, refractive index, optical rotation, viscosity (falling ball method), melting point, volumetric and potentiometric titration, AAS, FTIR, UV-vis, TLC, GC, HPLC, loss on drying, conductivity, determination of nitrogen by sulphuric acid, water content: semi-micro, residual solvents, sulphated ash, limit tests.

		determination, Disintegration (tablets, capsules, suppositories, pessaries), Dissolution , Friability of uncoated tablets), test for extractable volume of parenteral solution, particulate contamination: sub-visible and visible particles, Uniformity of Dosage Units	
	Identification	HPLC (UV-Vis, RI detection), GC (FID), TLC, UV-VIS spectrophotometry, FTIR, basic tests	HPLC (UV-Vis, RI detection), GC (FID), TLC, UV-VIS spectrophotometry, FTIR, basic tests
	Assay, impurities and related substances	HPLC (UV-Vis, RI), GC (FID), UV-Vis spectrophotometry, AAS, FTIR, volumetric titrations, optical rotation	HPLC (UV-Vis, RI), GC (FID), UV-Vis spectrophotometry, AAS, FTIR, volumetric titrations, optical rotation
	Micro-biological tests	Sterility test, microbiological examination of non-sterile products: microbial enumeration tests and tests for specified micro-organisms, microbiological assay of antibiotics	Sterility test, microbiological examination of non-sterile products: microbial enumeration tests and tests for specified micro-organisms, microbiological assay of antibiotics
	Bacterial endotoxin testing (BET)	Bacterial endotoxins test, (LAL, gel-clot method)	Bacterial endotoxins test (LAL, gel-clot method)
General information	Central Laboratory for Quality Control of Medicines and Medical Products (CLQCM) was established by Decree # 48 dated 20 Feb 2004. The Laboratory has been operative in the system of the *State Service of Ukraine on Medicines and Narcotic Drugs Control* since 25 Feb1998. Head of the State Service of Ukraine on Medicines and Narcotic Drugs Control was appointed by the Cabinet of Ministers of Ukraine, following a proposal from Minister of Health.		

	The main activities of the Laboratory within the state quality management system include: - Laboratory quality testing of APIs and post approval medicinal products in accordance with the established procedure followed by issuing corresponding quality certificates. - Laboratory quality testing of narcotic substances, psychotropic substances and precursors. - Methodological management of the laboratories operating within the system of State Quality Control of medicines.
History	The Laboratory was previously inspected by EDQM, WHO, National Accreditation Agency of Ukraine, State Service of Ukraine on medical products & drug control.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Quality Management System Personnel Training and Safety Documentation and Records Premises and Equipment Validation – Qualification –Calibration Laboratory Practices Reference standards – Reagents - Water
Restrictions	All QMS related documentation and records were written in local language, i.e. Ukrainian.
Out of Scope	N/A
Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
CAPA	Corrective action & Preventive action
DQ	Design qualification
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)
IQ	Installation qualification
IR	Infrared spectrophotometry
KF	Karl Fisher titration
LIMS	Laboratory information management system
MB	Microbiology

MR	Management review
N	Normality
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
OQ	Operation qualification
Ph.Eur.	European Pharmacopoeia
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PT	Proficiency testing
PTS	Proficiency testing scheme
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QM	Quality manual
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
TLC	Thin layer chromatography
TOC	Total organic carbon
URS	User requirements specifications
USP	United Stated Pharmacopoeia
UV	Ultraviolet-visible spectrophotometry or spectrophotometer
VMP	Validation master plan
VS	Volumetric solution

Part 2	Summary of findings and recommendations (where applicable)

1. Organization and management

An organization chart was available. The total number of staff with permanent contract accounted to 34 at the time of inspection. The Laboratory was headed by Dr Roman Markin and comprised of the following sections:

- QA department
- Department of Physico-Chemical control
- Department of Sample-registration
- Department of Microbiological control

The Laboratory had arrangements to ensure that its management and personnel were not subjected to commercial, political, financial and other pressures or conflicts of interest that might adversely affect the quality of their work. The Laboratory had a policy in place to ensure the confidentiality of information contained in marketing authorizations and test reports. All the staff had signed the declaration form on conflict of interest according to the applicable SOP. The signed forms were stored in the personnel file.

The Laboratory was also involved in various projects as detailed in the presentation provided by QA-Head.

The Laboratory was accredited by National Accreditation Agency of Ukraine, on 5 Aug 2019.

The identified deficiencies related to the organization and management were adequately addressed in the Laboratory's CAPA plan.

2. Quality management system

The Laboratory had established, implemented and maintained a QMS appropriate to the scope of its activities. It was ensured that the Laboratory's policies, systems, programs and procedures were described to enable the personnel to assure the quality of activities. The elements of QMS were documented.

The Laboratory's Quality Manual approved on 12 Feb 2020, defining the quality management system was reviewed. The QM was prepared by the Quality Assurance Unit and approved by the Laboratory director. Clear references were provided to the OMCL guidelines, WHO guidelines and ISO norms 17025 and 9001. All the sections and provisions required by the above-mentioned guidelines were adequately captured in the QM. The acknowledgement of the Quality Manual and its attachments were signed by the concerned staff, including impartiality.

Management review

SOP for Management Review (MR) was available, dated 23 Jan 2020 by which the systematic evaluation of the Laboratory's performance assessment was described. A Management Review was required to take place at least once a year. The last MR took place on 27 Jan 2020. All relevant documentation, including QA report, updates of QMS system, documented on the respective form and the record of the follow-up of the previous Management Review recommendations were available and reviewed. The respective actions were properly recorded in the LIMS software.

SOP for Risk assessment, dated 1 Feb 2016, as well as the respective risk registry were available and reviewed. Risks were identified, analysed and categorized in accordance with the applicable SOP.

Change control

The substantial changes since the last inspection were presented.

Internal audits

The activities of the Laboratory were systematically and periodically audited in accordance with SOP titled as "The procedure of internal audits". Audit plan for 2020 and 2019 and the audit report relating to the internal audit performed on 20 Sep 2019 were available. The quality manager was responsible for proper planning and organization of internal audits. The annual audit plan covered the most critical elements of the QMS, divided into 11 processes, such as qualification of testing of samples in the Microbiology Laboratory. The independency of the auditors was verified. Follow-up of the non-conformities were performed by a designated person. The audit records, together with the details of any implemented corrective and preventive actions were recorded in the LIMS database system.

Handling of deviations and CAPA

The QA Department monitored and managed the implementation of plans for corrective/preventive actions during daily performance of their duties and during follow-up of audits.

Complaints

There was no complaint reported since the last WHO inspection. The protocol for negotiations with the customer was in place.

The identified deficiencies related to the QMS were adequately addressed in the respective Laboratory's CAPA plan.

3. Control of documentation

The Laboratory had established and maintained a system of procedures to control all documents (preparation, revision, distribution, return and archiving). A master list identifying the current version status of SOPs was available. The need for updating documents was assessed at least once a year and documented on the Master list. Each SOP had a unique identifier, version number, date of implementation, reference to the previous version. The documents were released by the quality manager and available for the entire staff in the LIMS (read only). An SOP was in place comprising the authorization for copying and the identification of copies from official and controlled documents.

Relevant staff was trained on new and revised SOPs using a distribution list attached to the master copy of the respective SOP and the personnel acknowledged by signature that they were aware of the content.

4. Records

Analytical tests were recorded, including calculation and derived data, instrument use, calibrations and maintenance and sample receipt on templates, containing consecutively numbered pages. The records were signed. Records such as chromatograms and spectra were provided.

Retained samples of medicinal products and standard materials and test documents were stored in separate rooms with restricted access. The sample registration manager and archivist had the responsibility for keeping each archive respectively.

The documentation in the archive-cupboards was properly organized and a process for arrangement of documentation and handling of retrieval of documentation was properly implemented in practice.

The history of the randomly selected samples was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, archive), refer to the section 17 of this report.

The identified deficiencies related to the Records were adequately addressed in the respective Laboratory's CAPA plan.

5. Data processing equipment

An inventory of computerised systems was available.

Electronic data was backed up at appropriate regular intervals in accordance with SOP titled as "The guidelines for creating backup copies of electronic data". Software systems associated to the instruments were connected to a backup program. Additionally, data was regularly saved on an external hard drive, under appropriate supervision. Another backup copy was prepared once a year.

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. Calculation algorithms were properly tested and confirmed. The validated Excel spreadsheets were uploaded in the LIMS database system to provide protected access by QA who also supervised and handled the obsolete versions. The used spreadsheets were stored on the server in a specific folder. The sheets were also printed out to be attached to the analytical documentation.

Validation of computerized systems was initiated in accordance with an SOP for Computerized Systems validation protocol. This SOP was mainly related to the transfer of data from computer to the backup server for security of storage of electronic data. The transfer of data from LIMS database to the backup server was validated.

The Laboratory's LIMS database was launched in 2010.

The identified deficiencies related to the Computerized systems were adequately addressed in the respective Laboratory's 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 for all personnel involved in tests and/or calibrations, validations and verifications. The Laboratory also maintained the records of all technical personnel, describing their qualifications, training and experience.

The Laboratory had developed and introduced the personnel management system as defined in SOP for "Personnel Management", dated 21 Aug 2019. According to the procedures, the supervisors (the department heads and deputy directors) were responsible for the competence of personnel working with special equipment, carrying out the tests, evaluating results and signing test protocols. The quality manager was responsible for training of personnel. Requirements for the qualification and competence of personnel were defined in the corresponding quality management system document listing the skills, powers and duties. The competency matrix was provided as an annex to the QM.

The training of the staff consisted of both induction and on job training on methodologies, SOPs and safety in accordance with the applicable SOP dated 13 Aug 19.

The competency matrix which was compiled based on the trainings, competency tests and authorization letters clearly indicated the professional competencies of the entire staff. Randomly selected training records of analysts were reviewed.

The Laboratory participated in national and international proficiency testing schemes (PTS) and collaborative trials (interlaboratory comparison testing) according to its strategy and plans. The PTS samples were mainly provided by EDQM and/or "Metrology Service LTD" (National Ukrainian accredited proficiency testing provider according to ISO/IEC 17043). Lists of PTS and collaborative trials during last 3 years were available. A proof of registration for PTS, submitted by EDQM was presented to verify the Laboratory's participation plan for 2020. The documentation was dated 21 Oct 2019.

7. Premises

The Laboratory facilities were of suitable size and design to suit the functions and the operations. 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. The Laboratory provided separate rooms for storing flammable substances, fuming and concentrated acids and bases.

Microbiological testing was performed in a contained laboratory unit.

Laboratory premises were located on the second and third floors of the building at Kudryavska Street 10G, with chemistry and sample registration on the 2nd floor and microbiology on the 3rd floor. The administration and QA offices were located on 10B.

The access to the Laboratory premises was controlled by using audio-video system. Both buildings of the Laboratory were equipped with separate entrances with electronic locks. Layout of the Laboratory facilities was provided. Minor inaccuracies were discovered, discussed and then implemented at the time of inspection.

Controlled rooms in the Microbiology facility where culture preparation microbiology count took place were monitored by:

- Air monitoring by means of settle plates
- Monitoring of surfaces;
    - once a week, in operational condition
    - once a month; at rest
- Staff clothing

The identified deficiencies related to the Premises were adequately addressed in the respective Laboratory's CAPA plan.

8. Equipment, instrument and other devices

The equipment, instruments and other devices used for tests, calibrations, validations and verifications were required to be suitable for use.

When necessary/applicable, the equipment was calibrated/qualified by external service provider, i.e. State enterprise "All-Ukrainian state research and production centre for standardization, metrology, certification and consumers rights protection", accredited by ilac – MRA. The calibration and qualification of certificates issued by external service providers were required to be verified by designated staff.

Randomly selected equipment and/or related qualification documentation, together with respective SOP/instruction were reviewed to verify the adequacy of their calibration/validation certificates:

- Balance ME403T/A in use in the Microbiology facility
- Standard weights; class E2
- Autoclave Systec DX-100, used for sterilization in the Microbiology facility
- Incubator Binder BD 115, with three different temperature ranges, used in the Microbiology facility
- Bio-Safety cabinet ESCO FC2-4A1, used for culture preparation and Microbial Limit Count. The activities were segregated in time to minimize risks for cross contamination, false positive and false negative results. Sterility tests were always performed in an isolator.
- pH-meter 744 Metrohm, in use in the Microbiology facility
- pH-meter 827 pH lab Metrohm, in use in the Microbiology facility
- pH meter 913 pH Metrohm in the Chemical Laboratory
- Optical rotation MCP 200
- AAS (Atomic Absorption Spectrometer) – Vario 6FL
- Dissolution tester – VanKel VK7000, together with device used for the periodic qualification of the equipment
- Disintegration tester – VanKel VK 100
- UV-vis spectrophotometer UV VIS Cary 100
- HPLC HP1100, Agilent 1200
- Volumetric glassware
- Periodic verification of Micropipettes
- Gas chromatograph HP 6890 A, Agilent 7890A
- FT infrared spectrophotometer Cary 630 FTIR
- Friability tester PTF 20E

- Following incubators available in the microbiology laboratory:
  - INK-01, type BD-115, temperature: 43 °C
  - INK-02, type KB-115, temperature: 22.5 °C
  - INK-03, type B-6120, temperature: 32.5 °C
  - INK-04, type B-6120, temperature: 36 °C, qualified for 57.5/43/60 °C

Sterility tests were performed in a LaCalchene SOFT WALL HALF-SUIT isolator, installed in 1999. The installation was completed with adequate IQ/OQ/PQ, followed by training of the concerned staff. Furthermore, regular qualification and maintenance was assured in accordance with SOP for Instructions for use and maintenance of isolator LaCalchene. The last qualification was carried out on 04 Jun 19. The pressure and the temperature monitoring of the isolator was recorded in a logbook (manual) and in a data recording device. The electronic records were printed and kept annually.

The identified deficiencies related to the Equipment and devices were adequately addressed in the respective Laboratory's CAPA plan.

9. Contracts

The procedure for selecting and purchasing of the required services and supplies was described in the respective SOP. Services and supplies were only ordered from qualified suppliers/manufacturers.

The procedure for selection and evaluation of suppliers was performed in accordance with SOP titled as «The procedure of products and services suppliers' evaluation». List of service providers and suppliers was provided as a controlled documentation, dated 27 Jan 2020. The list was required to be revised once in every 12 months. Each provider was categorized with a coding as A – E in accordance with the applicable SOP. Evaluation and assessment of suppliers took place using a template, annually.

Testing of samples were not subcontracted at the time of inspection. Nevertheless, a procedure for subcontracting of testing was available.

10. Reagents

The reagents were labelled, once upon the receipt and once when the container was opened. The open containers were marked with a new expiry date in accordance with SOP for Quality Control of Reagents and Material. Labels of reagent contained content, manufacturer, date received and date of opening of the container, concentration, if applicable, storage conditions, expiry date and retest date, as justified.

Reagent solutions were prepared in the laboratory in accordance with the applicable SOP, and labelled on the container/glassware with the name of the reagent, date of preparation and initials of technician or analyst, expiry date or retest date, as justified and concentration, if applicable.

Two water preparation systems were used in the Laboratory in accordance with SOP for obtaining, using and controlling the quality of purified water and highly purified water:

- purified water preparation by distillation (Aqua distiller DE-40) – to be used for feed water for highly purified water and different volumetric solutions
- highly purified water by reverse osmosis and ion exchange (Simplicity UV, Millipore) – to be used for HPLC mobile phase, alkaline volumetric solutions and other tests.

The quality of water, i.e. microbial purity, conductivity and pH was regularly verified to ensure that the various grades of water met the appropriate specifications as per SOP for Obtaining, using and quality control of purified water and highly purified water. Microbial limit test was performed once in three months for purified water.

The CoAs related to the detergents recommended by dishwasher producer and used for cleaning of laboratory utensils and glassware were provided, together with SOP for washing and cleaning of glassware in the Microbiology control department, dated 22 Jun 2018.

11. Reference substances and reference materials

a) Reference substances and reference materials

SOP for registration, storage and use of reference standards and reference substances was available to ensure traceability of measurement results. Reference materials were mainly received from the customer together with the test request and the sample.

Following Reference standards were used for the respective activities, including qualification of equipment:

- Primary: pharmacopeial standard samples
- Secondary: standards certified by organizations authorized to certify working standards (e.g. Sigma-Aldrich, USA)
- Working Reference Standards: standards attested by medicines manufactures according to primary or secondary standards

Receipt and handling of reference standards, including dispensing were managed in LIMS, in a designated module by responsible staff. The containers were marked with a unique identification number assigned by the respective program.

Standard samples were stored in a room with restricted access (archive room) under appropriate controlled temperature conditions in containers with silica gel to protect against high humidity.

b) Reference cultures

In the process of carrying out microbiological tests, only standard test strains of microorganisms from the national collections with information on the traceability of the American collection of test strains (ATCC) or other international collections were used.

The procedure of the work with test strains of microorganisms was described in the SOP for the establishment of long- term use test strains, SOP for Obtaining and restoration of the microorganism test strains and SOP for creating temporary storage strains and strains of intended use. The inventory log of microorganism test strains and randomly selected respective CoAs were reviewed. The microorganisms were kept in the refrigerators, designated for the purpose, in lyophilized condition.

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

Each instrument was uniquely identified.

Balances were checked daily using internal calibration and regularly using suitable test weights. Requalification was performed annually using certified reference weights.

Records/logbooks were kept for items of equipment with information to identify the device, current location, maintenance carried out, history of damage, malfunction, modification or repair. Use of the instrument was also recorded. Usage of HPLC chromatography columns was recorded in a logbook.

For more details, refer to section 8 of this report.

13. Traceability

Test results were traceable, were appropriate, ultimately to primary reference substances.

Calibrations or qualification of instruments were generally traceable to certified reference materials and to SI units (metrological traceability).

14. Incoming samples

The Laboratory was not responsible for sampling of materials/product. Samples were received and stored by the Registration Department in the temperature-controlled (15-22 °C) Sample Room.

Upon receipt of the samples, registrars checked the integrity of packages and proper conditions of transportation (especially for thermally labile samples). If there were inconsistencies with the description, quantity, or the transporting conditions, corresponding marks were made in the delivery and acceptance certificate and a letter of notification to the State Administration of Ukraine on Medical Products describing the situation and asking for further action was issued.

Reception, registration, distribution, usage, storage and disposal of samples of medicinal products were managed in accordance with SOP for the procedure of handling the samples admitted for analysis in the department of Registration of samples.

A test request accompanied each sample submitted to the Laboratory and contained the QC analytical method based on the Ukrainian pharmacopeia or the medicine registration documentation. The Registration Department checked the test request documents, compared the amount of the incoming sample with the theoretical calculations (amount needed for the testing and for retention). Testing should be due within 1 month of the receipt.

Test requests were reviewed to ensure that the Laboratory had the resources to meet them and that the selected tests/methods were capable to meet the customers' requirements.

All delivered samples and accompanying documents were registered in LIMS database system to be assigned a registration number. An electronic register was kept in which the following information was recorded:

- registration number of the sample
- date of receipts
- unit to which the sample was forwarded

Prior to testing, the samples were stored safely, considering the storage conditions for the sample. The samples were sent for testing to the specific unit together with the test request by the responsible person.

The samples were divided to three approx. equal portions for submission to the laboratory:

- Immediate testing
- Confirmation of testing, if required
- For retention in case of dispute

After completing the testing and approval of the outcome (signing the analysis protocol by the supervisor) the performer of the analysis returned the remaining samples to the Sample Registration Department to be delivered to the archive.

The archive samples were stored for at least 6 months after the certificate of analysis was issued but not less than 12 months or until the expiry date. Samples of immunological products were stored until the expiry date. Samples provided on suspicion of fraud were stored for at least 2 years.

After the expiry date, the archival samples were destroyed in accordance with the procedure established in the respective SOP.

All tests were performed after receipt of test request.

15. Analytical worksheet

The analysts recorded information about samples, test procedures, calculations and results in analytical worksheets, which were completed by raw data.

The worksheets contained the following information:

- the date on which the analysis was started and completed
- reference to specifications and full description of the test methods, by which the sample were tested, including the limits; identification of test equipment used; reference substances, reagents and solvents employed
- interpretation of the results
- the conclusion whether the sample was found to comply with the specifications
- any deviation from the prescribed procedures

All values obtained from each test, including blank results, were immediately entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, were attached or were traceable to the electronic record file or document where the data was available.

The completed analytical worksheets were signed by the responsible analyst and verified, approved and signed by the supervisor. For corrections, the old information should be deleted by putting a single line through it; it should not be erased or made illegible. Alterations were signed by the person making the corrections and the date for the changes was inserted. The reason for the change was also given.

16. Validation of analytical procedures

Pharmacopeial and validated methods were verified only by system suitability testing as an integral part of applicable analytical procedures. These tests were carried out to confirm that equipment, software system, analytical operations and samples to be analysed contributed to the system.

The identified deficiencies related to the Validation and Verification were adequately addressed in the respective Laboratory's CAPA plan.

17. Testing

Together with the test records and results the following SOPs were discussed:

- SOP on Quality analysis of medicinal products by HPLC method
- SOP on Operation, storage, washing and maintenance of HPLC chromatographic column

Test procedures were described in the QC methods provided by the Ukrainian State Expert Centre - Medicines Agency.

The following main activities for microbiological testing were carried out:

- Sterility test
- Microbiological examination of non-sterile products: microbial enumeration tests and tests for specified micro-organisms
- Microbiological assay of antibiotics
- Bacterial endotoxins test (LAL, gel- clot method).

Procedures for these tests were prepared in compliance with the relevant Ph.Eur. methods.

The procedure for preparation and control of media was described in SOP for Preparation procedure of nutrient media for microbiological purity and sterility testing and SOP for Growth promotion test of the nutrient media used for sterility test.

SOPs for LAL-testing, to confirm declared sensitivity to the LAL reagent and SOP for identification of bacterial endotoxin by means of clotting method, and the respective testing documentation, including CSE & LAL certificates were also reviewed and verified.

Negative controls were performed for every microbiological test and positive controls were carried out during the test of suitability of procedure. Suitability of test procedure (sterility or microbiological purity tests) took place in accordance with SOP for Examination of suitability of the microbiological purity method and SOP for Examination of suitability of the sterility test method.

Four (4) randomly selected testing documentation were reviewed.

The identified deficiencies related to the Testing were adequately addressed in the respective Laboratory's CAPA plan.

18. Evaluation of test results and OOS investigation

An SOP was in place describing the conduct investigations of OOS test results. When a doubtful result (suspected OOS result) was identified, a review of the procedures applied during the testing process was undertaken by the supervisor and the analyst.

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

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, at least as experienced and competent as the first one.

Information about OOS were recorded in the LIMS assigned by a specific system-generated number.

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.

Four (4) randomly selected documentation relating to OOS investigations was reviewed.

The identified deficiencies related to the Evaluation of results and OOS investigations were adequately addressed in the respective Laboratory's CAPA plan.

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.

COA was signed by the Laboratory Director.

20. Retained samples

Retained samples were kept in the sample inspection room in their final pack and retained as required by the legislation.

For more details, refer to section 14 of this report.

21. Safety

Staff was wearing laboratory coats, including eye protection. Safety showers were installed. Rubber suction bulbs were used on manual pipettes. Safety data sheets were available before testing was carried out.

All the visitors entering the laboratory facilities should undergo a safety training/presentation. The safety rules were described in different documents, including Laboratory Safety Policy, Management system for laboratory safety and department specific safety instructions (86 generals, 46 for chemistry and 116 for microbiology). All concerned staff were trained on the respective instructions, by the laboratory manager or the designee.

The procedure of waste disposable was implemented in accordance with SOP for Disinfection of waste material.

Miscellaneous	
Assessment of the Laboratory Information File	The LIF was provided in English for inspectors' review. It was discussed, and the Laboratory was advised to provide the LIF in a controlled version.
Annexes attached	N/A

Part 3 – Conclusion – Inspection outcome

Based on the areas inspected, the people met, and the documents reviewed, including the CAPA plan provided for the observations listed in the Inspection Report, ***Central Laboratory for Quality Control of Medicines and Medical Products (CLQCM)***, located at ***10 G Kudryavska Street, Kyiv, 04053 Ukraine*** is 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 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.

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***
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