World Health Organization

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

PART 1	**GENERAL INFORMATION**
Laboratory Details	
Name of the laboratory	The Testing Center (TC) of the Territorial Branch of the Republic State Enterprise on the Right of Economic Management "National Center for Expertise of Medicines and Medical Devices" Medical and Pharmaceutical control committee of the Ministry of Healthcare of the Republic of Kazakhstan in Almaty City
Address of inspected laboratory	Baitursynov Street 40A Almaty, Kazakhstan 050012/A05B8B6
GPS Coordinates	43.25457° N 76.92642° E
Address of corporate office, telephone number and fax number	Astana city, Imanov street, 13. Kazahstan +77172235135 www.ndda.kz
Dates of inspection	13 – 16 February 2024
Type of inspection	Follow-up
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 • Relative density • Refractive index • Optical rotation • Loss on drying • Osmolality • Disintegration of tablets and capsules • Dissolution test for solid dosage forms; • Uniformity of content of single dosage forms • Uniformity of mass single-dose preparation	• Clarity and degree of opalescence of liquids • Degree of coloration of liquids • pH • Relative density • Refractive index • Optical rotation • Loss on drying • Osmolality • Particulate contamination • Visible particles • UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV

		• Friability of uncoated tablets • Particulate contamination: Visible particles • Uniformity of dosage units • UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV wavelength or photodiode array detection	wavelength or photodiode array detection
	Identification	• UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV wavelength or photodiode array detection	• UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV wavelength or photodiode array detection
	Impurities and related substances	• UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV wavelength or photodiode array detection	• UV-Visible spectroscopy • Thin layer chromatography • Liquid chromatography with either fixed UV wavelength or photodiode array detection
	Assay	• UV-Visible spectroscopy • Liquid chromatography with either fixed UV wavelength or photodiode array detection	• UV-Visible spectroscopy • Liquid chromatography with either fixed UV wavelength or photodiode array detection
	Bacterial Endotoxin Testing (BET)	• Bacterial endotoxins	

General information	The National Center was created by Government Decree of the Republic of Kazakhstan on 17 November 1997 № 1591 «About Establishment of Republican State Enterprise "Center for Medicinal Products "Dari-darmek" of the Ministry of Education, Culture and Healthcare of the Republic of Kazakhstan». In 2002 under Degree №1081 "Selected issues of the Republican state enterprise "Center for Medicinal Products "Dari-darmek" Ministry of Healthcare of the Republic of Kazakhstan», the National Center was re-organized by transforming to RSE on REM «National center for the expertise of medicines and medical devices» by Government Decree of the Republic of Kazakhstan on 2 Oct 2002 Physico-chemical Laboratory (PCL) was created in 1998. The Biological Test Laboratory (BTL) was created based on the Republican immune-biological laboratory (RIBL) in 2005. The Microbiology laboratory is a sub-Division of the BTL. TC provides the following testing activities: • PCL - Physical and chemical analysis, Identification, Assays and Impurities testing of Active Pharmaceutical Ingredients (API), capsules, tablets, injectable, powder, suspensions and other forms of medicines. BTL provides the following testing activities: • Biological assay of antibiotics, test for sterility, tests for microbial contamination using microbial and molecular biology methods, endotoxin testing, pyrogen testing, microbiological purity, sterility, toxicological (toxicity, pyrogenicity, local irritant effect, bacterial endotoxins, immunochemical; bacteriological TC was capable to perform methodologies described in the following pharmacopeias, as well as any analytical method within test requests: • State Pharmacopoeia of Kazakhstan • European Pharmacopoeia (Pharmacopoeia European, Ph. Eur.) • United States Pharmacopoeia (USP) • British Pharmacopoeia (BP) • Japanese Pharmacopoeia (JP) • The International Pharmacopoeia (Ph. Int.) In addition, the National Center carries out the following activities. • Development and updating of the State Ph. of the RK, EAEU Ph. • Conducting reference pricing • Consulting services for the expertise, conducting training, publishing a specialized journal • Translation instructions for the medicines and medical devices into the state language
History	The organization participated in WHO GBT benchmarking in September 2021 and PQM+ performed a peer audit in April 2021.

	The Laboratory was inspected by WHO PQ Team 19-22 July 2022
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Inspection was focused on CAPA implementation from previous PQT inspection. The following chapters of WHO good practices for pharmaceutical quality control laboratories guideline were also checked: • Organization and management • Quality management system • Control of documentation • Records • Data processing equipment • Personnel • Premises • Equipment, instrument, and other devices • Contracts • Reagents • Reference substances and reference materials • Calibration, verification of performance and qualification of equipment, instruments and other devices • Traceability • Incoming samples • Analytical worksheet • Validation of analytical methods • Testing • Evaluation of test results and OOS investigation • Certificate of analysis • Retained samples • Safety
Restrictions	The Laboratory documentation was provided in Russian language. One interpreter was available to assist the inspection team with translation. Note: the Lead inspector is fluent in Russian language
Out of Scope	The Microbiology laboratory, except of endotoxin testing
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**

1. Organization and management

The organization and management structure of the Laboratory, including responsibility, authority, and interrelationship of the personnel, were specified in the organizational chart.

The enterprise/organization was headed by the CEO-Chairman of the Management board. The Testing Center (TC) was a structural subdivision of territorial branch in Almaty headed by the TC Director. The territorial branch had its own Quality System department with a report line to the Director of the territorial branch and the Main Quality System Division at the Head Quarter (HQ).

The Enterprise comprised of:
- HQ in Astana
- Almaty Territorial Branch (including Testing Center (TC))
- Karaganda Branch (including Testing Laboratories)
- Taraz Branch (including Testing Laboratories)

Almaty TC was considered the main testing laboratory with the highest capacity and received the majority of samples for testing in Kazakhstan.

Almaty Territorial Branch comprised of:
- Quality System Department
- Testing Center:
    - Physico-chemical lab
    - Medical device test lab
    - Equipment maintenance division
    - Purchasing division
        - Receiving samples, distribution of samples, reference standards and reagents
        - Consumables, etc.
    - Biological tests lab
- Laboratory of pharmacological tests
- Scientific and educational Center
- Asset and accounting specialist
- Administrative and economic department

The Laboratory carried out its activities on the principles of legality, honesty, impartiality, and the exclusion of conflicts of interest in accordance with Policy in the field of ensuring the management system. The management and Heads of structural divisions of the TC were personally responsible for ensuring partiality (impartiality) and exclusion of conflicts of interest in the performance of their activities (official duties). To ensure impartiality and avoid conflicts of interest, all employees of the TC, in accordance with procedure for Personnel Management, signed the Declaration on confidentiality, objectivity, and exclusion of conflicts of interest form. The procedures were adequately defined in the Quality Manual.

In April 15, 2020, NCEM received an accreditation certificate indicating compliance with GOST ISO / IEC 17025-2019: testing of products in accordance with the declared scope of accreditation. Accreditation certificate № KZ.T.02.0010 valid until April 15, 2025.

2. Quality management system

Quality Manual was based on the requirements of the legislation of the Republic of Kazakhstan, GOST ISO/IEC 17025 -2019 (ISO/IEC 17025:2017) and ISO 9001:2015, GPPQCL/WHO requirements, as well as regulatory documents of the Enterprise.

Quality Management System of all branches was led by QMS coordinator from HQ in Astana.

6 January 2023 NCEM has received OMCL network quality management system attestation. Sections audited were:
- Physico-chemical laboratory
- Biological tests laboratory
- Medical devices laboratory

Statement of the audit: NCEM has been audited in accordance with the EDQM instruction ISO/02 on the QMCL Network Mutual Joint Audit Scheme. Attestation is valid until 16 June 2026.

Additionally, the laboratory testing functions have incorporated and applied the requirements, directives, and guidance of the following documents:
- GOST ISO/IEC 17025:2019 the Kazakhstan version of ISO/IEC 17025:2017, General requirements for the competence of testing and calibration laboratories
- Official Medicines Control Laboratory (OMCL) directives from the European Directorate for the Quality of Medicines and Health Care (EDQM)
- World Health Organization (WHO) guidelines for good practices for pharmaceutical quality control laboratories. WHO Technical Report Series (TRS), No. 957, 2010. Annex 1: WHO good practices for pharmaceutical quality control laboratories.
- Applicable section of WHO TRS, No. 957, 2010, Annex 2: WHO good manufacturing practices for active pharmaceutical ingredients;
- WHO Technical Report Series, No. 961, 2011, Annex 2: WHO good practices for pharmaceutical microbiology laboratories:
- WHO TRS, No. 1033, 2021, Annex 4: Guideline on data integrity

The Quality Manual was written in accordance with ISO 17025:2017 requirements.

The QMS documentation included the following four levels:
- Quality Manual, Policy and Objectives, Strategic Plan.
- Documents established through the development of the provisions of the Quality Manual, Policy, and Objectives, as well as describing the activities of the structural units and processes of the Enterprise
- Documents that ensured effective planning, implementation of processes and management of the activities of structural units separately
- Documents containing objective evidence of the actions performed and (or) results achieved records (orders, instructions, memos, plans, events, reports, forms, forms, protocols, contracts, journals, analytical sheets)

Business continuity

Business continuity plan was explained in the procedure “Business continuity and incident management”. Business continuity group of fourteen persons was responsible to ensure business continuity.

Business continuity action plan was made retrospectively and also prospectively. After the action plan was approved and saved on server, training was provided to all staff members. Action instructions and pictures were placed in different places in the laboratories and other locations. 22.01.2024 Almaty was affected by mild earthquake. Staff meeting/training was held, safe places during earthquake were identified and marked. Firefight training was also performed.

Complaints

During inspection SOP "Complaints and claims" was under review. Complaints and claims logbook was maintained by QA. Complaints and claims were received and investigated by corporate security and information department. In case complaint or claim was regarding laboratory performance Head of TC was notified and responsible persons were nominated for investigation.

Trending of data

TC has established and implemented the SOP "Ensuring the quality of results (intra-laboratory control, inter-laboratory comparisons, trend analysis)" to defined processes and requirements for proficiency testing and collaborative trails.

Tools used for trend analysis were:

- Pareto chats
- Control charts
- Stratification

Proficiency testing (PT)

TC annually participate in proficiency testing schemes provided by either ISO/IEC 17043 accredited providers or providers that follow the principles of ISO/IEC 17043.

When external proficiency test were not available, or as needed to monitor performance the TC organized proficiency testing schemes between the Territorial Branches of the «NCEM and MD».

Participation in the proficiency testing was explained in SOP "Ensuring the quality of results (intra-laboratory control, inter-laboratory comparisons, trend analysis)". It was explained that the laboratory yearly participated in 3 - 4 PTSs.

Management review (MR)

Management review (MR) was performed annually, covering, but not limited audit reports, complaints, and proficiency testing outcomes. The last Management review took place in February 2024. The list of participants was provided. Standard agenda and the list of participants was provided. An extensive report was provided with information about items reviewed during the meeting, including target, target date, and status of proposals. MR included trends, specified in trends SOP. Trends were compared with previous year numbers.

Risk Management Plan

Risk management policy was explained in the two procedures. Risks were identified, and the mitigation measures were defined. Report of risk analysis was carried out biannually. Trending of risks was done annually and reported during Management Review meeting. Risk register for 2024 was available and presented. Risks were identified by risk priority numbers.

Risk action plan for undesirable and unacceptable risks were prepared according to the risk register at least annually.

Change control (CC)

Change requests were managed in accordance with SOP Management of changes and improvements in laboratory activities.

In case of major change controls, action plan was created and specifying requested actions, responsible persons and dead line for closing CC. According to the SOP any delays should be acknowledged and reported to the QA division, further on QA reported to the Head of the TC. Change controls register was presented.

Audits

The laboratory activities were systematically and periodically audited. Internal audits were performed in accordance with SOP Internal audits. Internal audit schedule for 2024 was presented. According to the SOP internal audits should be carried out at least annually. Internal audits were conducted following requirements of internal policies and procedures, as well as with the requirements of ISO / IEC 17025, GPPQCL / WHO, and EDQM/OMCL guidelines. Audits were performed using checklists. Deviations from internal policy requirements, procedures, or standards were identified and corrected. Corrective actions taken in relation to an internal audit were analyzed and evaluated. CAPAs were proposed by respective Head of division and confirmed by QA. Implementation of actions were carried out according to procedure Management of nonconformities, corrective and/or preventive action.

Management of nonconformities of laboratory activities was explained in the SOP Nonconformities. Nonconformities were recorded in separate logbooks: (daily (routine), external and internal audits). OOS were recorded also in separate logbooks:

- Physico-chemical lab
- Biological testing lab
- Medical devices lab

Daily nonconformities were registered separately; logbook was kept by QA department. This logbook was common for all three laboratories.

Handling of deviations

Handling of deviations was explained in procedure Management of nonconformities and corrective action. Prcedure was applicable to any of deviations. Deviations were defined in Quality manual, dealing with non-conformities in laboratory was explained in separate SOP.

CAPAs were applicable to all nonconformities.

3. Control of documentation

Control of documentation was explained in procedure Documented Information Management. Procedure explained uniform requirements for the procedure for developing, agreeing, approving, putting into effect, registering, replicating, executing, storing, updating, amending, reviewing, canceling, and destroying documented information of the management system, including the integrated management system and its processes in the different divisions of the Ministry of Health of the Republic of Kazakhstan. The process of forming the nomenclature of cases, registration, and formation of cases, their destruction or transfer to permanent storage was defined in the relevant internal regulatory document of the Enterprise.

Each SOP had a unique identification number, version number, date of implementation, effective date and reference to the previous version. The procedures and the respective responsibilities were defined in the SOP for Documented Information Management Department.

Laboratory Quality management documents master list was available in form of validated excel spreadsheet and presented during inspection. According to the procedure Documented Information Management, documents should be revised every 5 years or as necessary.

SOPs were uploaded and maintained in an internal server, i.e., the QMS documentation system by Head office QA. All staff had read-only access to the system and the SOPs. The HQ QA department managed the system.

In case the new SOP was introduced or revised, notification email was sent out to all staff members. Before any SOP was implemented, self-training was required. The self-training was documented in the individual training binder and verified by their signatures. In case of additional training was required, the Quality Management department was responsible for providing the training. Upon request, the QA manager would give a presentation of the change details and present it to the employees.

Records

Records were made of analytical tests, including calculation and derived data, method validations/ verifications, instrument use, calibrations and maintenance, and sample receipt in logbooks containing consecutively numbered pages.

Records were kept in the laboratory archive, before being sent to the HQ archive facility. The documentation was indexed and archived in the facility as per the local requirements.

Separate procedure explained testing records management in laboratory. According to the procedure testing records (analytical worksheets, equipment's usage, copy of testing reports) were stored 1 year after specified documentation retention time. Documents retention time was specified by Ministry of culture and sport order.

4. Data processing equipment

An inventory of all computerized systems was available with the information about unique identification, purpose, validation status, physical or storage location of the software and related documentation, responsible or contact person.

Records on hardware configuration, installation, and changes (incl. software updates) were kept for Agilent associated with the OpenLab software system, which was component of test equipment. Electronic data was protected from unauthorized access.

SOP Agilent OpenLab software system and SOP for Waters Empower software system were available and discussed. Computer-generated, time-stamped audit trails for electronic records were maintained.

Electronic data was backed up at appropriate regular intervals according to a documented procedure.

Management of computer hardware and software, including the integrity and confidentiality of the input and collection, storage, transmission, and processing of data, was described in procedure Ensuring Data Integrity and Validation of computerized systems.

Personnel

According to the LIF Almaty Territorial Branch employed employees ninety five (95) analytical and support staff responsible for providing quality testing services to the medical and pharmaceutical control committee of the Ministry

of Health to support registration, market authorizations, lot release, and continuous quality monitoring of medicines and related products. TC itself employed thirty eight (38) technical and supportive staff members.

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

Job description of the Head of physico-chemical laboratory was checked.

Staff training was explained in two instructions. An experienced analyst should accompany new staff. The staff's ability to perform analytical testing was evaluated through a competency verification process for each method. Before analyst was qualified for a work, he/she was given to analyze already analyzed sample, RSD between test results was specified. The competency matrix and signature specimens were available. The frequency of re-evaluation of the staff competency was specified in training schedule. Training schedule for 2024 was available and presented.

5. Premises

The laboratory facilities were of suitable size and design to suit the functions and to perform the operations to be conducted in them.

Adequate storage facilities/places 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 (-70°C). The environmental conditions of these rooms were monitored and controlled.

Access to the laboratory facilities was restricted to designated personnel. The Laboratory's layout was available.

Microbiological laboratory premises were separated from physico-chemical laboratory. Endotoxin tests were carried out in separated, dedicated room under LAF.

Laboratory premises were seen clean and well maintained.

6. Equipment, instrument, and other devices

The laboratory had the required test equipment, instruments, and other devices for the correct performance of the tests and/or calibrations, validations, and verifications within the scope of its activities, including the preparation of samples and the processing and analysis of test and/or calibration data. Laboratory equipment and instruments were appropriately labelled.

7. Contracts

The Laboratory had a procedure for selecting service providers using a centralized Purchasing department. Purchasing of external goods and services was explained in SOP. The Purchasing department was responsible for supplying orders to the state units through a digital portal. The TC was only accountable for providing descriptions of design and materials related to the service providers and supplies. Procurement of goods was done on government level, following government legislation. A list of service providers that should not be used due to non-compliance was available in the government portal.

The Laboratory had not subcontracted any testing at the time of inspection.

8. Reagents

The reagents used were of appropriate quality and correctly labelled. Labels of reagent contained information about content, manufacturer, date of opening of the container, concentration, if applicable, storage conditions, expiry date, and retest date, as justified.

Reagent solutions prepared in the laboratory contained information about the name of the reagent, date of preparations and initials of technician or analyst, expiry date or retest date, as justified, and concentration, if applicable.

Volumetric solutions prepared in the laboratory were labelled with the name, molarity, date of preparation and technician initials, date of standardization and technician initials, and standardization factor.

Water quality was regularly verified to ensure that the various grades met the appropriate specifications. Laboratory used purified water and HPLC grade water.

HPLC grade water was generated by MilliQ system and use for preparation of mobile phases and sample preparations.

Purified water was generated by Elix system. Purified water was used for reagents/solutions preparation and rinsing of laboratory glassware after cleaning.

Purchasing of external goods and services was explained. TC was responsible for planning of goods and services purchasing for branches in Karaganda and Taraz. Goods and services were purchased by branches themselves.

Handling of reagents was explained. Data safety sheets were available for all reagents. Reagents were distributed to the laboratories upon request.

9. Reference substances and reference materials

The reference standards were provided by the applicant together with the respective certificate of analysis, already labelled. The Laboratory labelled the RS containers with an internal ID.

SOP Handling of reference standard was checked. To improve accountability of reference standards additional aisles: quantity of the incoming reference sample and quantity of the reference sample after analysis were introduced to the logbook.

The following information was kept on validated excel spreadsheet as a register of all reference substances:

- Identification number
- Name
- Source
- Storage conditions
- Amount
- Lot number
- Assay (when applicable)
- Ware content
- Expiry date

- CoA
- Date of receipt
- Application number
- Sample name
- Sample identification number
- Name of the person who received the RS
- Intended use

The identification number was recorded on the analytical worksheets whenever the reference substance was used.

10. 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. The equipment qualification program covering the internal and external qualifications were available.

Equipment management was explained in SOP. Laboratory equipment internal calibration and preventive maintenance was carried out by the Maintenance department. Laboratory equipment calibration was performed following EDQM guidelines. In case EDQM guidelines were not available, calibration SOPs were prepared. Equipment calibration, qualification and preventive maintenance schedules were available and presented for 2023 and 2024.

Balances were checked daily using internal calibration and three standard weights covering balance range. Requalification was performed annually by Maintenance department and an external body.

Instrument 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. Usage of the instrument was recorded.

Qualification of the new US-visible Mettler Toledo was checked.

SOP Chromatography column management was available. Upon receiving the new column, verification was carried out following EDQM guidelines. Annual column qualification schedule was available.

SOP Laboratory glassware management was available. Laboratory used only class A volumetric glassware for volumetric analysis.

Traceability
Test results were traceable to reference substances when applicable, equipment, instruments and reagents used.

11. Incoming samples
The laboratory was not responsible for sampling of products.

Samples were collected and sent to the TC by three authorities depending on the source of samples:
The samples provided through registration and variation applications were sent to the Applicant Service center located at Abylaikhan avenue, 63, Almaty, Kazakhstan. The Marketing Authorization applicant or distributors provided the samples to:

- Pharmacy committee (in case of dubious products)

- Other medical centers (in case of counterfeit products).

Sample management procedure explained:
- Incoming samples: receipt, registration, distribution
- Retain samples
- Samples for destruction

There were two forms of test requests which accompanied each sample submitted to the laboratory:
- Marketing authorization samples
- Market surveillance samples
- Doubt samples from the market
- Inter-laboratory samples
- Eurasian Economic Union economical union samples

Initially samples were received at Applicants service center and collected by responsible person for samples receiving unit. Incoming samples were manually registered in the sample logbook. Unique identification was assigned to every sample received and traceable through all documentation.

There were two forms of test requests which accompanied each sample submitted to the laboratory:
- Marketing authorization samples
- Market surveillance samples

The test requests were reviewed by the Head of Physical-Chemistry laboratory to ensure that the laboratory had the resources to meet the request target and that the selected tests/methods were capable to meet the applicable requirements.

All delivered samples and enclosed documents were assigned a registration number. The samples were registered in the respective logbook in chronological order. A register was kept in which the following information was recorded: All delivered samples and enclosed documents were assigned a unique registration number. The samples were registered in the respective logbook in chronological order. A register was kept in which the following information was recorded:
- Registration number of the sample
- Date of receipt
- Application number
- Type of sample
- Sample name
- Manufacturer
- Country of manufacturing
- TC ID number
- Expiry date
- Storage conditions
- Discretion of the sample
- Quantity in total
- Unit to which the sample was forwarded

- Quantity distributed to the units
- Date of distribution
- Signature of person who collected the sample
- Date of test report

Person from the Procurement Division, responsible for receiving samples, performed a visual inspection to ensure that labelling conformed with the information in the test request at the Applicant Service Center. The required shipment conditions were monitored by using data logger.

Prior to testing, the samples were stored safely, taking into account the storage conditions for the sample in the locked cupboards. The required quantity of samples needed for testing was sent to the branch together with the test request by applicant service center in Astana. After the completion of the analysis, the remaining samples were returned to the sample storage area and documented on the respective form to be retained with the rest of the samples in another storage area on the first floor for further transfer for utilization.

Upon arrival to the TC, responsible person for sample handling checked all information delivered together with the sample. Afterwards samples were moved to specific storage places. Access to the sample storage places was restricted to responsible person.

Storage
The samples were stored safely, taking into account the storage conditions. The storage conditions, including temperature and humidity were monitored using a calibrated thermometer and psychometer. Samples were returned to the storage after the completion of the analysis.

12. Analytical worksheet
Procedure Records management in laboratory was checked. Procedure was applicable, but not limited to:
- Analytical worksheets
- Log books
- Spreadsheets
- Test reports

The analysts recorded information about samples, test procedures, calculations, and results in analytical worksheets completed with raw data, except for endotoxin tests. Endotoxin tests results were recorded in laboratory logbook. Practice in the laboratory was that one analyst carried out all required tests.

The worksheets contained the following information:
- The date on which the analysis was started and completed;
- Information about received samples (quantity, batch number and etc.);
- A reference to specifications and full description of the test methods, by which the sample was tested, including the limits; identification of test equipment used; reference substances, reagents, and solvents employed
- Documentation called normative document with the respective specification for testing was available for each medicine. For registration samples, all the tests should be performed
- Interpretation of the results and calculations
- The conclusion whether or not the sample was found to comply with the specifications
- Deviation from the prescribed procedures, if any

The completed analytical worksheets were signed by the responsible analyst and verified, approved, and signed by another analyst and then by Head of Laboratory.

Analytical worksheets (WS) were purchased preprinted. Each individual worksheet had unique identification number. Upon arrival WS were checked for correct ID numbers. Worksheets were issued by Head of physico-chemical laboratory and register in logbook.

13. Validation of analytical procedures

The procedures employed for testing were submitted by the applicant and verified by the assessors in the National normative standard pharmacopeia. The Laboratory did not perform any method validation.

The method verification policy was described. Method verification was carried out every time laboratory performed the test.

14. Testing

Test procedures were described in the respective normative document and allowed analysts to perform the analysis in a reliable manner.

During the course of inspection inspectors followed sample of Ketoralak tablets 10 mg. The following tests were performed and cross checked with test results and equipment used:

- Identification by HPLC
- Total impurities by HPLC
- Assay by HPLC and UV

15. Evaluation of test results and OOS investigation

SOP Evaluation of results outside the requirements of specifications was in place describing the conduct of investigations of OOS test results. OOS were registers were paper and laboratory based. When a doubtful result (suspected OOS result) was identified, the supervisor and the analyst undertook a review of the procedures applied during the testing process. Investigations were carried out according to phase 1A: Obvious lab error, 1B: lab investigations using check list, to establish laboratory error or not, hypothesis testing and Phase II: retesting.

The laboratory issued analytical test reports based on information recorded in analytical worksheets. Test reports were checked by the Head of laboratory and finally approved by the Head TC.

Procedure for Test results was checked. Tests were recorded on analytical worksheets. Initially all test results and calculations were checked by another analyst, afterwards records, test results and calculations were checked and approved by the Head of laboratory. Procedure also explained rounding of results and dealing with borderline results. According to the procedure once in a quarter selective control was performed by Specialist QA choosing full document package.

Calculations were done using hand calculators and validated excel spreadsheets. List of validated spreadsheets was available and presented. Spreadsheets names were linked to the test methods. These spreadsheets were saved on server.

Spreadsheets all cells, including calculations, were locked so that formulas could not be accidentally overwritten. Free access was only given to cells to be filled in with data. Calculation algorithms were tested with another validated

software or by a pocket calculator. A known dataset was used for the verification of the software. A screenshot of the Spreadsheets spreadsheet used for calculation was provided as evidence and kept with the rest of the respective analytical sheets. The sheets were made available in a secured directory on the server with a specific path number on the computers used to evaluate analytical results. The spreadsheets were version controlled, and only the valid ones were available for the analysts.

Validation of spreadsheets was explained. Validated spreadsheets were approved by QA. In case spreadsheet is updated or the new spreadsheet introduced: information emails were sent out to all staff members.

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
- The statement whether the sample complies with the requirements

SOP Assessing borderline results was available and checked.

16. Certificate of analysis (The test report)
- The test report was also used as certificate of analysis to be sent to the "Department of specialized Expertise" located in the Head office in Astana. The following information was captured in the test report:
- Sample ID number
- Name of the customer
- Type of analysis
- Reason for analysis
- Manufacturer
- Lot number
- Manufacturing date
- Expiry date
- Number of samples
- The date on which the tests were started and completed
- Normative documents
- STP
- Test results
- A conclusion as to whether or not the sample was found to be within the limits of the specification

17. Retained samples
Retained samples were kept in their final pack and retained as specified, depending on the type of sample. Marketing authorization samples were kept 1 months after Testing report. In case of OOS samples were kept for 3 months.

In case samples would be received on behalf of WHO retention time was specified:
- Expiry date + 1 year or 5 years which is longer

18. Safety
Staff was wearing laboratory coats. Safety showers were installed. Rubber suction bulbs were used on manual pipettes. Safety data sheets were available.

Miscellaneous	
Assessment of the Laboratory Information File	The uncontrolled English version of the Laboratory Information File was submitted for WHO prequalification.
Annexes attached	N/A

PART 3 - CONCLUSION

Based on the areas inspected, the people met and the documents reviewed **The Testing Center of the Territorial Branch of the Republic State Enterprise on the Right of Economic Management "National Center for Expertise of Medicines and Medical Devices" Medical and Pharmaceutical control committee of the Ministry of Healthcare of the Republic of Kazakhstan in Almaty City,** located at **Baitursynov Street 40A Almaty, Kazakhstan** was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories.

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
https://www.who.int/publications/m/item/trs957-annex1

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
https://www.who.int/publications/m/item/trs961-annex2

3. 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
https://www.who.int/publications/m/item/annex-4-trs-929

4. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4

https://www.who.int/publications/m/item/annex-4-trs-1033

5. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight 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
https://www.who.int/publications/m/item/trs986-annex2

6. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
Short name: WHO TRS No. 957, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-957

7. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
Short name: WHO TRS No. 957, Annex 3
https://www.who.int/publications/m/item/trs957-annex3

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
Short name: WHO TRS No. 961, Annex 6
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex6-gmp-sterile-pharmaceutical-products.pdf

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
Short name: WHO TRS No. 961, Annex 7
https://extranet.who.int/prequal/sites/default/files/document_files/TRS_961_Annex7_2011.pdf

10. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 96, Annex9)
Short name: WHO TRS No. 961, Annex 9
https://www.who.int/publications/m/item/trs961-annex9modelguidanceforstoragetransport

11. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3

Short name: WHO TRS No. 943, Annex 3
https://www.who.int/publications/m/item/trs943-annex3

12. Guidelines on heating, ventilation, and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8
Short name: WHO TRS No. 1010, Annex 8
https://www.who.int/publications/m/item/Annex-8-trs-1010

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.
Short name: WHO TRS No. 981, Annex 2
https://www.who.int/publications/m/item/trs981-annex2

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3.
Short name: WHO TRS No. 981, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-981

15. WHO guidelines for preparing a laboratory information file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series, No. 961, 2011, Annex 13.
Short name: WHO TRS No. 961, Annex 13
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs961-annex13-guidelines-preparing-laboratory-information-file.pdf?sfvrsn=54d1f397_2

16. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4.
Short name: WHO TRS No. 992, Annex 4
https://www.who.int/publications/m/item/trs992-annex4

17. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature–sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5.
Short name: WHO TRS No. 992, Annex 5
https://www.who.int/publications/m/item/trs992-annex5

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
https://www.who.int/publications/m/item/trs1010-annex10

19. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
Short name: WHO BE guidance or TRS996 Annex 9
https://www.who.int/publications/m/item/annex-9-trs-966

20. Guidance for Good chromatography practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-fourth report, (WHO Technical Report Series, No. 1025, 2020), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications/m/item/trs1025-annex4

21. Good manufacturing practices: guidelines on validation (adopted, subject to the changes discussed by the Expert Committee - WHO Technical Report Series, No. 1019, 2019)
Short name: WHO TRS No. 1019, Appendix 3
https://www.who.int/publications/m/item/trs1019-annex3

22. WHO model certificate of analysis (WHO Technical Report Series, No. 1010, 2018)
Short name: WHO TRS No. 1010, Annex 4
https://www.who.int/publications/m/item/trs1010-annex4

23. Good manufacturing practices: water for pharmaceutical use (WHO Technical Report Series, No. 1033, 2021)
Short name: WHO TRS No 1033, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-1033

24. Guidelines on pre-approval inspections (WHO Technical Report Series, No. 902, 2002, Annex 7)
Short name: WHO TRS No 1033, Annex 7
https://www.who.int/publications/m/item/trs902-annex7

25. Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (WHO Technical Report Series No. 1003, 2017)
Short name: WHO TRS No 1033, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-1003