

**Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Quality Control Laboratory**

Part 1	General information		
Inspected laboratory details			
Name of Laboratory	Republican Control and Analytical Laboratory (RCAL) of the Republican Unitary Enterprise Centre for Expertise and Testing in Health Care Ministry of Health of the Republic of Belarus		
Address of inspected laboratory site	83 Dzerzhinsky Avenue (8 th Floor) 220045 Minsk Republic of Belarus		
Inspection details			
Dates of inspection	05-07 December 2018		
Type of inspection	Routine		
Introduction			
Brief description of testing activities	Type of Analysis	FPP	API
	Physical/ Chemical Analysis	pH, density, refractive index, optical rotation, water content, conductivity, residual solvents, limit tests, friability, disintegration, dissolution, uniformity of dosage units	pH, refractometry, refractive index, optical rotation, viscosity, melting point, loss on drying, water content, heavy metals, residual solvents and limit test
	Identification	HPLC (UV-Vis, DAD, RI, detection), GC, TLC, UV-VIS spectrophotometry, IR	HPLC (UV-Vis, DAD, RI, detection), GC, TLC, UV-VIS spectrophotometry, IR
Assay, impurities and related substances	HPLC (UV-Vis, DAD, RI, detection), GC, TLC, UV-VIS spectrophotometry, volumetric titrations	HPLC (UV-Vis, DAD, RI, detection), GC, TLC, UV-VIS spectrophotometry, volumetric titrations	

General information about the laboratory	The Republican Control and Analytical Laboratory (RCAL) was under the supervision of the Republican Unitary Enterprise Centre for Expertise and Testing in Health Care which was established in 1997. This structure comprised of several laboratories and services including the Laboratory of Pharmacopoeial and Pharmaceutical Analysis and the Republican Clinical and Pharmacological laboratory. All three laboratories were housed on the 7 th and 8 th floor of a multipurpose building. RCAL was officially transferred on the 8 th floor of this building on 23 April 2018. The new facilities included an HPLC laboratory as well as a wet chemistry and instrumentation laboratories. Under new legislation which became effective on 16 th November 2018, RCAL became responsible for conducting sampling and testing of products on the market. The laboratory was accredited in accordance to national standard STB ISO/IEC 17025-2007. RCAL participated in the project of the European Commission BELMED which aimed at promoting the modernization of the healthcare system, adaptation of the main laboratories for testing medical products to international standards, prevention of non-communicable diseases and the promotion of healthy lifestyle. As part of this project RCAL had started upgrading its Quality System to meet ISO 17025:2015 standards.
History	This was the third WHO inspection. The previous WHO inspection was carried out during 13-14 May 2014. The laboratory was also inspected in 2018 by Republican Unitary Enterprise «Belarusian State Accreditation Center» (State Enterprise «BGCA») in relation to the national standard STB ISO/IEC 17025-2007.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Quality Management System including Management Review, Quality Assurance and complaints Personnel Training and Safety Documentation and Records, including sample processing and OOS handling Premises and Equipment, including calibration Validation – Qualification of computerized systems Validation of analytical methods Evaluation of test results Laboratory Practices Reference standards – Reagents – Water
Restrictions	Not applicable
Out of scope	The laboratory did not have a section for microbiological tests.

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
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 the findings and comments
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1. Organization and Management

The laboratory (RCAL) was transferred to its new premises in April 2018. Due to a change in legislation which in turn changed the scope and focus of the laboratory and because of the European Commission's project (BELMED) which aimed at modernizing and adopting national laboratories to international standards, RCAL were restructuring their processes, operations and Quality System.

Organizational and managerial structure were defined in organization charts. However, organograms were not up to date due to restructuring of the laboratory. The laboratory had managerial and technical personnel with the authority and resources needed to carry out their duties. There were weekly management review meetings, but they were not documented. The laboratory had planned to ensure that its management and personnel were not subject to commercial, political, financial and other pressures or conflicts of interest that might adversely affect the quality of their work. Each member of staff had to annually sign a conflict of interest declaration.

The laboratory had a policy in place to ensure the confidentiality of information included in marketing authorizations and test reports. Appropriate CAPA for all observations regarding organization and management were implemented and were considered adequate

2. Quality management system

The laboratory had established, implemented and maintained a quality management system according to the national standard STB ISO/IEC 17025-2007. A Quality Manual defining the principles of the QMS was available but due to on-going changes and weak documentation practices it did not fully meet WHO GLP standards

According to the QM, there were four levels of documentation:

- Quality system's Policies and goals
- QM
- SOPs
- Working Instructions

The policy was endorsed by senior management as part of the QMS. The distribution list for the QM and the respective training documentation were available and reviewed.

Operations and activities of the laboratory were systematically and periodically audited by the QA-Unit, using appropriately trained and qualified staff.

Audit plans for 2017 and 2018 together with the audit report for November 2018 and the process for recording and handling of CAPA plans and evaluation of their effectiveness were reviewed.

3. Control of documentation

All laboratory documentation was in Belarusian. The laboratory established and maintained a system of procedures to control all documents (preparation, revision, distribution, return, archiving) in a proper manner. A list of SOPs identifying the current version status and distribution of documents was available. Each controlled document had a unique identifier, version number and date of implementation. The documents were released by the Head of QA and Head of laboratory and were available at the relevant location. A database (Automated Information System – AIS RCAL) that included several modules, was used for registering laboratory operations and monitoring activities.

4. Records

In general, records to different laboratory operations were created and archived including but not limited to analytical tests, calculations and derived data, instrument use, calibrations and maintenance. Different modules were established in AIS-RCAL database for registering training sessions and plans, recording audits and CAPAs, maintaining the inventory of reference standards and tracing receipt and analysis of samples. Nevertheless, all records were also maintained as hard copies including OOS investigations and complaints.

The procedure for record control and management was briefly discussed. Records were provisionally kept in locked cupboards at the site for one year prior to their transfer to an offsite archive facility. The offsite facility was managed by the Center for Examination and Tests in Health Service as well as the transportation of records. Documentation were archived for 5 years without considering the maximum shelf-life of the pharmaceutical products. The access to archived documentation was restricted to authorized personnel.

5. Data processing equipment

An inventory of all computerized systems was available with information on unique identification, purpose, validation status. The organization had developed a database called Automated Information System (AIS-RCAL) which was tailor made to laboratory operations, consisting of modules for recording information on sampling documentation, training of staff, CAPA plan, deviations, reference standards, chromatography columns, instrument service including calibration of device, water purification etc. The computerized system was briefly demonstrated. All staff had access to AIS with different access rights which were defined in the applicable SOP.

SOP for management and control of the computerized system configuration when new software was installed, or a version update, was available.

Electronic data from standalone laboratory work stations and instruments were transferred to a server located in a secure area of the building, by using an external portable hard drive. The original data on work stations' hard drives was deleted after transfer was completed. Chromatograms and pertaining data were printed out, signed, checked and approved before becoming part of the analytical record. The results of the analyses were entered in AIS-RCAL. No spreadsheets were used for calculations. The laboratory had established validated software for performing the necessary calculations. Printouts were checked, signed and approved

It was noted that there were standalone workstations operating on Windows XP. These work stations were not connected to analytical equipment, but they were connected to AIS-RCAL database. The laboratory should consider and assess the risk of security bridging since this operating system is not supported by Microsoft anymore.

6. Personnel

The total number of staff accounted to 30 at the time of inspection, including 14 analysts. All staff were based on permanent contracts and had the necessary education, training, technical knowledge and experience for their assigned functions. Responsibility, authority and interrelationship of personnel was specified in their job descriptions and the respective SOP. The laboratory maintained up to date job descriptions for all personnel. The job description of the QA manager was reviewed. The template was signed and dated by both the supervisor and the incumbent.

Laboratory roles were categorized in the applicable SOP and staff received the respective training based on their role category. Training of personnel on new or revised SOPs took place according to the procedure for training which was made available. Furthermore, there was a list of applicable staff annexed to the end of each procedure which was described in the SOP for SOP. Presence of staff in training sessions was documented by their signature. However, a training matrix for SOP training was not available. As part of the BELMED project personnel attended external training provided at EDQM premises in Strasbourg.

7. Premises

The laboratory facilities were new and of appropriate size and design to serve the functions and to perform the operations to be conducted in them. Environmental conditions were monitored, and the facilities were kept clean and tidy. Separate storage facilities were maintained for secure storage of samples, retained samples, reagents, laboratory accessories and reference substances, if necessary, under refrigeration (2-8 °C) and deep freeze (-20 °C & -8 °C) temperatures. Samples and retained samples were initially kept together in a sealed plastic box. They were separated after completion of testing. Retained samples were stored for three months and then they were either discarded or donated to hospitals under a written protocol. The laboratory facilities were accessed by a key card and the use of access cards were restricted to designated personnel. The physico-chemical laboratory consisted of several separate rooms, including rooms for balances, HPLC equipment, sample handling and a room for other analytical equipment and storage of samples and reagents in proper conditions. The laboratory was equipped with three refrigerators and two freezers.

8. Equipment, instruments and other devices

Equipment, instruments and other measuring devices used for testing, calibrations, validations and verifications were suitable for use as they met relevant standard specifications. They were qualified and/or calibrated regularly either internally or by external national institutes. RCAL was transferred to its new premises in April 2018 and as a result all equipment had to be reinstalled and in certain occasions reassembled before being reinstalled. Reassembly and reinstallation as well as requalification was carried out by a third party. A contract was available. A plan for equipment requalification was presented. Four standalone Agilent HPLCs running on Chemstation (Rev B04.03) software were installed in a chromatography dedicated room. An NIR instrument was available but no library had been established since equipment was new and it had not been used. Qualification of the IR equipment was presented, and the certificate of the polystyrene film used for calibration was made available. PQ of HPLC was performed by laboratory personnel and spot checks on the calibration and qualification of the column oven and the flow rate accuracy were made. It was noted that there was no appropriately installed balance dedicated to weighing hazardous substances, but the laboratory had already planned for the installation. Class A volumetric glassware was used in the laboratory.

9. Contracts

In general, there was no subcontracting of testing. Resources and equipment of laboratories of the Republican Unitary Enterprise Centre for Expertise and Testing in Health Care were available for conducting any analyses that could not be carried out by RCAL (e.g. periodic microbiological testing of PW). HPLC equipment re-installation and requalification was contracted out and the laboratory had established contracts for these activities.

10. Reagents

In general, reagents used in the laboratory were of appropriate quality and correctly labelled. The laboratory maintained an inventory for reagents; their stocks were monitored. Solutions prepared in the laboratory were labeled and stored appropriately; preparation records were available. Spot checks on labels of HPLC mobile phase solutions and buffers were made.

Water purification equipment (Thermo scientific Gen Pure) using reverse osmosis, was installed in the laboratory. There was no water loop installed. Two types of water were generated:

- Purified Water
- Water for Chromatography.

Conductivity, pH, oxidizable substances tests were carried out in-house. Microbiological tests were carried out by another laboratory of the Republican Unitary Enterprise Centre for Expertise and Testing in Health Care. The calibration of conductivity meter was reviewed.

11. Reference substances and reference materials

Reference substances were used. According to the system established by the laboratory, the manufacturer or importer of the product to be tested, was responsible for providing the standards and supportive documentation. In rare occasions working standards provided from the manufacturers were used. Reference standards were registered in AIS-RCAL database and their use was monitored. They were stored and used in a manner that did not adversely affect their quality. Official, pharmacopoeial standards were used for the purposes described in the corresponding monographs.

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

Each instrument was uniquely identified by labels with information about the status of the calibration and the date when recalibration was due. Seven balances were checked daily using internal calibration, using suitable test weights. Additionally, the balances were calibrated by external authority, i.e. BeLGIM (Belarussian State Institute of Metrology) to verify the linearity, accuracy and precision of instruments. The eccentricity was carried out by the laboratory according to the instruction provided by BeLGIM. Records of equipment were maintained in AIS-RCAL database including maintenance and calibration. The manufacturer's manuals were available.

13. Traceability

Test results were traceable to equipment use and calculations made in the database. Test results from worksheets were transferred to the database after hard copies were checked and approved

Standard equipment used for internal calibrations (e.g. stopwatch, thermocouple) were appropriately stored and certificates were available.

14. Incoming samples

Under the new legislation implemented on 16 November 2018, RCAL was made responsible for conducting sampling and testing of medicinal products on the market. A database belonging to the Ministry of Health was used to risk rank products and derive the sampling plan. RCAL was responsible for evaluating one risk category and include the results in the database. The final sampling plan was established and approved by the Ministry of Health.

Sampling was carried out by laboratory representatives according to a written protocol. The quantity of collected samples allowed for at least two rounds of testing. In addition, another quantity of the sampled product/batch was quarantined at the manufacturer/importer to be used in case of dispute. Samples were sealed in a plastic box and a copy of the sampling protocol was given to the manufacturer/importer. Although the laboratory could collect samples from hospitals and pharmacies, samples were only collected from manufacturers and importers.

Upon receipt of the samples at the laboratory they were registered in the AIS-RCAL database and then transferred to a closet where they were kept under lock and key, considering the storage conditions of the samples. Temperature sensitive products were immediately transferred to a refrigerator. A test request accompanied each sample and contained the adequate information.

- description of the sample,
- specification to be used for testing,
- required storage conditions.
- MSDS
- Manufacturer's certificate of analysis

The traceability of samples from receipt, throughout the stages of testing, to the completion of the analytical test report was ensured through AIS-RCAL database. The following information was recorded:

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

The samples were assigned to a specific analyst together with the test request by the laboratory supervisor. The execution of the testing of the samples was based on "First in- First tested" arrangement. Visual inspection of samples was carried out by the laboratory staff to ensure that labelling conformed with the information contained in the 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. Calculations were verified and signed by the laboratory supervisor before being recorded in the database. The records in the database were then printed out, reviewed and approved by the Head of the laboratory. All graphical data 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 Head of the laboratory.

16. Validation of analytical procedures

System suitability tests were employed prior to analytical tests for verification of pharmacopoeial methods. Belarusian Pharmacopoeia monographs and E.Ph monographs were used by the laboratory unless indicated otherwise. However, it was not considered that these monographs relate to active substances and not FPPs and as a result appropriate validation was not carried out. In case of modified compendial methods there was no provision for method transfer and verification. When pharmacopoeial methods were used for FPP for the first time, it was not demonstrated that no interferences arose from the excipients present in the formulation. Appropriate CAPA were applied following the inspection.

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. Test results were recorded in analytical work sheets and entered in the AIS after review of the laboratory supervisor and Head of the laboratory.

The laboratory participated in both national and international proficiency testing schemes. All analytical qualitative and quantitative methods were planned on a rotational basis, within 5 years, to be qualified by proficiency testing schemes. The laboratory used different qualified analysts when participating in the proficiency testing of the same method. The annual scheme for 2018, dated December 2017 was reviewed as well as the results of proficiency tests carried out in 2017

18. Evaluation of test results

An SOP was in place describing registration and investigation of OOS results, but it did not fully meet current standards. The laboratory revised the procedure and applied appropriate CAPA following the inspection.

19. Certificate of analysis

Following completion of the analytical work, review and approval by the Head of the laboratory a certificate of analysis was issued. The certificate included test results and established specifications and it was appropriately dated, signed and approved

20. Retained samples

Retained samples were not kept separated from testing samples, upon their receipt. After completion of testing, the remaining samples were kept in their final pack and retained as required by the legislation or by the originator of the request.

21. Safety

In general, there were measures in place to safeguard personnel. Protective clothing was available, including eye protection, masks and gloves. Safety showers were installed. Rubber suction bulbs were used on manual pipettes and siphons. Staff were instructed in the safe handling of glassware, corrosive reagents and solvents and particularly in the use of safety containers or baskets to avoid spillage from containers. MSDS were available to staff together with the rest of documentation for incoming samples

Part 3	Conclusion – Inspection outcome
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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, ***Republican Control and Analytical Laboratory (RCAL)*** located at ***83 Dzerzhinsky Avenue, 220045 Minsk; Republic of Belarus*** 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 5	List of WHO Guidelines referenced in the inspection report
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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 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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
7. 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**
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
8. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
9. 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
10. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
<https://www.who.int/publications-detail/978-92-4-000182-4>

11. WHO Guidelines for preparing a laboratory information file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 2011), Annex 13.

Short name: WHO TRS, Annex 13

http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparingLaboratoryInformationFileTRS961Annex13.pdf?ua=1TRS%20961:%20Annex%2013:%20WHO%20guidelines%20for%20preparing%20a%20laboratory%20information%20file