# WHO PUBLIC INSPECTION REPORT

## Quality Control Laboratory

### Part 1: General information

<table>
<thead>
<tr>
<th>Name of the QC Laboratory</th>
<th>Testing Centre for Evaluation of Medicinal Products Quality of the Federal State Budgetary Institution “Scientific Centre for Expert Evaluation of Medicinal Products” of The Ministry of Health of The Russian Federation (FSBI “SCEEMP”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical address</td>
<td>Schukinskaya street 6, building 1, Moscow 123182, Russia</td>
</tr>
<tr>
<td>Date of inspection</td>
<td>16 – 20 May 2016</td>
</tr>
</tbody>
</table>
| Type of inspection        | Inspection of additional five laboratories:  
  - *Laboratory for Control and Coordination*  
  - *Microbiology Laboratory*  
  - *Laboratory of Biotechnological Products*  
  - *Laboratory of Nano-medicines, Cell and Gene Therapy Product*  
  - *Laboratory of Vitamins, Hormones and Synthetic Analogues* |
| Type(s) of testing included in the inspection | Chemical, physical, microbiological |

### Summary of the testing activities performed by the QC Laboratory

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physico – Chemical analysis</td>
<td>pH, density, refractive index, optical rotation, water content, loss on drying, residual solvents, limit tests, disintegration, dissolution, uniformity of dosage units (mass, content)</td>
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</tr>
<tr>
<td>Identification</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC , TLC, UV-VIS spectrophotometry, IR, basic tests</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC , TLC, UV-VIS spectrophotometry, IR, basic tests</td>
</tr>
<tr>
<td>Assay, impurities and related substances</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC (FID, TCD), UV-VIS</td>
</tr>
</tbody>
</table>
Part 2: Summary

General information about the laboratory and site
The main function of the Testing Centre is evaluation of medicinal products’ quality pursuant to the tasks assigned to it by the Ministry of Health of the Russian Federation in accordance with the Federal Law 61-FZ of 12.04.2010 “On circulation of medicines” as amended, other orders of the Ministry of Health, as well as other laws and regulations of the Russian Federation, and local normative acts governing the activities of the FSBI “SCEEMP”.

The FSBI “SCEEMP” is formed of 4 expert divisions: the centre for finished pharmaceutical products evaluation, the centre for evaluation and control of medicinal immunobiological products, the testing centre for quality evaluation of medicinal immunobiological products, and the testing centre for medicinal products quality evaluation.

The Testing Centre for Medicines Quality Evaluation was formed of the following 10 laboratories:
- Control and coordination laboratory
- Laboratory of antibiotics (European directorate for the quality of medicines (EDQM, WHO)
- Laboratory of chemico-pharmaceutical preparations № 1
- Laboratory of chemico-pharmaceutical preparations № 2 (EDQM, WHO)
- Laboratory of nano-medicines, cell-therapy and genetic therapy products.
- Laboratory of biotechnological products
- Laboratory of herbal medicinal products and homeopathic medicines
- Laboratory of vitamins, hormones and synthetic analogues
- Pharmacology laboratory
- Microbiology laboratory
- Laboratory for control of radiopharmaceuticals and radiopharmaceutical reagent kits

The inspection’s focus was on the following laboratories:

Laboratory for Control and Coordination
Control and coordination laboratory is responsible for organizational and methodological support of the process of medicinal products’ evaluation; for receiving drug samples; and performing gas-liquid chromatography (GLC) testing. The laboratory had the following groups:
- Group responsible for control and coordination
- GLC sector
Microbiology Laboratory
Microbiology laboratory is responsible for performing microbiological testing of medicines as part of the process of their authorization. The laboratory had the following groups:
✓ Group responsible for preparatory work
✓ Group responsible for microbial quality testing
✓ Group responsible for sterility testing

Laboratory of Biotechnological Products
Laboratory of biotechnological products is responsible for evaluation of biotechnological products, genetically engineered products, blood substitutes and other groups of medicines as part of the process of their authorization. The laboratory had the following groups:
✓ Group responsible for HPLC
✓ Group responsible for general chemistry
✓ Group responsible for atomic absorption spectrometry
✓ Group responsible for receiving and distributing drug samples that are submitted for evaluation
✓ Technical group

Laboratory of Nano-medicines, Cell and Gene Therapy Product
Laboratory of nano-medicines, cell-therapy and gene-therapy products was responsible for qualitative and quantitative chemical analysis of medicines by NMR-spectroscopy, mass-spectroscopy, gas and liquid chromatography and atomic emission spectroscopy. The laboratory had the following groups:
✓ Group responsible for HPLC and mass-spectrometry
✓ Group responsible for elemental analysis and NMR
✓ Group responsible for cell-therapy and gene-therapy products

Laboratory of Vitamins, Hormones and Synthetic Analogues
Laboratory of vitamins, hormones and their synthetic analogues is responsible for evaluation of medicines that are classified as vitamins, hormones and their synthetic analogues according to their structure or pharmacological action and related chemicals and pharmaceuticals as part of the process of their authorization. The laboratory had the following groups:
✓ Group responsible for chemistry
✓ Group responsible for atomic absorption spectrometry
✓ Group responsible for receiving and distributing drug samples that are brought to the laboratory for evaluation

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Laboratory for Control and Coordination (hereinafter referred to as the LCC) with a Gas Chromatography Sector (hereinafter referred as the GLC Sector)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical/chemical analysis</td>
<td>Gas chromatography</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>Identification</td>
<td>Gas chromatography</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>Assay, impurities and related substances</td>
<td>Gas chromatography</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>The Microbiology Laboratory (MB)</td>
<td>tests MPs for sterility and microbiological quality, including sub-visible mechanical particles</td>
<td></td>
</tr>
<tr>
<td>Physical/chemical analysis</td>
<td>Sub-visible mechanical particles</td>
<td>Sub-visible mechanical particles</td>
</tr>
<tr>
<td>Microbiological tests</td>
<td>Microbiological enumeration test</td>
<td>Microbiological quality</td>
</tr>
<tr>
<td>The Laboratory of Biotechnological Products (BTP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical/chemical analysis</td>
<td>Potentiometry</td>
<td>Solubility</td>
</tr>
<tr>
<td>Identification</td>
<td>Solubility</td>
<td>Dissolution</td>
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</tr>
<tr>
<td>Assay, impurities and related substances</td>
<td>UV-spectrophotometry</td>
<td>IR-spectrophotometry</td>
</tr>
<tr>
<td>The Laboratory of Nano medicines, Cell and Gene Therapy Products (NP)</td>
<td>UV-spectrophotometry</td>
<td>IR-spectrophotometry</td>
</tr>
<tr>
<td>pH, Water content</td>
<td>Loss of drying</td>
<td>Gas and liquid chromatography</td>
</tr>
<tr>
<td>The Laboratory of Vitamins, Hormones and Synthetic Analogues (VH)</td>
<td>UV-spectrophotometry</td>
<td>IR-spectrophotometry</td>
</tr>
<tr>
<td>Physical/chemical analysis</td>
<td>Visual examination</td>
<td>Gravimetric analysis</td>
</tr>
<tr>
<td>Identification</td>
<td>TLC</td>
<td>UV-spectrophotometry</td>
</tr>
<tr>
<td>Assay, impurities and related substances</td>
<td>HPLC with electronic laser light scattering detector (ELSD) and diode array detector (DAD)</td>
<td>GC-MS</td>
</tr>
<tr>
<td>Physical/chemical analysis</td>
<td>Visual examination</td>
<td>Gravimetric analysis</td>
</tr>
<tr>
<td>Identification</td>
<td>TLC</td>
<td>UV-spectrophotometry</td>
</tr>
</tbody>
</table>
Similarly to the last WHO inspection, the main function of the five laboratories was to test products, API and excipients as part of product registration using test procedures submitted by either applicants or directly by manufacturers.

**History of WHO and/or regulatory agency inspections**

This was the third WHO inspection of this site. Last WHO inspection was carried out in September 2015 and focussed on Laboratory of chemico-pharmaceutical preparations № 2 and on the Laboratory of antibiotics. This inspection was carried out because the FSBI “SCEEMP” applied for prequalification of additional five laboratories.

The laboratory was also inspected by the EDQM and accredited to ISO/IEC 17025 standard. The accreditation certificate was valid until 2018.

**Focus of the inspection**

The inspection focussed on the quality management system and on the areas of quality control testing prequalified by the WHO.

**Inspected Areas**

The following areas of the WHO good practices for quality control laboratories were covered in this inspection:

- Quality system
- Control of documents
- Records
- Data-processing equipment
- Personnel
- Premises
- Equipment, instruments and other devices
- Reagents
- Reference substances and reference materials
- Calibration, verification of performance and qualification of equipment, instruments and other devices
- Traceability
- Incoming samples
- Analytical sheet
- Validation of analytical procedures
- Testing
- Evaluation of results
- Certificate of analysis
- Retained samples
- Safety
2.1. Organization and management

The organization of the laboratory was defined in an organization charts for all organization and different laboratories.

The Quality Managing System (QMS) reporting scheme was the following: Laboratory QA officer for each of the laboratory → Responsible person for QSM of the testing center (Quality Officer) → Head of the QMS division of the FSBI “SCEEMP” → Deputy General Director for Quality Evaluation (Quality Manager) → General Director.

The QMS division of the FSBI “SCEEMP” of the Ministry of Health of Russia comprised of three departments, namely: implementation of QMS, audit of QMS, and metrological support for equipment qualification and calibration by third party.

The laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in their job descriptions. A Provision on Quality Officers was approved by the General Director. Each Quality officer confirmed reading and acceptance of the Provision by signing in the job description register.

2.2. Quality management system

Management Review (MR)

MR was performed once per year. The last management review was done in April 2016. According to the management review standard operating procedure (SOP) management reviews covered:

• Analytical results and results of internal audits
• Proficiency testing, non-conformances
• Management of quality system records
• Corrective and preventive actions
• Complaints
• Customer responses
• Changes in the work plan
• Staff training
• Resource planning
• Results of the previous management review
• Recommendations to improve the quality system.

MR report was reviewed for 2015; it was very detailed document and contained trends for different subjects as bars and pies from 2011.

Corrective actions

The SOP “Corrective actions” was reviewed during inspection September 2015, no changes. It described two types of corrective actions. Immediate corrective actions and long-term corrective actions were defined along with the responsible persons. The corrective actions had to be approved by the head of the centers.

There was a description of how the corrective actions were performed, starting with the registration of the non-conformity, a registration of the corrective action, drafting and approval of a plan, followed by implementation and evaluation. Efficiency of the corrective action is reviewed, and additional corrective actions are taken if necessary. All the data on
corrective actions performed are listed in the Corrective actions record. Information on nonconformities found, results of analyses carried out, and corrective actions taken is included into a report for management review and Nonconformity register.

**Preventive actions**
The SOP “Preventive actions” was reviewed during inspection September 2015, no changes.

**Internal audits**
Internal audits were performed in accordance with ISO/IEC 17025 and WHO guidelines. Observations and corrective actions, responsible person, timeline and date of completion were documented in the Audit report or Act.

The SOP “Organization and performance of internal audits was reviewed during inspection September 2015, no changes. The plans were drafted ahead of time and the audits in the laboratories were required to be performed at least once a year. According to the MR eleven internal audits were carried out in 2015.

**Change controls**
It was noted during the inspection that the draft SOP “Change controls” was available, but the SOP was not checked because it was not yet implemented.

2.3. **Control of documentation**
The SOP “Management of standard operating procedures and working instructions was reviewed during inspection September 2015, no changes. It stated that by October 30, a work plan was established listing all of the SOPs to be reviewed for the next year.

Hard copies were distributed to responsible persons and a register is kept for each document of distribution. Each document has a validity of 3 years, after which it is reviewed. If there are no changes, validity is extended for another 3 years but version number remains the same. Documents can be reviewed prior to 3 years if required. Before implementation of a new SOP, when a document is approved by the deputy general director, after its signature, the old version of the SOP is withdrawn and the new version is distributed and training with implementation should be done within 15 days of sign-off.

The same procedures were applicable to all laboratories.

2.4. **Records**
Electronic records of HPLC, GC, IR and UV analyses were saved on the c:/ drive of each instrument. Back-ups were performed once per month on a portable hard-disk. It was performed by selecting the main folder where all analyses were stored. The SOP “Backup procedure for meta-data for instruments”, was reviewed. It applied to all equipment capable of recording electronic data. Back up frequency was specified as not less than once in two weeks in the SOP if connected to the network, but once a month if standalone.

The data was stored on a cluster of servers that are located as clouds in different areas.
2.5. Data-processing equipment
HPLCs, GC, dissolution (UV), UV and IR instruments were linked to computers operated by their respective software.

All Excel calculation spreadsheets were revalidated once per year by entering the same values (initial data) as before and reentering it. If they get the same results as initially, it confirms that the formulas were still the same. All cells that contain formulas were password protected. They were located on a specific section of the central server.

2.6. Personnel
The SOP “Organization of training for employees of the testing centers” was reviewed during inspection September 2015, no changes. Initial training, periodic, unplanned and internal training were described.
Internal training was organized as:
- Planned
- Unplanned
and
- Lectures
- Practical training
- Seminars
- Instructions
- Self-education

After practical training via mentoring by an experienced staff member, the analysis of a known sample was done.

Every five years analysts had to pass attestation by the Ministry of Health.

2.7. Premises
As seen during the inspection, the laboratory premises were spacious, well maintained, clean, and tidy and provided adequate room for laboratory activities. The laboratory environment was appropriate for performing different tests.

Qualification report of Microbiological laboratory premises was reviewed. The Laboratory premises were designed by external organization and were in operation from 2013. Qualification was also performed by external organization.

One independent air handling unit (AHU) was provided to supply air to the Microbiological laboratory. For air supply 100 % fresh air was used in all rooms.

2.8. Equipment, instruments and other devices
The laboratories had required test equipment, instruments and other devices for the correct performance of the tests and calibrations, validations and verifications, including the preparation of samples and the processing and analysis of test and/or calibration data. Test equipment, instruments and other devices were verified, qualified and calibrated regularly.
2.9. Contracts
No contract analyses were performed.

2.10. Reagents
The SOP “Planning and organization of purchasing of laboratory equipment and material supplies for the testing centres” was reviewed during inspection September 2015, no changes. Each laboratory had a responsible person to check the inventory. The reagents were usually ordered from Merck and Sigma, or according to the catalogue which is submit in the dossier by the companies.

The SOP “Receipt, inventory and storage of reagents and materials in the center” was reviewed during inspection September 2015, no changes. It stated that upon receipt, the delivery documents and certificate of analysis or other certificates, were checked. A warning was given that if certificates of analysis were not available, the reagents could not be accepted. There were different rules regarding what have to be verified for local vs. international manufacturers. For locally sourced products, month and year of production, if it is less than 6 months, the expiry date and storage conditions were specified. For the reagents made outside of Russia, the reagents must have the name of the manufacturer, the name of the product, the expiry date or retest date, the quality of the reagent, like HPLC, GC quality or otherwise, when the analysis was done, number of the batch or lot number and the storage/transportation conditions. The expiry date should be verified (not more than 60% of the shelf-life should have been elapsed). If there was no expiry date, or range, it cannot be used in the laboratory. When the materials were stored in cupboards, they were registered added to the inventory. When reagent bottles were opened, the nature of the reagent was taken into consideration and the expiry date was set to 3 years for stable and dry reagents, but not more than half of the expiry date given by the manufacturer. For liquids and non-stable solids, a shelf life of 1 year or no more than half of the expiry date given by the manufacturer was set from date of opening. If there was no manufacturer information on the expiry date or shelf-life, the laboratory requests an expert to determine stability/shelf-life of the reagent. The inventory was maintained electronically.

The SOP “Preparation of media” was reviewed during inspection September 2015, no changes. It stated that the pH meter had to be calibrated before starting the work, as well as the analytical balances. The media batch number had to be assigned. The Russian pharmacopoeia or manufacturer’s instructions were followed. The pH was checked before and after. There was a separate SOP for media sterilization.

The SOP “Sterilization of Media” was reviewed during inspection September 2015, no changes.

When a batch of media was received, the quality was verified by doing growth promotion test.

2.11. Reference substances and reference materials
The SOP “Handling of reference standards” was reviewed during the inspection September 2015, no changes. It stated that on receipt the integrity of packaging and expiry date were verified. There were 2 types of reference standards. For pharmacopoeial reference standards, validity was verified on the internet and manufacturer’s working or reference standards, on the certificate of analysis. Mostly pharmacopoeial reference standards were used.
The Laboratory got reference standard substances only with specific work orders. The amount of reference substances was usually only sufficient for the task performed. They do not use previously opened standard.

The reference standards, once opened, were stored in their own separate refrigerator for opened standards. As noted during the initial WHO inspection, all reference and impurity standards required for analysis were supplied by either applicants or manufacturers. Each reference material was supplied with its certificate of analysis. On receipt, reference materials were stored at appropriate storage conditions until required by analysts.

Reference materials with certificates of analysis were also supplied by applicants / manufacturers alongside with drug samples.

The SOP “Procedure of drug sample acceptance for conduction of drug quality evaluation in pursuance of tasks set by the Ministry of Health of the Russian Federation” was reviewed during inspection September 2015, no changes.

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

The calibration programme was the same as during the last WHO inspection September 2015, no changes. Calibration of equipment / instruments were recorded in detailed self-made computer program “Metrological data base” what showed history of calibration and all calibration certificates and many other information e.g. location of equipment / instruments, status of equipment / instruments, identification number etc.

The SOP “Level III qualification of liquid chromatographs” was reviewed during inspection September 2015, no changes.

Analytical balances daily verification was performed, every 4 months extended calibration was performed. The SOP was based on EDQM guideline.

The HPLC Agilent for 1100 VWD RID qualification documentation was reviewed. It was performed once a year. The SOP “Calibration and check of performance for analytical balances” was reviewed.

For gas chromatography, the SOP “Qualification of gas chromatographs” was reviewed during inspection September 2015, no changes. It specified all of the necessary qualification requirements. This was done in house, but the state metrological testing still had to be done annually. The calibration SOP was based on EDQM guidelines.

KF titrator ID number XX qualification report was reviewed. Qualification was performed using Hydranal water standard. Calibration was performed once per day.

pH ID number XX calibration was performed once per day. pH usage was recorded in the log book.
In the Laboratory of Vitamins, Hormones and Synthetic Analogues there were several Agilent HPLC operated by Chemstation. Columns usage was registered in log books.

Infra-Red spectrophotometer ID XX internal calibration was performed once in three months. The following parameters were calibrated:
- Wavelengths accuracy
- Resolution
- Zero test
- Signal noise
- Energy detector coefficient
- Contamination
- Throughput test

IR calibration SOP was based on EDQM guidelines.

Last dissolution equipment ID XX internal calibration - mechanical and chemical was performed on 6 November 2015.

For dissolution, the SOP “Qualification of the instrument used for dissolution testing” was reviewed during inspection September 2015, no changes. It specified shaft verticality tests, eccentricity, vessel verticality, basket positioning, and temperature testing was carried out twice per year. This was done by the laboratory metrology department. Chemical testing was done twice per year using prednisolone testing. Degassing was done using a Distek equipment or through heating and stirring, or filtration through a 0.45 micron filter. The prednisolone test results for the 30 minute time-point, were shown and were considered satisfactory and in line with USP requirements.

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

2.13. Traceability
Test results were traceable to analyst, analytical instruments, equipment, reagents, reference substances and test procedures.

2.14. Incoming samples
Records were kept for all incoming samples as per standard operating procedures of the laboratories. There was a central registry recording registration and distribution of the samples. Records of incoming samples were properly kept by logging them in a register. A sample laboratory sheet with tests to be performed and limits was generated for each sample at the time of logging. Samples were inspected on receipt and appropriately stored until testing started.

2.15. Analytical worksheet
Analysts recorded tests performed, raw data, calculations and results in analytical worksheets and logbooks. Calculations were randomly checked by supervisors. Sufficient details were recorded in logbooks and analytical worksheets to establish traceability.
2.16. Validation of analytical procedures
The SOP on method transfer entitled “Method transfer” was reviewed during inspection September 2015, no changes. It specified that only system suitability testing was performed for pharmacopoeial methods for active pharmaceutical ingredients. For related substances tested in active pharmaceutical ingredients, if a method was used for related substances which were not listed in the monograph, then transfer was required. For finished products, system suitability, repeatability, precision and accuracy had to be done for assay. System suitability, repeatability and sensitivity had to be done for related substances tested in finished products. If a manufacturer’s method was used, method transfer consisted of system suitability, repeatability and accuracy for assay. System suitability, repeatability and sensitivity were done for related substances. An example was reviewed and included verification of peak asymmetry, column effectiveness, peak area precision (% RSD for 6 injections – 10.0% limit for peak area in the example that was seen, with reference to the manufacturer limits), retention time, separation, accuracy of the preparation of the standard solutions using 2 standard preparations.

Manufacturers usually submitted method validation along with the dossiers which was reviewed by the laboratory. When discrepancies were noted with the manufacturer’s results, an investigation was done by the laboratory on the root cause. Sometimes, the method specified chromatographic conditions which were discrepant with those of validation. The manufacturer was usually informed of any discrepancy in test results and a decision was taken based on the response. In most of the cases, when a laboratory informs a manufacturer of difficulties in method transfer, the issue will be resolved through the provision of supplementary method transfer data.

2.17. Testing
Methods received with incoming dossiers were scanned by the Ministry of Health. When the task from the Ministry of Health arrives, an expert commission has access to the database. The testing center counts the number of samples necessary and transmits the information to the Applicant. The analyst got the full documents. The sample, the reference standard and the documents come at the same time. Storage and transportation conditions from the manufacturer to the center were described in the documents accompanying the samples. The samples were then shifted to the laboratory. Any expert or analyst, who had access to the specific product samples and dossiers, got the scanned documents. The specification and test procedure were accessed electronically.

In the archive room, documents from 2014, 2015 and 2016 were kept. Documents were kept for up to 2 years – after 2 years, they were kept by an external archiving company Delice Archive for an undetermined period (permanently kept).

Laboratory for Control and Coordination
The file for XX tablets along with qualification of the instruments was reviewed. The file contained the following documents:
- Testing order from MoH of Russia (standard form):
  - Specified parameters to be tested
  - Number of the reference to the letter from the Ministry of Health of Russia
  - Batch number
  - Number of samples
  - Name of the manufacturer
• Manufacturers standard test procedure (STP)
• CoA of reagents used
• CoA of the reference substance
• CoA of the XX sublingual tablets
• Analytical worksheet - AW (downloaded from data base by the person who performed the test). AW every page was signed by analyst who performed the test and person who checked the results.

Laboratory of Biotechnological Products
The file for XX for preparation of suspension for injection along with qualification of the instruments was reviewed.
The file contained the following documents:
• Testing order from MoH of Russia (standard form)
• Protocol of the expert committee specifying the tests what should be carried out
• Manufacturers letter – delivery of samples
• List of all documents (reviewed – sent out)
• Protocol – calculation of amount of samples required for analysis
• Method validation protocols/reports from the dossier
• Standard test method from the manufacturer – variations and approved standard test method
• Specifications
• Analytical worksheets of different analysis
• Analytical results form from Pharmacological laboratory (LAL, toxicology tests)
• Analytical results form from Microbiological laboratory (sterility test)
• Analytical results form from Laboratory for Control and Coordination (content of methylene chloride)
• Laboratory of Biotechnological Products was leading laboratory for this product and laboratory was distributing samples to above mentioned laboratories according to the form XX.
• Analysis protocol (document what was sent to the MoH of Russia)
• Conclusion – stating the method is acceptable and remarks from the laboratory and sample status

Laboratory of Nano-medicines, Cell and Gene Therapy Product
The file for XX API along with qualification of the instruments was reviewed. The file contained the following documents:
• Testing order from MoH of Russia (standard form):
• Letter: samples
• CoA of the XX
• CoA of the reference standard
• Work order from MoH
• Standard test method (manufacturer)
• Analytical worksheet - AW (downloaded from data base by the person who performed the test). AW every page was signed by analyst who performed the test and person who checked the results
• Analytical test results
Laboratory of Vitamins, Hormones and Synthetic Analogues

The file for XX capsules along with qualification of the instruments was reviewed. The file contained the following documents:

- Testing order from MoH of Russia (standard form):
  - Appearance
  - Average weight
  - Dissolution (HPLC)
  - Impurities (TLC)
  - Assay (HPLC XX acid)
  - Microbial tests (enumeration test)
- Protocol of the expert committee specifying the tests what should be carried out
- Protocol – calculation of amount of samples required for analysis
- Manufacturers letter - deliver of samples, reference standards and HPLC column
- Standard pharmacopoeia tests method
- New standard test method related to the change of manufacturing site location
- Analytical work sheets - AW (downloaded from data base by the person who performed the test). AW every page was signed by analyst who performed the test and person who checked the results
- Analytical test results

The laboratory was leading laboratory for the analysis of the product.

Microbiological laboratory:

The media used for environmental monitoring was purchased already made.

The SOP “Environmental monitoring” was reviewed. According to the SOP the following monitoring was performed:

- Settle plates
- Contact plates
- Finger dabs

The SOP “Sterility test using membrane filtration” was reviewed. According to the SOP Laboratory can used membrane filtration and direct inoculation method. Sterility tests were performed according to the Russian Pharmacopoeia.

The SOP “Growth promotion test of prepared media” was reviewed during inspection September 2015, no changes. The SOP stated that the growth promotion test was performed for each batch of media.

Media storage period was following Russian pharmacopoeia requirements. If was usually used quickly, but always checked for sterility and growth promotion. The media preparation logbook was reviewed.

The file for XX film coated tablets was reviewed. According to the request from MoH of Russia the following tests were carried out:

- Total microbial count
- Total yeast’s and moulds
- Escherichia coli
Tests were carried out according to the Russian Pharmacopoeia XII. Medias used and inoculation methods were the same as per harmonized pharmacopeia method. Readymade media’s were used for analysis. Medias CoAs and growth promotion tests were part of the file.

The SOP “Work with master strains” was reviewed during inspection September 2015, no changes. Not more than 3 sub-cultures were performed. Master strains were received as disks which were assumed to be at the 3rd passage level. The Laboratory approach was that from the test strain, the lyophilization and it was put on the disk, counts for 3 passages. The maximum that they could use were 5 passages from the master strains. The number of test tubes was recorded when subdividing a sub-culture.

Autoclaves for media sterilization and destruction were equipped with thermocouples. Temperature and pressure was printed out during sterilization / destruction cycles. Chemical indicators were used for each media sterilization cycle; biological indicators were used once in six months. Autoclave XX validation report from 13 April 2016 was reviewed.

Proficiency testing scheme (PTS)
Laboratories participated in EDQM PTS:
• Laboratory of vitamins, hormones and synthetic analogues (March 2010 – dissolution testing of tablets, UV and February 2016 – volumetric determination of maleic acid and phenylalanine). The PTS 161 results were reviewed.
• The Laboratory of nano-medicines, cell-therapy and genetic therapy products (September 2013 – HPLC related substances). The PTS 141 test results were reviewed.
• Laboratories participated in the Ukrainian Pharmacopoeial Scientific Center for Quality of Medicines PTS:
  • Laboratory of biotechnological products and Laboratory of nano-medicines, cell-therapy and genetic therapy products (September 2013 – identification by IR)

Laboratories participated in the LGC standards PTS:
• Microbiological laboratory (December 2014 – identification of microbial organisms and micro low level test)

2.18. Evaluation of test results
The SOP was reviewed during inspection September 2015, no changes. It stated that evaluation of 3 replicates was performed using %RSD – with limits specified depending on the number of retests (maximum of 6 specified).

The register was maintained on Excel spreadsheets for 2013, 2014, 2015 and 2016.

The SOP “Control over the tests non-compliant with the established requirements” was reviewed during inspection September 2015, no changes. It contained a flow chart describing the process to be followed. It stated that if no root-cause was found, the results were evaluated by another analyst, or by another laboratory. Reference was made to the SOP entitled “Test result evaluation”.
The SOP “Test results evaluation” was reviewed during inspection September 2015, no changes. It stated that analytical results were first checked by the group lead who checks the analytical worksheets, formulas and calculations, followed by the head of the laboratory, who only performs an overall check. It was the expert’s responsibility to transfer the data to the computer to print out the report (called protocol) of the analysis. The report (or protocol) was signed by the expert who was responsible for the analyses and by the head of the laboratory.

2.19. Certificate of analysis (CoA)
The Laboratory did not issue CoAs. Tests results were reported in the Test Protocol form and this protocol was sent only to the MoH of Russia as part of the Expert Committee conclusion.

2.20. Retained samples
Retained samples were appropriately stored. The samples were kept until the end of their expiry date. Considering the purpose of testing, this was considered satisfactory.

2.21. Safety
Laboratory personnel wear appropriately attired with protective clothing while working in the laboratory and safety instructions were followed. Portable hand-held emergency water eye shower bottles were available in the Chemical laboratory. The main stock of flammable liquids and organic solvents were kept outside of the laboratory in a separate building.

New chemicals, when received, were stored in the MSDS sheet registry.

Before analysts started their analyses, they were required to read the MSDS sheets associated to the reagents that they had to use. A general safety procedure had to be read and documented by each analyst. The laboratory did not verify whether analysts actually read the MSDS sheets.

The SOP “Management of the liquid chemical waste” was reviewed during inspection September 2015, no changes. The name of the waste and where it should be stored was included. For instance, acetonitrile and organic solvents had to be placed in polyethylene canisters of not more than 2.5 L. Hexane had to be placed in non-transparent glass bottles. Acetic acid had to be placed in glass bottles (used for Karl Fisher). There was a detailed list and table of chemical reagents with precautions to be taken.

Part 3: Conclusion
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken, the following laboratories:

- Laboratory for Control and Coordination
- Laboratory of Biotechnological Products
- Laboratory of Nano-medicines, Cell and Gene Therapy Product
- Laboratory of Vitamins, Hormones and Synthetic Analogues
- Microbiology Laboratory

of the “Scientific Centre for Expert Evaluation of Medicinal Products” of The Ministry of Health of The Russian Federation, located at Shukinskaya Street, 6, building 1, Moscow, was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories for the following expertise:
<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physico – Chemical analysis</td>
<td>pH, density, refractive index, optical rotation, water content, loss on drying, residual solvents,</td>
<td>pH, density, refractive index, optical rotation, water content, loss on drying, residual solvents,</td>
</tr>
<tr>
<td></td>
<td>limit tests, disintegration, dissolution, uniformity of dosage units (mass, content)</td>
<td>limit tests, disintegration, dissolution, uniformity of dosage units (mass, content)</td>
</tr>
<tr>
<td>Identification</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC, TLC, UV-VIS spectrophotometry, IR, basic tests</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC, TLC, UV-VIS spectrophotometry, IR, basic tests</td>
</tr>
<tr>
<td>Assay, impurities and related</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC (FID, TCD), UV-VIS spectrophotometry, volumetric titrations</td>
<td>HPLC (UV-VIS, RI, DAD detection), GC (FID, TCD), UV-VIS spectrophotometry, volumetric titrations</td>
</tr>
<tr>
<td>substances</td>
<td>Microbiological enumeration test</td>
<td>Microbiological quality</td>
</tr>
<tr>
<td>Microbiological tests</td>
<td>Microbiological enumeration test</td>
<td>Microbiological quality</td>
</tr>
</tbody>
</table>

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.