### Part 1: General information

<table>
<thead>
<tr>
<th>Name of the QC Laboratory</th>
<th>Official Medicines Control Laboratory (OMCL) Laboratory of HALMED</th>
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<tbody>
<tr>
<td>Physical address</td>
<td>Agency for Medicinal Products and Medical Devices (HALMED), Official Medicines Control Laboratory (OMCL), Ksavarska cesta 4, 10000 Zagreb, Croatia</td>
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<tr>
<td>Date of inspection</td>
<td>20-22 July 2015</td>
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<tr>
<td>Type of inspection</td>
<td>Routine inspection</td>
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<tr>
<td>Type(s) of testing included in the inspection</td>
<td>Chemical, Physical, Microbiological</td>
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#### 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>
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</table>
| Physical/chemical analysis | - appearance  
- clarity and degree of opalescence of liquids  
- degree of coloration of liquids  
- test for extractable volume of parenteral solution  
- potentiometric determination of pH  
- conductivity  
- refractive index  
- relative density  
- loss on drying  
- loss on drying (vacuum)  
- determination of nitrogen by sulphuric acid  
- optical rotation  
- viscosity  
- water content: | - appearance  
- clarity and degree of opalescence of liquids  
- degree of coloration of liquids  
- test for extractable volume of parenteral solution  
- potentiometric determination of pH  
- conductivity  
- refractive index  
- relative density  
- loss on drying  
- loss on drying (vacuum)  
- determination of nitrogen by sulphuric acid |
| Microbiological tests                         | - sterility tests               | - sterility tests               |
|                                             | - microbial purity             | - microbial purity             |
|                                             | - bacterial endotoxins test    | - bacterial endotoxins test    |
|                                             | - pyrogens test                | - pyrogens test                |
| Other                                       | - disintegration of tablets and capsules | - disintegration of tablets and capsules |
|                                             | | |
suppositories and pessaries
- dissolution test for solid dosage forms (Basket apparatus)
- dissolution test for solid dosage forms (Paddle apparatus)
- resistance of crushing of tablets
- uniformity of mass of single dose preparation
- uniformity of content of single-dose preparation

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**Part 2: Summary**

*General information about the laboratory and site*
HALMED was established in 2003 by decision of the Croatian Government merging Institute for Drug Control and Institute for Control of Immuno-biologicals.

Overall, HALMED had 211 employees with 29 employees (eleven with university degrees) working for the OMCL. It was recently added to the bench marking of medicines agencies (BEMA).

The OMCL was part of the EDQM OMCL network. It had the duties of performing the control of medicines, for the Ministry of Health during:
- the procedure for granting marketing authorization
- market surveillance
- release of batches for the market (biological products)

In 2013, there were 255 products sampled from the market.
In 2014: 532
In 2015: 145 until the end of May.

There were three departments: Biological Laboratory Department, Physical-Chemical Laboratory Department and the Office for Pharmacopoeia.
History of WHO and/or regulatory agency inspections

The laboratory was audited by WHO in 2005-2006 under the scope of vaccine prequalification. It was prequalified in 2006 by the WHO as a competent national regulatory authority for vaccines. It had received the following audits:
- Mutual joint audit of WHO and EDQM in November 2005
- Mutual joint mock audit by the EDQM in April 2008
- EDQM audit from 5 to 7 March 2013 (37 methods were attested by the EDQM).

For the first time last year, the laboratory participated in the proficiency testing scheme (PTS) of WHO.

Focus of the inspection

The inspection focussed on the WHO good practices for pharmaceutical quality control laboratories (GPPQCL).

Inspected Areas

The inspection covered the following sections of the WHO GPPQCL text:
- Organization and management
- Quality management system
- Control of documentation
- Records
- Data-processing equipment
- Personnel
- Premises
- Equipment, instruments and other devices
- Contract
- 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 procedures
- Testing
- Evaluation of test results
- Certificate of analysis (test report/protocol)
- Retained samples
- Safety

Laboratory information file (LIF)

The LIF from 2013 was available in time for preparation of the inspection.
2.1. **Organization and management**
The QMS system was established in 2005.

Management review was performed at least once a year for all departments including the OMCL. The management review date was set each year. Summary reports were submitted and evaluated. It included party complaints/appeals, crisis management, effectiveness of communication, inter-laboratory comparisons and other important factors according to the opinion of the heads, as well as improvements and objectives to be attained at the following period. Management review records were available to all laboratory staff. The number of the non-conformances was given in detail in the Management Review for every division.

HALMED QA was responsible for the quality assurance of the OMCL, as well as for the other departments and QA contacts were within each department.

2.2 **Quality system**

**Internal audits**

These were delivered annually for the OMCL for all of the ISO 17025 chapters and used a set of forms for risk assessment, internal audit programme, audit team assignment, internal audit plan, internal audit checklist, internal audit report, survey and report on corrective actions.

A detailed process of preparation, performance, evaluation and follow-up was described. Auditors were trained on relevant ISO norms.

Planned and unplanned audits were performed. Unplanned audits are performed in case of situations requiring an immediate verification.

The elements verified could be either general to HALMED or specific to the OMCL.

A checklist along with recorded results/follow-ups was recorded in the MAPIS (in-house SQL database used for different QA topics). MAPIS also included detail enabling the tracking of resolution of non-conformities. The system included provisions for differentiating corrective actions and improvements (added value), and follow-up was strictly performed regardless, with flexible timelines.

The last internal audit of the OMCL was done on 09 July 2015. The previous audit was performed on 22 April 2015.

**Non-conformities/Out-of-specification (OOS) test results**

The procedure for OOS results was reviewed. The analyst notified the supervisor who opened the non-conforming work application. The form for OOS results was shown to inspectors. It included a detailed list of elements to be verified as part of root-cause investigations. If there was a conclusion of a laboratory error, corrective action (such as submitting a variation and re-education of personnel or revision of SOPs) was taken and initial results rejected. Confirmed OOS results were obtained when there was no laboratory error revealed by investigation and when retesting confirmed the initial result.

Each investigation was assigned an ID number and all of the necessary details were recorded, such as, for instance, the corrective action plan registered in MAPIS.
Deviations
There were two ways to handle deviations:
- Deviations considered as non-significant, minor changes, having no influence on interpretation and quality of the testing result, were recorded in the analyst logbook only. This was defined in the SOP “Assurance of quality of testing results”. Examples included modification of the volume of the test solution, as long as the concentration of the final solution remained the same, or modification of cuvette length in UV/VIS spectrophotometry, or usage of reference material from a different supplier. Deviations to analytical methods were not specifically identified as deviations, but since all of the necessary details are recorded in the analyst logbooks and approved by the section supervisor prior to proceeding with the analysis, this was considered acceptable.
- Deviations classified as “Any other deviation”, were handled as non-conformances (According to SOP QA-OP-002 “non-conforming work and corrective actions”). The process of documentation of non-conformances would be started by the analyst and evaluated by the supervisor.

Change controls
A procedure for change control was available. There were three groups of changes: Regular, Urgent, and Temporary. An overview could only be given with the help of file directories in the network. Most of the change controls filed were for the removal and replacement of equipment. In 2015, equipment was transferred to the new laboratories and re-qualification of equipment was tracked. Thus, the corrective action was performed in order to enable the listing and numbering of changes to be up to date, and to provide adequate full traceability on the number of changes undertaken, their target dates, whether they have been fully implemented, on whether further action was awaited.

Proficiency testing scheme
PTS and collaborative trials were done as external quality assurance. There were two cycloserine samples from the WHO under testing. The laboratory’s objective was to perform as many tests as possible for the EDQM proficiency tests. It was recommended to have a summary report available for all PTS.

2.3 Control of documentation
Control of internal documents was managed by detailed SOPs (QA-OP-0003 and QA-RU-0003) on drafting and preparation of SOPs and use of forms, respectively.

SOPs were saved on the dedicated network drive and were available through a controlled spreadsheet with links to the current versions of the SOPs.

When a SOP was replaced with a new version, a notification email was sent to groups of people that had to implement the new SOP. The new version of the SOP was accessible within the IT domain.

SOPs were adequately controlled with approval date, implementation date and version numbers as well as a historical list of changes in annex.

2.4 Records
Electronic signature systems were implemented, but in process of being perfected because of bugs in the new system. It would be important for the laboratory to secure the necessary corrections to the system by the service provider.
Detailed laboratory notebooks were maintained by each analyst. Pages were numbered and the data was verified by a second person.

2.5. Data-processing equipment
A description of the current IT system was presented by HALMED. It was managed using a General SOP on Validation of Computerized Systems”, a SOP entitled “Software inventory” and SOP “IT system disaster recovery”.

According to the SOP on “Data Backup”, several daily backups of changes were done on an hourly basis. Full backups were done overnight. Additionally, there was a parallel real-time backup on an external server. Daily backups were kept for thirty days. Annual backups were kept for one year.

Archiving of data was done according to the archiving ordinance adopted by the management of HALMED following the legal obligations of the authority. Evidence of analytical results was kept permanently in the database. Documentation on paper was archived for at least 6 years.

Additional electronic documents, such as HPLC data, were permanently stored in the appropriate directories. This was regulated by the SOP “Raw data”. According to this SOP, the heads of department assigned the folder title for storing raw data in electronic form as well as the exact location of the file storage on the agency servers. Data should be stored in the read only format. Raw data should not be changed, adjusted, corrected nor deleted.

Analytical worksheets, logbooks for equipment and methods were archived for 6 years according to the explanation given by the responsible staff. HALMED actually uses an external service provider for archiving of these and other paper documents.

The closing of logbooks and the archiving was described in the SOP about record control. Opening and closing of logbooks will be documented in the list of logbooks.

Calculations were performed using excel® spreadsheets which were saved and readily retrievable. In the case of complex analyses which were not frequently performed, the excel spreadsheets were not validated but calculations were verified manually and this was recorded in logbooks. Frequently used excel spreadsheets were locked.

2.6. Personnel
There were 29 staff members in total in the OMCL according to the opening meeting presentation.
There were ten permanent IT staff members ensuring the adequate function and compliance of the IT systems of HALMED.

Training was recorded electronically in DAIS (Digital document management system). Training records were requested for staff having recently joined the laboratory. Introductory training and a mentorship program were provided and tracked through electronic means. Training programme was defined and successful training of every single procedure was documented.
Employees acknowledged their job descriptions as an annex to their contracts.

The qualification of analysts was tracked using two elements, a qualification spreadsheet and another excel spreadsheet, listing all of the SOPs in which a staff member was trained. There were no statistical acceptance criteria or comparability test of the analyst’s result versus a theoretical value per se.

The qualification matrix (competence profile) was available. Every single method was listed together with the information about the people allowed to do the test.

2.7 Premises
The reception office for samples was in the ground floor of the main building. After registration, samples were stored in the laboratory area.

One part of the laboratory area, including the microbiological laboratory, was established in the second floor of the main HALMED building. Additional laboratories were constructed in the area of the former animal house. The size of the animal house was reduced since the number of required animal testing was reduced significantly.

Premises were suitable for the physicochemical and microbiological activities conducted and were very well maintained. All of the necessary space was available with appropriate segregation.

The microbiological laboratory was equipped with HVAC technology. All other laboratories (including storage areas) had controlled temperature/humidity conditions, monitored by a computerised system.

Storage of materials
Separate storage facilities were maintained for the storage of samples, reference substances and reference materials. Storage facilities were equipped to store materials at room temperature, under refrigeration (2–8°C) or frozen (< -20 C).

All specified storage conditions were controlled, monitored and data were kept at the computerised monitoring system.

Part of the samples was stored in cabinets in the corridor. One air conditioning unit was installed for climate control. As a corrective action the sensor for temperature monitoring was re-installed after temperature mapping was performed.

Bottles with compressed gases for laboratory use were stored outside the building and connected with the pipeline system.

A separate room for flammable liquids was situated in the basement together with Novec™ 1230 Fire Protection system.

2.8 Equipment, instruments and other devices of chemical laboratory
Physicochemical testing
- High performance liquid chromatography (HPLC):

There were ten HPLCs.

All columns are tested upon receipt and periodically, at least once per year and adequate records were maintained.
Computer access rights are controlled through the network with roles and user rights in Windows security technology. Back-ups were performed three times daily locally and were backed up to a secondary location. The data was backed up through Windows DPM (Data Protection Manager). Four times a year, there were freeze back-ups. Annual back-ups were performed on disks with 2 storage systems, one at a primary location in the building and one at a secondary location at a rental data centre (disaster recovery centre).

Only the data set that goes into the final report was backed up. Preliminary test injections were not retained but were performed for method validation/verification purposes only.

Date and time change was locked in Windows.

- **Fourier-transform infrared spectroscopy (FTIR):**
  FTIR spectrophotometer was available and marked as “Out of use”.

- **Gas Chromatography (GC):**
  There was a GC available under repair at the time of the inspection.

- **Ultraviolet-Visible spectrophotometry (UV-Vis):**
  There were two pieces of equipment. One of them was a service provider replacement since 2013. The data was saved on the network. The instrument logbook was reviewed. The service provider replacement was in acceptable working condition.

- **Inductively coupled plasma mass spectrometry (ICP-MS):**
  This was new equipment that was under qualification.

- **Dissolution testing apparatus:**
  There were two dissolution testing equipment. They were in acceptable working condition.

- **Analytical balances:**
  There were seven balances available. They were in acceptable working condition.

- **Karl Fisher:**
  Coulometric KF titrator and volumetric titrators were available. The data obtained was automatically conveyed to a workstation operated using LabX software and was saved on the network. They were in acceptable working condition.

- **Other testing equipment:**
  Osmometry, viscosimetry (identified as pending qualification since the recent move from the other part of the laboratory).

**Microbiological testing**

- **Autoclaves, Incubators:**
  One autoclave (used for the sterilisation of glassware and the decontamination / treatment of waste) and six incubators were installed.

Handling, maintenance and qualification of incubators was described in corresponding SOP.
Temperature mapping was done once a year. Seven critical places were chosen for every incubator. The specification was set at 22.5±2.5°C and 32.5±2.5°C (sterility testing, testing for microbial purity). An additional incubator was used for E. coli (43±1.0°C).

For the autoclave, decontamination and sterilization loads were strictly separated. A cleaning programme was in place for internal and external environment of the autoclave after decontamination loads.

Calibration labels were fixed at the equipment. Printouts from the autoclave were filed to document the sterilisation cycle together with information about the Bowie & Dick test, biological indicator and vacuum test.

As a corrective action, check of the correct time and temperature of the sterilisation cycle has been added to the relevant form (F-0652/1, 03 October 2013).

- **Isolator used for sterility testing:**
  The positive pressure fixed wall isolator was equipped with two transfer chambers and was used for sterility testing.
  Isolator and transfer chambers were sanitized with vaporized hydrogen peroxide (VHP) every working day.
  Gloves from the isolator were changed every two years.

  Qualification of isolator, regular maintenance and monitoring during the process of sanitization and processing was documented.

  Particle monitoring and leak testing for the isolator was done once a year, with “at rest” conditions during the requalification of the isolator by an external company.

  Isolator usage was documented in a logbook.

  Materials and equipment used for the environmental monitoring were documented.

  The form used to document the sterility test was filled at the computer (test results, results of additional reading, and results of environmental monitoring).

  Initial qualification documents were available for DQ, IQ, OQ and PQ.

  The observations raised from this section have been satisfactorily addressed and it will be verified during future inspections.

- **Microbiological monitoring:**
  The document “Sterility test” was available and included information with regard to monitoring.
  During every run monitoring with settle plates was performed.
  Once a month finger tips of the gloves should be monitored after the process together with swab testing of the isolator chamber.
  Monitoring of the environment during sterility testing was done with two settle plates.
  Incubation period was five days (32.5 and 25.5°C). Limits were given in the SOP (there should be no growth).
- **Testing for microbial purity of non-sterile products:**
The area for non-sterile product evaluation was inspected. The area was classified as grade D.
HEPA filtered air was provided and the room was held in overpressure to the other areas. A building management system (BMS) was in place.
A safety cabinet was installed and classified as grade A.
Microbial monitoring was in place (settle plates during the sample preparation process).
A logbook was available.

### 2.9 Contracts

**Subcontracting of testing**
Tests were not sub-contracted to outside parties. Contracts were established only for maintenance and repairs as well as equipment qualification.
Contract testing was performed for Montenegro.

**Purchasing services and supplies**
The SOP “Evaluation of the supplier and service providers” with the list of the approved suppliers were available.
For reagents the suppliers were listed but not the producers.
According to annual evaluation, suppliers for test strains and media for microbiological testing were complaint. Suppliers without compliance (more than five minor, more than one major or one critical non-conformances) were deleted from the list. But there was no need for such action during the last years according to the information given by HALMED.
Forms for the evaluation of the supplier or any documentation about the initial evaluation of the suppliers were not available.

### 2.10 Reagents

**Reagents**
Reagents were stored in lockers in the corridor area of the chemical laboratory. During the good receipt procedure, certificates were checked and internal label for the reagents was generated. Information about receipt date, expiry date of unopened container and after first opening was included.

**Water**
Potable water was used to supply the water generation unit.
Softener, reverse osmosis unit and mixed-bed ion exchanger were installed.
Change of the ion exchanger was done around every 2 two months (if conductivity would be higher than 0.1 µS/cm).

Two types of water were used:
- **Purified Water:**
  SOP “Purified water” was available.
  Specification was in accordance with the Ph. Eur. Monograph about purified water.
  Conductivity was measured every day.
  TOC: was measured four times a year; chemical testing was done annually.
  Microbiological testing of purified water used for chemical testing was done two times a year starting from end of 2014. TOC monitoring by an external laboratory was done in the past.
  Samples were taken from two existing user points.
  For microbial monitoring, a filtration method from the European Pharmacopoeia was used.
- Ultrapure Water:
A unit for ultrapure water was used for the generation of ultrapure water used for chemical testing, e.g. for HPLC.
This device was equipped with an internal quality check unit. The final filter was part of the installation.
Additional microbiological monitoring of ultrapure water should be implemented to evaluate correct interval for the change of the final filter (this was a recommendation given during the inspection).

Reagent solutions prepared in the laboratory
There were no observations. Labelling was done appropriately.

2.11 Reference substances and reference materials
The related SOP for reference materials was reviewed.
A computerised database of reference standards was available together with information about the storage place and the expiry date was part of the information included in the database.

A certificate from the manufacturer was available for one of the checked working standards. Additional documentation, e.g. about the way of the establishment of the standard, was not available. Initial evaluation about the suitability of the standard was missing but this was resolved in the laboratory’s CAPAs.

The observations raised from this section have been satisfactorily addressed and it will be verified during future inspections.

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

Equipment qualification
The general SOP on equipment qualification was presented. All phases of qualification and relevant documentation were described.

Instructions for maintenance, calibration and requalification were reviewed.
The OMCL maintained an electronic list of all equipment along with a list for the last and next re-qualifications.

Problems with the equipment / events were documented in the logbook available for every equipment in use.

Calibration / verification of performance
Performance verification was performed and checked for analytical balances, dissolution equipment, hardness tester and IR instrument.

2.13. Traceability
Traceability to reference standards, balances and instrument used was acceptable from the records reviewed during the inspection.
2.14. **Incoming samples**
Samples were recorded and attributed a number in a browser based application. Test reports were saved in the system. Records included product, test code, date of receipt, name of analysis, the name of the person checking the request for analysis among other parameters. Another section of the database included the parameters to be tested, specification limits and test results.

2.15. **Analytical worksheet**
Analyst logbooks combined with excel calculation spread sheets, along with analytical reports were used. This combination of different means of recording the data, along with the instrument logbooks and raw data was considered acceptable.

2.16. **Validation of analytical procedures**
Method validation, including transfer of methods (transfer from the pharmacopeia methods, transfer from the method from the marketing authorisation) was described in a general SOP. The OMCL general document for validation of analytical procedures was the basis for the current SOP. In the case of transfer of methods from the manufacturer, system suitability tests were done and documented. Details of transfer were described in the SOP for the respective method.

2.17. **Testing**
The example of dissolution quantitated by UV-Visible spectrophotometry was reviewed. Assurance of the quality of results was done by taking five readings of each sample. Appropriate records were maintained in the analyst laboratory notebook. Raw electronic data was transferred to processing computers and the results were manually taken and added to calculation spreadsheets. Data transfer accuracy was verified and was considered to be acceptable in the example that was reviewed.

**Biological and microbiological testing**

**Bacterial endotoxin testing**
Testing was done with gel-clot method. For the gel-clot method, thermoblock and lab-pipettes were used. Logbooks for the thermoblock were available. Every use was documented. Analysis was documented in the analyst logbook for this method. Further documentation was done on the form used for the documentation of details (e.g. sensitivity, inhibition, calculation of results).

The SOP for qualification of thermostatic equipment and checking of the temperature was available. Chromogenic kinetic as well as turbidimetric kinetic method was going to be implemented within a short timeline. Method validation was in progress.

**Sterility test**
The SOP “Sterility test” was available. Only ready-made culture media were used.

Growth promotion tests: For every new batch and shipment growth promotion test was done in accordance with related SOP.
All media used during the testing of sterility and microbial purity were tested. Requirements of the European Pharmacopoeia were fulfilled. Certificates of analysis for lyophilized microorganisms with expiry date were available.
Incubation temperature: Incubation was performed in accordance with European Pharmacopoeia requirements.
Method suitability test: Test for the suitability of the method in the presence of the specific product was not done on a regular basis.
Examination of the media was done and documented during and after the incubation period of fourteen days.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

Tests for the microbial purity of non-sterile products
The SOP on the microbial enumeration test was reviewed.
The observations raised from this section have been satisfactorily addressed.

2.18. Evaluation of test results
Data was transferred to a document management system in the form of PDF files and a system was in process of being implemented with audit trailing of any changes made to the PDFs. The target date for implementation was September 2015.

Non-conformity and OOS investigations were opened upon evaluation of non-conforming results.

In cases of customer request, uncertainty calculations are performed as per the related SOP. Calculation uncertainty was performed manually and recorded in detail in analyst logbooks.

The SOP stated that excel statistical tools should be used, but no specific excel spreadsheet had been developed as of yet.

In general, the final test results appeared acceptable and were summarized in clear and concise test reports.

2.19. Certificate of analysis (CoA)
This area was not inspected due to time constraints.

2.20. Retained samples
Retained samples were not usually kept because according to the local legislation, retained samples should be kept by the marketing authorization holders.

Pdf scans of boxes and leaflets were kept.
Inspectors suggested to implement a procedure to ensure the availability of portions of the sample for confirmatory testing in case of disputes.

2.21. Safety
The laboratory had a health and safety expert and was declared in compliance with local regulation. Laboratory coats and glasses were worn whenever required. The consultation and attestation to have read the material data safety sheets were imposed in order to ensure that all risks are known.
Waste disposal was performed once every two weeks. The safety representative verified laboratory activities and whether the rules are respected or not every week.
All waste collected in the laboratory had to be removed the same day to avoid hazards. Special clogs were worn in the laboratory – only protective footwear was allowed.

Safety cabinets were maintained and calibrated on a routine basis.

Environmental measurements for solvents were performed. Waste waters had to be tested. A dedicated area was available for preparation and testing of cytotoxic/genotoxic materials.

Safety eye showers and an appropriate number of chemical fumehoods were available in all laboratory sections.
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 OMCL of the Agency for Medicinal Products and Medical Devices (HALMED), Official Medicines Control Laboratory, located at Ksaverska cesta 4, 10000 Zagreb, Croatia, was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories for the scope activities listed below:

- Physical/Chemical analysis of finished pharmaceutical products and active pharmaceutical ingredients
- Microbiological analysis of finished pharmaceutical products and active pharmaceutical ingredients

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 three years, provided that the outcome of any inspection conducted during this period is positive.