

## WHO PUBLIC INSPECTION REPORT (WHOPIR)

### Quality Control Laboratory

#### Part 1: General information

Name of the QC Laboratory	Ezequiel Dias Foundation Octavio Magalhães Institute (IOM) Medicines Service Laboratory		
Physical address	Minas Gerais, on the Conde Pereira Carneiro street, Belo Horizonte, Brazil		
Date of inspection	23-25 March 2011		
Type of inspection	Prequalification of Medicines Programme		
Type(s) of testing included in the inspection	Quality control of starting materials and products (physical/chemical analysis and microbiology).		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Physico – Chemical analysis	pH, water content, loss on drying, density, disintegration, dissolution, friability, uniformity of dosage units (mass, content).	pH, water content, loss on drying, density
	Identification	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, UV-VIS spectrophotometry, FTIR, basic tests.	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, spectroscopy (UV-VIS, FTIR, GC /MS, basic tests
	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
Assay, impurities and related substances	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, UV-VIS spectrophotometry, FTIR, volumetric titrations, potentiometry; determination of related substances/ impurities,	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, UV-VIS spectrophotometry, FTIR, volumetric titrations, potentiometry, determination of related substances/impurities, degradations products	
Summary of the testing activities performed by the QC Laboratory			



		degradations products	
	Biological tests	Sterility test, microbial limit tests, bacterial endotoxins test (LAL)	Sterility test, microbial limit tests, bacterial endotoxins test (LAL)

**Part 2: Summary**

***General information about the laboratory and site***

The Institute Octavio Magalhães (IOM) belongs to the Foundation Ezequiel Dias (Funed) and is located in Belo Horizonte. The IOM works in cooperation with the National Agency for Sanitary Vigilance Agency (ANVISA), state and local health surveillance, state of Minas Gerais. IOM is the Central Laboratory of Public Health of Minas Gerais.

The laboratory Quality Management system was based on standard ABNT NBR ISO / IEC 17025 - general requirements for testing and calibration laboratories.

Most of the inspection time was spent in the physico-chemical and microbiological laboratory.

The main function of the inspected physico-chemical and microbiological laboratory was to test medicinal products. Physico-chemical laboratory during the year tested approximately 150-200 products.

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

The laboratory has not been previously inspected by WHO.

***Focus of the inspection***

The inspection focused on the quality management system, physico-chemical and microbiological activities of the laboratories.

***Inspected Areas***

The following areas were covered in this inspection:

- 2.1. Organization and management
- 2.2. Quality management system
- 2.3. Control of documentation
- 2.4. Records
- 2.5. Data-processing equipment
- 2.6. Personnel
- 2.7. Premises
- 2.8. Equipment, instruments and other devices
- 2.9. Contracts (should it be 2.9 or 9?)
- 2.10. Reagents
- 2.11. Reference substances and reference materials
- 2.12. Calibration, verification of performance and qualification of equipment, instruments and other devices
- 2.13. Traceability
- 2.14. Incoming samples

- 2.15. Analytical worksheet
- 2.16. Validation of analytical procedures
- 2.17. Testing
- 2.18. Evaluation of test results
- 2.19. Certificate of analysis
- 2.20. Retained samples

### **2.1. Organization and management**

The laboratory was legally authorized and had managerial and technical personnel to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures. Management and personnel were not subject to commercial, political, financial and other pressures or conflicts of interest.

### **2.2. Quality management system**

The organization of the Medicines service (SMSC) laboratory was defined in an organization chart. Fundação Ezequiel Dias (FUNED) had four boards. The laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in their job descriptions. The head of laboratory and deputy head were available to provide adequate supervision to the laboratory analysts and technical staff.

A signature register of all employees was available.

Records were kept for all incoming samples using standard written operating procedure. The laboratory had a central registry dealing with registration and distribution of samples. Records of incoming samples were appropriately logged in a register and in the software sample management system. Samples were inspected on receipt and appropriately stored until testing started.

Procedures and documents (SOPs) were approved and available for the laboratory employees to perform different procedures and tasks. Procedures and documents (SOPs) were available at the work station computers. Laboratory staff was allowed only to print out the procedures and documents (POSs). There were several password controlled access levels to the procedures and documents. Reference to some of the SOP reviewed during the inspection is given in the following sections of the report.

### **2.3. Control of documentation**

An SOP for document control was available for review during the inspection. The document and its application were considered to be satisfactory. A two year review period was assigned to each document. However, if required, documents were reviewed before the due date.

The following documents, but not limited, were reviewed during the inspection:

- "Mapping of training needs"
- "Evaluation of results of physico/chemical and microbiological drugs results"
- "Preparation and distribution of samples for analysis"
- "Customer service and treatment complaints"
- "Internal audits"
- "Critical review of quality system"
- "Control of the quality system documents"
- "Control of registers"
- "Anomaly treatment"



- "Issuance, forwarding and filing of analytical reports"
- "Logistics" and flow chart
- "Evaluation of suppliers"
- "Inspection of critical products"
- "Verification of Pharmacopeia methods"
- "Cleaning of the materials and glassware"
- Calibration schedule 2010/2011
- PM schedule 2011.

Documents were stored in the laboratory for two years and afterwards moved to the main archive and stored there for 10 years. Main archive was fire proof and equipped with an alarm system.

#### **2.4. Records**

Analytical data were recorded in analyst work sheets and were fully traceable to samples, instruments, test procedures and reference standards. Records related to laboratory activities such as instrument qualification, calibration, raw data, test results and reports were appropriately stored in a chronological order. Software - sample management system (SMP) - was used in the laboratory. Analytical raw data was entered to the system by the responsible analyst or technician and verified by the head of the laboratory.

#### **2.5. Data-processing equipment**

HPLCs, UV and IR instruments were linked to computers operated by their respective software. All raw data generated by these instruments were stored as hard copies and electronically on a server. Hard copies of raw data were kept; the system was in place to back-up the raw data from the server, which was located elsewhere.

#### **2.6. Personnel**

An organization chart showing the hierarchical arrangements, responsibilities and reporting lines in the laboratory was available.

Current job descriptions were available. Documents were signed and dated by the relevant employees.

The job descriptions were kept in personal files. The following job descriptions were reviewed and found to be satisfactory:

- Head of laboratory
- Laboratory technician

For each laboratory staff, a folder containing the following information was available:

- Responsibilities
- Competency list
- Starting date
- Qualifications
- Training

Interactions with staff during the inspection showed that most staff members had been with the laboratory for a considerable time. This enhanced staff competency in different analytical techniques and instruments and performing different tests.

Training files for:

- Head of laboratory

- Laboratory technician
- Supervisor of Microbiology Laboratory
- Microbiology Laboratory Technician

were checked and found to be comprehensive.

The chemical and microbiological laboratories annually participated in the proficiency testing schemes organized by the World Health Organization, Regional office for the Americas (AMRO/PAHO) and Programa Nacional de Control de Qualidade (PNCQ).

### **2.7. Premises**

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. Physico-chemical laboratory consisted of several separate rooms, one room was dedicated to chemical tests (dissolution, disintegration, friability, pH and potentiometrical titration) and other room to HPLC, GC and UV instruments.

Laboratory glassware was washed manually in a separate room. All glassware with the exception of volumetric glassware was dried in ovens at 50°C. The clean glassware was appropriately stored in cupboards and distributed to other work areas for easy access to analysts. The whole process of glassware washing, handling and storing was performed appropriately.

Reagents were stored in separate room.

The environmental conditions were monitored, controlled and documented. Environmental conditions were controlled by the wireless system, provided with alarms. The following were connected to the system:

- Physico-chemical laboratory
- Instrumental laboratory
- Reagent storage room
- Sample storage room
- Ovens
- Dissolution equipment
- Desiccant cabins
- Fridge and freezer
- Microbiological laboratory
- Incubators

Temperature monitoring results were printed out monthly.

The Microbiology Laboratory consisted of a sterility testing suite, a testing room containing two biological safety cabinets and a general work area with refrigerators and incubators and other general equipment. The area was clean and tidy and in good repair.

Sterility testing was carried out in a biological safety cabinet situated in room classified as Grade C. Air supply to the area was HEPA filtered. Access to the area was through an entry room and a series of 3 change rooms. The walls were smooth and the ceiling, wall and floor joints covered. There were adequate pressure differentials between the testing room, the change rooms and the support room and the outside laboratory. Pressures in the testing room and the support room were monitored with manometers (digital).

Microbiological environmental monitoring of the sterility testing area was performed monthly, after cleaning and during testing according to the SOP "Environmental Control of Sterility Area of Microbiology Laboratory".

Biological safety cabinets used for non-sterile testing were monitored according to the SOP "Procedures for hygiene and control of air services of biochemistry, medicines, sanitised products and cosmetics and microbiology and microscopy". Results were within limits.

### **2.8. Equipment, instruments and other devices**

The physico-chemical laboratory was well equipped to perform almost all pharmacopoeial tests for finished dosage forms. All analytical instruments, equipment and other measuring equipment had been purchased from reputable manufacturers.

Laboratory used only class A glassware. This glassware was verified every two years and calibrated every 4 years.

The temperature of incubators and refrigerators was monitored continuously with a probe inserted in the chamber. The probe was connected to an alarm system.

- SOP's were available for the operation and maintenance of equipment.

### **2.9. Contracts**

The laboratory had a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing. The laboratory had procedure in place to evaluate suppliers of critical consumables, supplies and services, maintained records of these evaluations. List of approved suppliers was available. Annual calibration of all equipment was contracted out to several external, accredited organizations. The contracts with external organizations were available.

### **2.10. Reagents**

Laboratory reagents were purchased from reputable suppliers.

All reagents, chemicals and solvents were appropriately stored. The stocks were regularly monitored. All purchased materials were inspected on receipt and then logged into a database. The date when the reagent was received, opened, and expiry data were recorded on the "reagent control forms".

Titrimetric determinations were rarely performed in the laboratory. The solutions were labelled and stored appropriately, preparation records were available and traceable to the reagent batch/lot numbers and expiry dates.

Water supplied by a millipore system was used for all tests. The system had on-line conductivity test.

Media used in the Microbiology Laboratory was prepared by the central media preparation area according to the SOP "Liquid, semi-solid, solid media production flow". Dried media was tested for suitability before it was released for use. It was stored in the controlled location.

### **2.11. Reference substances and reference materials**

Two persons were responsible for dealing with reference standards. Reference standard register and usage log books were available and traceable to the analysis these were used for. Reference standards were stored in the chemical laboratory in locked desiccators (humidity controlled box), fridge and freezer. Before use, reference standards that had been stored in the fridge or freezer were relocated to the desiccator to reach room temperature. Laboratory used only pharmacopeia reference standards.

Reagents and solvents, acids and bases were stored in the reagent storage room. Only limited quantities of these materials were kept in the main laboratory.

In the Microbiology Laboratory reference cultures were obtained from INCQS (National Reference Laboratory in Rio de Janeiro). The strains were originally derived from ATCC or NCTC strains. The cultures were maintained according to the SOP "Control of Growth and Maintenance of Strain" and were subject to purity checks, gram stain and presumptive identification. Working cultures were less than 5 subcultures from the original source strain.

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

Equipment items were uniquely identified and log books were available for all instruments. Calibration of instruments was carried out annually by the external accredited contract organizations. Calibration certificates with the details of actual tests performed, results and acceptance criteria, were available from the agencies. Details of the tests and results were available for assessment at the time of inspection.

All laboratory equipments were properly labelled with unique identification numbers and calibrations labels indicating date of calibration and due calibration date.

pH meters were verified with standard buffer solutions before use. A number of analytical balances were available. These were verified daily using three standard weights. In addition, all balances were calibrated by the external agency annually.

Dissolution and disintegration instruments were verified before use and calibrated annually by external agencies.

HPLC and UV instruments also were calibrated annually by external organizations.

HPLC new columns were received together with CoA and column performance was verified before use. Columns were properly labelled and stored. Column log book was available and presented to the inspectors.

HPLC verification tests were carried out every three to six months. UV verification tests were carried out every three months. Verification records were available and presented to the inspectors.

In the Microbiology Laboratory refrigerators and incubators were subjected to temperature mapping annually. Temperatures of incubators and refrigerators were recorded daily. In addition each incubator and refrigerator included a probe that was attached to an alarm system and recording system in the physico/chemical laboratory.



Biological Safety Cabinets were calibrated twice annually by an accredited external agency. Balances were calibrated annually and verified daily.

### **2.13. Traceability**

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

### **2.14. Incoming samples**

As explained before, records were kept for all incoming samples using the standard operating procedure. The laboratory had a central registry dealing with registration and distribution of the samples. Records of incoming samples were properly kept by logging in a register and software. A sample laboratory sheet with tests to be performed and limits was generated for each sample at the time of logging in the software. 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 work sheets. Calculations were checked by the head of laboratory. Sufficient details were recorded in analytical work sheets to establish traceability. This was confirmed by verifying several analytical work sheets and CoA.

### **2.16. Validation of analytical procedures**

The laboratories did not develop or validate pharmacopoeia methods.

Physico-chemical laboratory carried out verification of pharmacopoeia methods according to written procedure.

The sterility test validation procedure was included in the sterility test procedure "Bacterial and Fungal Sterility Testing". The procedure followed the requirements of the European Pharmacopoeia.

Non sterile products were validated for count using procedure "Verification of Inhibitory Capacity".

### **2.17. Testing**

The samples were tested in accordance with the state surveillance programme.

Test results were recorded in analysts' analytical work sheets as discussed earlier and print outs from instruments were stored with sample information and CoA. System suitability criteria were fulfilled when defined in the method.

In the Microbiology Laboratory testing of non-sterile products was carried out according to the SOP "Counting of Bacteria and Fungi in Non-Sterile Products and Raw Materials" and SOP "Research for Pathogens in Non-Sterile Products and Raw Materials". The methods and specifications for results were appropriate and results were reported appropriately. Organisms recovered were presumptively identified; organisms unable to be identified presumptively were identified by VITEK.

Bacterial endotoxin testing was carried out according to the SOP "Assay of Bacterial Endotoxins in Samples of Medicines". The method was compatible with the procedure of the European Pharmacopoeia.

Sterility testing was carried out according to the SOP "Assay of Sterility for Bacteria and Fungi". The procedure was acceptable.



#### **2.18. Evaluation of test results**

Test results were duly reviewed by the head of laboratory. The review included completeness and accuracy of results. Before accepting it was confirmed that test results met the relevant specifications.

Out of specification results (OOS) of chemical testing were investigated according to written procedure. The OOS procedure for a sterility testing failure followed the requirements of the Brazilian Pharmacopoeia.

#### **2.19. Certificate of analysis**

Certificates of analysis (CoA) of a number of products were reviewed. The reviewed CoA were satisfactory and included all necessary details. The CoA was signed by the responsible analyst and head of the laboratory and approved by the coordinator of the division.

#### **2.20. Retained samples**

Retained samples were appropriately stored. The samples were kept until the end of analysis. If the product did not comply with the specifications the retained samples were kept till the expiry date of the product.

#### **2.21. Safety**

Laboratory personnel were appropriately attired with protective clothing while working in the laboratory and safety instructions were followed. Emergency water shower was available in the Chemical laboratory. Material safety data sheets (MSDS) were available to staff for general reagents and chemicals used in the laboratory.

### **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, Ezequiel Dias Foundation Octavio Magalhães Institute (IOM) Medicines Service Laboratory, located at Minas Gerais, on the Conde Pereira Carneiro street, Belo Horizonte, Brésil, with WHO Good Practices for Pharmaceutical Quality Control Laboratories was considered to be operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories.

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

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