

**Prequalification of Medicines Programme  
WHO PUBLIC INSPECTION REPORT (WHOPIR)  
Quality Control Laboratory**

**Part 1: General information**

|                                                                  |                                                                                                 |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of QC Laboratory                                            | Comisión para el Control de Calidad de Medicamentos (CCCM)<br>(Drug Quality Control Commission) |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
| Physical address                                                 | Br. Artigas 3223, Montevideo 11800, Uruguay                                                     |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
| Date of inspection                                               | 19-21 August 2013                                                                               |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
| Type of inspection                                               | Routine                                                                                         |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
| Type(s) of testing included in the inspection                    | Physical, chemical, microbiological testing                                                     |                                                                                                                                                                                                                      |                                                                                                                                                                                                                      |
| Summary of the testing activities performed by the QC Laboratory | Type of analysis                                                                                | Finished products                                                                                                                                                                                                    | Active pharmaceutical ingredients                                                                                                                                                                                    |
|                                                                  | Physical/<br>Chemical analysis                                                                  | pH, water content, loss on drying, density, neutralizing capacity, dimensions, disintegration, dissolution, uniformity of dosage units (mass, content)                                                               | pH, water content, loss on drying, melting point, density, neutralizing capacity                                                                                                                                     |
|                                                                  | Identification                                                                                  | HPLC (UV-VIS, DAD, fluorescence, RI detection), TLC, spectroscopy (UV-VIS, FTIR, AA/EA), basic tests                                                                                                                 | HPLC (UV-VIS, DAD, fluorescence, RI detection), TLC, spectroscopy (UV-VIS, FTIR, AA/EA), basic tests                                                                                                                 |
|                                                                  | Assay, impurities and related substances                                                        | HPLC (UV-VIS, DAD, fluorescence, RI detection), TLC, spectroscopy (UV-VIS, FTIR, AA/EA), volumetric titrations, potentiometry, polarimetry<br>Determination of related substances/ impurities, degradations products | HPLC (UV-VIS, DAD, fluorescence, RI detection), TLC, spectroscopy (UV-VIS, FTIR, AA/EA), volumetric titrations, potentiometry, polarimetry<br>Determination of related substances/ impurities, degradations products |
|                                                                  | Microbiological                                                                                 | Sterility test,                                                                                                                                                                                                      | Sterility test,                                                                                                                                                                                                      |

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|  |       |                                                                                                                                                                  |                                                                                                                                                                  |
|--|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | tests | microbiological tests of non-sterile products (TAMC, TYMC, and specified micro-organisms tests), bacterial endotoxins test (LAL), microbial assay of antibiotics | microbiological tests of non-sterile products (TAMC, TYMC, and specified micro-organisms tests), bacterial endotoxins test (LAL), microbial assay of antibiotics |
|--|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## Part 2: Summary

### ***General information about the company and site***

The Comisión para el Control de Calidad de Medicamentos/ Drug Quality Control Commission (hereafter referred to as CCCM) started their activities in 1968, but was formally established in 1970 by the Ministry of Public Health (hereafter referred to as MSP) based on the Agreement signed between the MSP and the Pharmaceutical Industries, which was approved by the Decree of the Executive Power N° 232/970 (in 1970). It is a non-profit organization working in cooperation with the Drug Control Laboratory Evaluation Division of the MSP as a Functional Unit with common Manager and Deputy Manager appointed by the MSP, hierarchically depending on the Department of Medicines.

The objective of the CCCM is to monitor the quality of the medicines which are consumed in the country. When quality requirements are not complied with, the CCCM submits a technical report (through the Technical Director) to the authorities of the MSP, which is the only institution authorized to implement the corresponding corrective measures or penalties, or any other action applicable. The CCCM also provides services to third parties.

There were 28 staff members in the laboratory, 11 of them working in the chemical sector and 8 of them working in the microbiology laboratory (MB).

Since 2001, the laboratory participated in proficiency testing through WHO and other organizations.

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

The CCCM expressed its interest in prequalification in October 2009 and the first inspection was performed by WHO inspection team within the Prequalification procedure on 25-26 March 2010. The object of this report is the second inspection performed by WHO inspection team.

The CCCM was audited and certified by the LATU Sistemas Quality Austria according to ISO 9001:2000 and had a certificate valid until 23 October 2014. They are currently following the model of ISO 9001:2008. A follow-up audit was performed on 21 October 2012. Another audit was scheduled for 3 October 2013.

### ***Focus of the inspection***

The inspection focussed on the inspection covered the following sections of 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
- Retained samples
- Safety

## **2.1. Organization and management**

CCCM was legally authorized to perform the above-mentioned tests and to perform market sampling at different points, such as pharmacies and hospitals. The CCCM had managerial and technical personnel with the authority and resources needed to carry out their duties. The organization and management structure of the laboratory was adequately defined.

## **2.2. Quality system**

The quality management system (QMS) covered all the departments of CCCM. The QMS was based on the ISO 9001:2008 requirements. In addition, it followed the requirements of the WHO Good Practices for pharmaceutical quality control laboratories. There were no changes in the QMS since the last inspection; however several improvements were introduced. The following elements were updated/implemented and improved:

- Quality Policy (QP).
- Quality Manual (QM).
- Functions Manual -
- A specific register was created to ensure confidentiality and lack of conflict of interests.

- Quality system documents and records were converted to PDF files in view of reducing reliance on a paper-based system.
- Recording of Non-Conformities and CAPAs was improved.
- The new security manual was introduced.
- The organization chart was updated.

The processes were clearly described and very well documented, as well as their interactions, through policies, procedures, instructions, plans, programmes and records. Indicators were regularly measured in order to achieve continuous improvement and customer satisfaction.

The QMS was defined in a comprehensive Quality Manual available to all staff. The QMS was composed of independent sections, each of them with tracking of changes and a list of related documentation. The Quality Manual presented the structure of the QMS documentation.

The roles and responsibilities of the different positions were described in the Manual of Functions MFCCCM, which included an organization chart. A list of permanent staff members and their respective substitutes was defined in the “Substitution List”

#### **Customer service and management of complaints:**

Complaints could be received by any staff member. Customer complaint forms were available at the entrance of the laboratory and could be filled by anyone coming to the laboratory. This form was also available on the laboratory’s website. Complaints received were recorded and followed up in the complaint follow-up list (register). The SOP on management of customer’s complaints was reviewed. Complaints were recorded in a specific form.

There were no complaints received in 2013.

The quality unit was responsible for the management of the complaints. Top management, consisting of the technical director and general administrator, was responsible for their closure. The Technical Director was responsible for technical complaints while the general administrator was responsible for administrative complaints.

When received, complaints were forwarded to the Quality Unit. A responsible person was assigned to each complaint to deal with corrective actions with the aim of solving the problem. An updated list of complaints was available in a specific form. The follow up of complaints was adequately documented.

#### **Internal audits:**

Internal audits were properly planned, executed, documented and followed up according to the SOP. The quality management system was reviewed once per year in line with the requirements of both ISO 9001 and WHO Good practices for pharmaceutical national control laboratories.

In 2013, four internal audits were carried out in total, for an approximate duration of 2 days each time. Internal auditors were qualified by observing at least one inspection every 2 years.

External and internal trainings were given to each auditor on a yearly basis. Properly qualified (criteria were predefined and a training programme was carried out in order to become a qualified internal auditor), and they were independent from the audited areas.

In addition to non-conformities (NC), opportunities for improvement were identified during internal audits. Detected NCs were checked at the next audit and they were only closed when appropriate measures had been put in place which demonstrated their efficiency. Template tables were established after each audit including opportunities for improvement and non-conformities along with a listing of whether the corrective action was implemented, date of closure, comments, and responsible person.

**Non-conforming (NC) work/Corrective and preventive actions (CAPA):**

The SOP management of non-conformities was reviewed. The objective of this SOP was to define the responsibilities and related authorities for the treatment of non-conformities. Non-conformities were recorded in a specific form. There was a separate form for non-conformities form for the MB laboratory. Follow-up of non-conformities was recorded in a separate form. Report of Non-conformities and CAPAs was used for detection of the root cause of non-conformity and proposed CAPAs and expected results (improvement) of implementation of CAPAs. This form was signed by the staff member responsible for the CAPAs and the Head of the related section and the responsible person for the non-conformity process.

The SOP “Management of corrective and preventive actions” was reviewed. The SOP had two forms: Preventive action report form and follow up of preventive actions form.

**Management review:**

The general SOP “Quality Management System Review” specified what topics had to be discussed during the meeting and how to evaluate possibilities for improvement, implement changes in the QMS including possible change to the Quality Policy and Quality objectives.

For the preparation of the Management meeting, the quality unit had to prepare an evaluation of effectiveness of CAPAs, resources and investments and other related documents as audit report, statement of non-conformities detected and complaints

Management review was carried out twice per year. The technical year ended on 31 October of each calendar year. Partial revision was carried out at least once per year, usually in July. Complete management review was carried out at the end of the technical year.

The partial management review, dated 23 July 2013, was reviewed and found to be adequate.

Meeting minutes were reviewed and found to be comprehensive. Minutes were prepared by the Head of Quality/Physical/ Chemical analysis. All participants signed the report and also signed that they received a copy of the report.

**Proficiency testing:**

Since 2001, CCCM actively participated in inter-laboratories tests sponsored by:

- WHO
- PAHO
- KNMP – FIP (Federation of International Pharmacists)
- Pyroquant Diagnostic GMBH, Germany
- LGC Standards, United Kingdom
- Centro Nacional de Control de Calidad/ National Center for Quality Control CNCC, Peru

All results were found to be satisfactory.

**2.3. Control of documentation**

The SOPs “Elaboration of Documents”, “Control of Quality System Documentation” and “Control of the QMS register” described the management of documents of the QMS (elaboration, coding, distribution, revision, etc.). Hand written changes were not allowed on the original documents. Hand-written changes were nevertheless allowed to the registers.

Procedures were signed and dated, but it was not specified on the actual procedures whether the date shown was a date of implementation, date of elaboration or date of approval.

The maximum validity period of procedures was of 5 years. However, in general, changes were made on a much more frequent (i.e., yearly) basis. In each document, there was identification of whether a document expiry date is mandatory or not as well as whether the document should be distributed only electronically or in hard-copies as well.

A master list of updated QMS documents was electronically available to all staff. Availability of QMS documents was ensured through the documented distribution of controlled electronic version of the documents in PDF. Electronic documents were “read-only” documents. When changes needed to be made to documents, the Quality Unit (QU) supplied the responsible person with a Microsoft Word<sup>®</sup> version of the document. Some of the documents were available as certified hard copies, for example, equipment operation instructions. When the new version of the documents was available, the “Notification to staff” was issued and persons had to sign the notification to prove that they were aware of the new version of the document. Transmission and receipt lists were kept for all procedures. Staff was notified when the version was changed and record was kept of the date of when the document was received by the relevant head of department.

Changes in procedures/instructions were also tracked in the table of history of changes at the end of each document.

Retrieval of obsolete copies was documented and obsolete originals were stamped and archived under lock and key at the Quality Assurance unit. Destruction of obsolete copies was documented in a form.

Templates used to record data (forms) were either annexes of procedures/instructions or they had an independent status. In any case they could be updated independently. Distribution of forms was tracked in a list of distribution as well.

Each template had a code number and a version number.

## **2.4. Records**

Management of records was described in SOP “Control of the QMS register”. Records destruction was explained in SOP “Control of Quality System Documentation” and in a specific form. Expiry date of documents was specified in a specific list. The list specified how long documents should be kept, for example analytical protocols for 10 years, norms and Pharmacopoeias for 5 years. Documents that were no longer considered necessary were destroyed using a paper shredder.

During the inspection, records of training, receiving of samples, temperature control, distilled water quality control, reference substances, preparation of reagents, calibration and qualification of equipment, analytical worksheets, certificates of analysis, complaints and NC/CAPA were reviewed.

It was noted that a central archive was not available at the laboratory. Documents were kept in separate individual archives at different locations in the building. The conditions of storage were nevertheless deemed acceptable in general.

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

The procedure entitled “Management of IT” was reviewed. The data was saved on the server with 2 external disks, one located in a safe held by a contract company.

According to the procedure in place, computer systems in the laboratory had a program entitled “Cobian backup” which performed automatic back-ups of the data. The IT assessor was a consultant that performed verifications on back-ups once per week. A list of these back-ups was maintained in register which included a weekly checklist of the equipment for which backups had to be done.

## **2.6. Personnel**

There were a total of 28 members of staff working full time at the laboratory. No contract or short term staff was used.

The list of job descriptions for personnel working in chemical laboratory was presented to inspectors. It specified the responsible persons (e.g. for reference standards, reagents, equipment etc.), the first and second deputy was also specified. Notification of personnel regarding their job descriptions was reviewed. Notification was signed by each individual working at the laboratory.

The manual of functions dated 26 April 2013 was reviewed. The manual was used to describe job descriptions for each delegable and non-delegable position and function. Duties associated to delegated and non-delegated functions were shown in a separate list. Notification of

personnel regarding their delegated duties was presented to inspectors. Notifications were verified to have been signed by each individual.

The SOP dealing with staff education and competence was available. The responsible person of each sector recorded staff training needs in a specific document. Based on these records, the Quality Assurance unit elaborated a training programme. It was also possible to carry out non-planned trainings if necessary. Attendance to internal trainings was recorded.

There was an SOP available for induction on new staff. For new members, a training plan was elaborated containing quality system topics as well as technical topics. After the training, the person had to evaluate the training received. Less than 1 year after the training, the responsible of the sector had to evaluate the efficacy of the training and the objective's fulfilment.

There were competency matrixes available, showing which members of staff were qualified to perform each different analytical test for the Microbiology sector and for the Chemistry sector. In the microbiology area, competence was maintained by means of regular testing and verification and participation in inter-laboratory studies in accordance with the SOP entitled "Management of the technical competencies in the microbiology sector". The procedure and criteria used stated that the test had to be performed at least once a year (both plate and filter method), by the analyst for the competency to be maintained.

In both the chemistry and microbiology sectors, the last date of performing each test was included in the competency matrix, for each analyst.

This area was considered to be acceptable well documented overall. Training was performed in accordance with pre-established schedules and adequate records were kept. However, in order to better prove and document the acceptance of the technical qualification of staff, it would be useful to define quantitative criteria in advance.

## **2.7.Premises**

The laboratory premises were considered to be acceptable in size and suitable for storage and performing of the analyses. Temperature and humidity were routinely controlled and recorded in the different areas of both sectors. Premises were kept clean and tidy to ensure safe work.

### **Chemistry sector:**

The premises given to perform physicochemical analysis were considered to be acceptable in general.

### **Microbiology sector:**

Temperature, humidity and air pressure differentials were routinely monitored. In the Grade A biosecurity cabinet, controls by sedimentation, using petri dishes, were performed while doing the analyses. Other controls included microbiological testing of the incubators using plates located on the first and third shelves. Contact plates were also used in the laminar airflow bench. Results were recorded in controlled forms. Schematic diagrams were available showing each sampling area, both overall and in detail.

Trending was performed for each relevant laboratory area. The alert and action limits were of set up for each respective area. These areas were monitored at the time a test took place. TSA media was used. Full traceability was seen to the test results, dates, lot number of the prepared media, lot number for the dry media, type of media and brand name, and from the strain preparation that was directly used to the source ATCC reference strain.

It was noted that a new procedure was implemented in 2012, to allow better traceability to the reference strain by including both the code and the ampoule number.

Filter integrity testing was performed once per year for the HEPA filters installed to the laminar airflow and biosafety cabinets. DOP was used as the reference for filter performance.

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

Both sectors had the required test equipment, instruments and other devices for the correct performance of the tests, calibrations, validations and verifications. The Lists of equipment were available for both sectors.

Different pieces of equipment at the laboratory, including HPLCs, dissolution testing equipment, computerized systems and glassware were inspected.

Excel spread sheets, used to perform most of the test related calculations, were verified once per year. They were locked and password protected.

## **2.9. Contracts**

Services such as metrology, qualification and equipment maintenance were sub-contracted. The laboratory did not subcontract any of the routine analyses assigned to them. The laboratory nevertheless had contracts with service providers.

## **2.10. Reagents**

### **Purchases:**

Reagent stock and dates of expiry were monitored using a register. As per the new system in place in the laboratory, reagent bottles were labelled with their opening dates. This new procedure was implemented in 2011.

A new SOP dealing with all purchases was updated. Purchases were centralized - for the whole laboratory, usually office supplies and specific purchases for each laboratory sector. Laboratory reagents and solutions purchases were done through purchase orders. At reception, delivered products were verified against specifications, packaging was inspected to detect any damage during the transportation, labels and expiry dates (if applicable) were verified. Afterwards purchases were registered in a specific form. If all checks were satisfactory, the purchase was released for use by the coordinator in charge of the stock of materials, who updated the stock accordingly. After that, the products were brought to the requesting sector. If a delivered product was not compliant, a supplier non-conformity record was filled-in.

**Evaluation of suppliers:**

Evaluation of suppliers was properly done according to the SOP. The SOP was revised after the last inspection. Suppliers were evaluated once per year according to a scoring system. Criteria considered were quality of the product, historical information, price and time for delivery. The following scoring system was used:

A – Reliable

B – Acceptable

C – Unreliable

**Solvents:**

The quality standard for commercial solvents was defined as per USP.

**Water:**

Water was produced internally and complied with the PhEur monograph for purified water (PW). Conductivity and pH was tested on daily basis, oxidants once per month, chlorides and sulphates were tested every 6 months, nitrates and heavy metals were tested once per year. Microbial tests were carried out every six months. PW analysis was available and presented to the inspectors. PW system was cleaned regularly and cleaning was recorded and records presented to the inspectors. Ready-made Petri film aqua plates were used for microbiological control of the water. Growth promotion test was carried out upon the receipt of each batch of the plates.

**Reagent solutions prepared in the laboratory:**

Reagent solutions prepared in the laboratory were adequately labelled. For more information see the previous WHO report.

**Culture Media:**

In the Microbiology sector, dehydrated culture media were used to prepare ready-to-use culture media. All culture media was listed and a code number was assigned to each one.

The quality of each batch of culture medium was controlled by performing the growth promotion test according to the harmonized USP, European Pharmacopoeia and JP.

**2.11. Reference materials**

The SOP entitled “Standard management”, was reviewed. This SOP was applicable to the management of reference standards in the Chemistry and Microbiology sectors. There were no major changes to the procedure. For more details see the previous WHO report.

Chemistry sector

Pharmacopoeia reference standards (USP, Ph.Eur., Ph.Int. etc.), when available, were used for regular market monitoring. Working standards, supplied by the manufacturer were used when the product first batch entered the market. Working standards (WS) were received together with Certificates of Analysis (CoA). Manufacturers were requested to qualify WS against Pharmacopoeia standards and specify this in the CoA. The specific WS CoA was seen and WS qualification/analysis was traceable to the USP reference standard specific Lot No. - Sometimes manufacturers supplied - Pharmacopoeia standards instead of WS.

### Microbiology sector

All strains were listed in the List (register) OMIC2005D\_01 of microorganisms. The register for all strains included all the required information. All of the strains required for sterility tests and microbiological enumeration test were available. The strains were adequately stored under safe and controlled conditions.

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

The SOP Control of equipment was reviewed. The SOP explained how to identify the equipment, classification of equipment (e.g. out of use, out of service and obsolete), general terms of calibration and verification of equipment and corrective and preventive maintenance of equipment's. This SOP was applicable for the chemical and microbiological laboratory equipment.

### Chemistry sector

Equipment, instruments and other devices used were regularly calibrated, validated and verified according to a calibration and verification plans:

- List of equipment's and instruments
- Plan of maintenance
- Equipment and instruments Calibration Plan
- Equipment and instruments Verification Plan

### Other equipment and accessories

Automatic pipettes were calibrated once per year by external agency. A specific calibration certificate was reviewed as an example.

Overall, all calibrations/ verifications were properly recorded. Records for calibrations/verifications included all the required information.

Equipment or instruments giving suspects results or shown to be defective were labelled "out of order".

### **2.13. Traceability**

The reference material(s), equipment(s), reagent(s), culture media, analyst(s), calculation(s) were suitably recorded in the analytical report and therefore traceability was deemed suitable and sufficient.

### **2.14. Incoming samples**

The laboratory was responsible for sampling. The corresponding sampling plan, including sample size defined in accordance to tests prescribed, was defined.

The medicines analyzed came from:

- Sampling scheduled by the Technical Manager
- Donations received by the MOH
- Complaints handled by the Pharmacovigilance Unit of the Department of Medicines and other departments of the MOH

Sampling was done on:

- Pharmacies, private medical care units, hospitals and drugstores
- Manufacturers and importers of medicines

Objectives for sampling were:

- Having planned samples for analysis
- Preserve and ensure security of samples
- Ensuring transparency of the process

All of the relevant data related to sampling was recorded in numbered forms called “acta” that are carried by the 2 samplers of the laboratory. Samples were collected according to their working plans. These were established from the non-planned activities and planned activities plans. These were taken from the Ministry of Health database.

Each sampler had their own sampling “acta” book with 3 carbon copies. The sample identity numbers were sequentially assigned by each sampler. The number started with the sampler’s initials. Each set of carbon copies had a unique identification number.

Traceability was ensured through the entrance of sample information in the database called Se SEM (system of follow up of samples and products). Each sample was taken in triplicate, 1 for the manufacturer, 1 retained sample and 1 sample for analysis. The customer samples were kept by the customer. Retention samples and customer retention samples were used for reanalyses if the customer was not satisfied with the outcome. In this case, the customer sample would be tested at the laboratory together with the retention sample. Retention samples were kept for 1 month if the analysis was within specification limits, if not; they were kept for 12 months.

Samples for analysis were kept separately in both the microbiology and chemistry sectors.

Refrigerator monitoring was performed in 2 ways: one temperature and humidity indicator, and 1 data logger.

Incoming samples were verified to be large enough to enable, if required, replicate analysis as well as to retain sample. However, the laboratory stated that the quantity of samples received was often too small to allow full performance of tests.

## **2.15. Analytical worksheet**

The analytical worksheet (AW) provided all of the required information. All the values obtained from each test, including blank results, were entered on the analytical worksheet. Page numbering, including the total number of pages, the name and signature of the analyst was recorded on each AW page. AW provided adequate information. The analytical worksheets were signed by the analyst and verified, approved and signed by the supervisor on separate sample form.

The calculations were made using Excel datasheets.

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

### Chemistry sector:

Validation was claimed to be performed for in house methods or other methods that were modified. However, in practice, this was not done for all tests.

Changes to manufacturer's methods were stated not to be allowed unless authorized by the laboratory heads (this was outlined in the procedure on physicochemical controls). The SOP on analytical determinations stated that if the changes were beyond those allowed in USP 1225, the method should be revalidated.

### Microbiology sector:

The procedure on Biological and microbiological assays, stated that each and every method is validated.

The suitability of the sterility test was verified using *S. aureus*, *P. aeruginosa*, *Cl. sporogenes*, *B. subtilis*, *C. albicans* and *A. niger*. It was not clear however, if it was performed in the presence of the product, as this was not documented in the forms but this was stated to have been performed since it was required by the USP Chapter 71 on sterility testing.

The laboratory always verified the absence of inhibition activity for all products.

## **2.17. Testing**

The activity report for November 2011 to October 2012 was reviewed. It stated that in total, 1039 samples had been tested in the year, for both chemistry and microbiology. The different types of samples were trended. In total, the number of individual tests performed was 6944.

Chemistry sector: a total of 2209 tests were done, including 223 dissolution tests and 352 assays were conducted between November 2011 and October 2012.

Microbiology sector: the laboratory conducted, between November 2011 and October 2012, a total of 196 sterility tests, 3 tests on antibiotics, as well as 1431 tests for specific microorganisms.

Assay tests were performed using duplicate preparations.

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

Samples were tested in accordance with the work plan of the laboratory. Test procedures were described in sufficient detail. Any deviation from the test procedure was approved and documented.

Specifications were obtained from the specifications archive, which included:

- Pharmacopoeias (USP, European Pharmacopoeia, International Pharmacopoeia and British Pharmacopoeia) in their corresponding version in force.

- Manufacturer's specifications. It was defined in the instruction that protocols were considered valid up to four years from receipt and that they could be used to analyse similar drug products for which no specifications were available.

There were 2 SOPs available for doubtful (atypical) results investigations.

#### Microbiology sector:

The SOP applicable to atypical microbiological results was explained in a specific SOP "Handling of Out of Specification (OOS) results". The document had several check lists, for example:

- a specific check list was used to investigate sterility OOS results.
- a specific check list was used to investigate enumeration test and test for specific microorganisms OOS results.
- a specific check list was used to investigate endotoxin OOS results.
- a specific check list was used to investigate sterility OOS results in case inhibitors were detected during the sterility test.
- a specific check list was used to investigate antibiotics dosage OOS results.

A specific OOS investigation was reviewed and found to be adequate.

Doubtful (atypical) results were carefully investigated whenever obtained.

#### Chemistry sector:

The SOP entitled "Manejo de resultados atipicos o fuera de especificaciones" was reviewed. It stated that if an OOS result is obtained, the analysis should be repeated. If the repeat confirmed the OOS, the investigation was closed. If it did not confirm the OOS, another test was performed. In total, if 2 test results confirmed the OOS, the investigation was closed and the product was declared OOS. When 2 compliant results were found out of 3, the average of the 2 passing results was declared in the certificate of analysis.

OOS investigations performed using both a checklist with areas to record observations and using a flowchart as well, which was included in each individual OOS. A binder was kept at the laboratory with all OOS reports.

### **2.19. Certificate of analysis (CoA)**

A certificate of analysis (quality control report) was prepared for each batch of a product. A specific CoA was reviewed as an example. The reviewed CoA contained requested information and was adequately filled and signed by the Deputy of Technical director. Internal quality form was signed by the analyst who performed the tests and by the Head of the quality and chemistry sectors. An internal quality form and CoA were issued based on results recorded to the analytical work sheets.

### **2.20. Retained samples**

Retained samples were kept in the final pack packaged in white-coloured paper, in locked closets, with restricted access to personnel, in rooms protected from solar light and taking into

account the precautions for those requiring special storage conditions. Samples were retained for 2 months from issuance of the corresponding report.

### **2.21. Safety (General Rules)**

**Safety measures:** the Safety manual MSCCM was available to all staff and was found very detailed. There was one person responsible for security.

Equipment for individual protection and safety instructions were available and used according to the SOP as well as poster displays on the walls and on laboratory doors. Fire extinguishers were periodically revised and refilled and were accessible in all areas. All staff was trained on the use of fire extinguishers as well as on risks linked to the use of reagents and disposal of waste.

Both full safety showers and eye showers were available.

All staff was trained on first aid measures. First aid material was available and one person was responsible to check and fill it according to instruction.

An emergency plan was available in the SOP.

MSDS sheets were available for all staff members.

Flammable solvent stock was kept in a separate built-for-purpose construction.

### **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 and planned, the ***Comisión para el Control de Calidad de Medicamentos/ Drug Quality Control Commission (CCCM), Uruguay***, was considered to be operating at an acceptable level of compliance with in compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories for the scope activities listed below:

- Physical/Chemical and 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 3 years, provided that the outcome of any inspection conducted during this period is positive.