



**WHO PUBLIC INSPECTION REPORT**

**(WHOPIR)**

**Quality Control Laboratory**

**Part 1: General information**

Name of the QC Laboratory	Adcock Ingram Ltd. - Research Development and Implementation		
Physical address	1 Sabax Road, Aeroton, Johannesburg, 2013 South Africa		
Contact person and email address.	Ms. Kim Hobbs, RD&I Manager		
Date of inspection	18 – 20 April 2011		
Type of inspection	Routine		
Type(s) of testing included in the inspection	Chemical, physical		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	Physical/Chemical analysis	pH, water content, loss on drying, friability, disintegration, time, tablet hardness, dissolution, viscosity, density dimensions	pH, water content, melting point, loss on drying
	Identification	IR, TLC, HPLC, and basic tests	IR, HPLC, TLC and basic tests
	Assay, impurities and related substances	HPLC and UPLC (uv-vis, DAD, RI detection), volumetric titrations, determination of released substances and impurities	HPLC and UPLC (uv-vis, DAD, RI detection).
	Microbiological tests	NA	NA
Stability studies	Performed under conditions of 25°C/60% RH, 30°C/65% RH		



		and 40°C/75% RH	
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## **Part 2: Summary**

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

This site was first opened in 2000 with the purpose of testing products manufactured by the local and international manufacturing sites belonging to Adcock Ingram.

Many changes have recently been made at the site. The installation of new stability chambers was planned.

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

The laboratory was last inspected by WHO in 2007. The last regulatory inspection was performed by the MCC of South Africa in 2008.

The inspection focussed on the quality management system, physico-chemical analyses, identification, assay, related substances, dissolution testing, as well as stability studies, as these were the areas of quality control testing prequalified by WHO.

### ***Inspected Areas***

#### Day 1

After a short company presentation, inspectors proceeded to the review of the following documents:

- Research and development analytical laboratory organizational chart.
- CAPAs from the last inspection.
- Quality manual.
- Procedure entitled "Post importation release sample receipt".
- Procedure entitled "Post importation release of third party products intended for sale".
- Procedure entitled "Sampling of imported finished goods".
- Procedure entitled "Investigation of out-of-specification (OOS) and out-of-trend (OOT)".
- OOS register and selected OOS Reports.
- OOT register.
- Procedure entitled "Creating, Updating and Control of Standard Operating Procedures".
- Procedure entitled "Deviation management".
- Procedure entitled "Procedure for change control".
- Procedure entitled "Reference and Working standards".

In the afternoon, inspectors proceeded to the laboratory and examined the following:

- Qualification of Ultra High Performance Chromatography (UPLC) apparatus (review of maintenance records, performance verification and calibration records and deviation / incident report for selected instruments).
- Qualification of High Performance Liquid Chromatography (HPLC) apparatus'.
- Dissolution testing apparatus (performance verification tests).



- Refrigerator and freezer for the storage of reference standards.

## Day 2

After the presentation of observations from the previous day, inspectors proceeded to the laboratory floor and examined the following instruments:

- Reagent and solvent storage areas.
- Hardness tester.
- Titrators (including the Karl Fisher titrator).
- Glassware.
- Balances (calibration and daily verification records).
- Melting point apparatus.
- pH meter.
- UV spectrophotometer.
- FTIR spectrophotometer and operation log, monthly performance verification procedure, reports and electronic data.
- Disintegration testing apparatus.
- Stability chambers (25°C/60% RH, 30°C/65%RH, 40°C/75%RH and refrigerator at 5°C.)
- Electronic BMS system monitoring records and operational qualification protocol.
- Vernier caliper and associated calibration records.

Documents reviewed included the following:

- Validation schedule for the laboratory.
- Qualification records for acyclovir secondary standard.
- Procedure on computerized system validation.
- Contract for computerized system validation with external agency.
- SOP for validation of excel spreadsheet.
- Contract agreement for providing GAMP based computer systems & software validation services for R&D unit at South Africa.
- Procedure entitled "Management of Empower data".
- Procedure entitled "Empower Project Creation and Management".
- Review of the finished product specifications, selected analytical reports and analytical method validation.

## Day 3

After giving the list of observations from the previous day, inspectors proceeded to the laboratory for the review of electronic data for selected analyses.

Inspectors then proceeded to the inspection of the water systems and safety features of the laboratory (fumehoods, showers and eyewashes, flammable storage room, etc.) The column storage room and the procedure for their receipt and tracking were also examined.

The following documents were also reviewed:

- Training files for selected members of staff.
- Procedure for "Weight agreement and system drift".



- Procedure for sanitization of the water purification systems for the laboratory.
- Registers for monitoring of the water and for maintenance of the laboratory water system.
- Procedure for management of HPLC and UPLC columns.
- Raw electronic data for selected products and batches.
- Procedure for staff training.
- Training record of SOP on Review, Approval and authorization of analytical documents.
- Handling, Maintenance and Labelling of resolution and impurity / Degradation solutions.
- Draft SOP entitled "Analysis of Materials/Products by External Analytical Laboratory".  
Note: the draft SOP should be revised to state that the SOP applies to all types of testing, not just on stability samples as it applied only to the analysis of stability samples.
- Audit report for contracted laboratory.
- Contracts with companies responsible for performing stability testing.

Other areas assessed included:

- Supplier approval.
- Signature register.
- Generation of certificates of analyses.

***List of persons (and their positions) met during the opening/closing meeting***

See attendance record sheet (retained, for office records).

**2.1 Organization and management**

The organizational and managerial structure in place was adequate to ensure that the laboratory would fulfil its responsibilities. Specific units and responsibilities had been described (the laboratory included an analytical development section, a stability testing division and a release division which also included the testing of 3<sup>rd</sup> party imports). The supervision of staff was considered to be adequate - there were sufficient numbers of supervisors relative to other members of staff.

**2.2 Quality management system**

The quality management system was effectively implemented and maintained as described in the laboratory's quality manual. An exhaustive number of SOPs were available, covering all of the necessary areas. Some of the SOPs, however, were quite recent (April 2011) and were not yet fully implemented, but the company had already set target dates with regards to their full implementation (e.g., SOP which covered the expiry dating and recording of reference substances). Incoming samples were being tracked for the purposes of reporting to Sales & Marketing and captured only information from the warehouse. However, a new sample receipt register was in process of being fully implemented to ensure that all of the necessary information is captured for planning purposes, such as product batch number, expiry date, the name of the analyst whom was allocated for testing and the date released.



### **2.3 Control of documents**

Documentation control was considered to be adequate in that:

- Most documents were available with a unique identifier version number and date of implementation. The register of SOPs should have nevertheless been dated in order to ensure that it was the most recent version available.
- All of the SOPs were up to date.
- Logbooks were controlled documents which had been released by QA.
- Staff had been trained on all of the new SOPs prior to their implementation date. Implementation was effectively conducted in all cases examined but full implementation was still in process for some of the SOPs examined. The company has committed to complete this implementation shortly.
- Authorized SOPs were available in their relevant locations.

### **2.4 Records**

All records examined were quickly and easily retrievable. Certificates of analyses and OOS records contained the necessary information (e.g., batch number, initiating department and date, product name and batch number, test, analyst, analytical instrument, cause, corrective/preventive actions (for OOSs), approval date, etc). In a few cases, documentation of OOS's could nevertheless have been improved. The company has committed to adequately correct the associated procedures.

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

HPLC/UPLC data was processed using adequate systems. Administrator privileges and audit trails were in place to prevent any unauthorized modifications to injection runs or to analytical reports. Computer system validation was in process of being completed. The company had plans in place for the validation of excel spreadsheets which had been verified and were locked, colour coded and password protected according to the company's corrective and preventive action.

### **2.6 Personnel**

Personnel were adequately trained, as evidenced by the training records which had been consulted for 3 members of staff, as examples. Up to date training programmes were available for all staff members and described the essential training to be provided during the year. Job descriptions were available and signed off. Analysts had the necessary credentials to perform their work.

### **2.7 Premises**

Premises were clean and provided sufficient space for the conduct of all necessary activities. The company is in the process of commissioning new stability chambers in order to ensure that all of the planned activities can take place.



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

The analytical equipment being used was modern and adequately maintained. The company was in process of purchasing a new FTIR spectrophotometer to ensure full compliance with requirements regarding the protection of data.

## **2.9 Contracts**

Contracts were adequate in general and did not allow sub-contracting. Some issues were raised regarding auditing activities.

## **2.10 Reagents**

There was no SOP specific to the purchase of reagents, solvents and other laboratory materials but all were purchased from reputable suppliers as per the laboratory's general practices. This was addressed in the company's corrective and preventive actions.

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

Working reference standard vials were labelled when opened for the first time with the date of opening and had a validity of 1 month from the date of opening. The procedure on reference and working standards did not state that working standards should be standardized against a primary reference standard. This and other minor revisions were made in the company's corrective and preventive actions.

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

Calibration and verification of performance was found to be adequate in general. It was usually performed as per schedule and in a reproducible manner, as per the applicable SOPs. Qualification still remained to be completed for the building management system and the stability chamber alarms.

## **2.13 Traceability**

Analytical results were traceable to a working or primary reference standard. Certified standards were traceable to the National Metrology Institute of South Africa when pertinent.

## **2.14 Incoming samples**

Incoming samples were stored in the general laboratory area. The environmental conditions were controlled by the building management system. Sample verification was thorough and captured in a form which was attached to each analytical report. The form for sample verification included shipping carton conditions, temperature records, sampling, physical inspection, label copy checks (immediate label, package insert, carton), packaging checks and temperature printouts when available.



### **2.15 Analytical sheet**

Analytical worksheets were considered to be complete in general and to contain an adequate amount of detail. Weights and all other critical measurements were printed and signed off by analysts and review functions.

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

Most of the company's analytical procedures had been developed and validated in-house. Validations examined were found to cover all of the necessary parameters.

### **2.17 Testing**

Test procedures were described in sufficient detail to allow analysts to execute them in a reproducible manner.

### **2.18 Evaluation of results**

The evaluation of test results was adequate in general, except for out-of-specification results. The company has addressed this issue in their corrective and preventive action.

### **2.19 Certificate of analysis**

Certificates of analyses contained all of the necessary information and were generated using a paper-based procedure.

### **2.20 Retained samples**

Retained samples were not covered during this inspection as retention samples were not being kept by the laboratory but in the adjoining pilot plant area instead. According to company procedures, these samples were kept for 1 year after the product's expiry date as per the local regulations.

### **2.21 Safety**

The laboratory complied with safety requirements. Showers and eyewashes were adequately maintained and available near workbenches. Solvents were stored in a separate room with its own extraction unit and a grated floor.



### **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, *Adcock Ingram RD&I Aeroton* 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.