World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Quality Control laboratory
(WHOPIR)

Part 1	**General information**		
Laboratory Details			
Name of the laboratory	Adcock Ingram Healthcare (Pty) Ltd - Research & Development		
Address of inspected laboratory	1 Sabax Road, Cnr. Adcock Ingram Avenue and Sabax Road Aeroton Johannesburg, 2013 South Africa		
Address of corporate office, telephone number and fax number	1 New Road, (c/o New Road & 7th Street) Midrand South Africa Switchboard tel.: +27 11 635 0000		
Dates of inspection	13 – 15 October 2021		
Type of inspection	Routine inspection		
Introduction			
Brief description of testing activities	*Type of analysis*	*Finished products*	*Active pharmaceutical ingredients*
	Physical/ Chemical analysis	pH, water content, loss on drying, friability, disintegration, tablet hardness, uniformity of dosage units (mass, content), tablet dimensions, dissolution, viscosity, density/specific gravity, redispersibility time, resuspendability and sedimentation rate	pH, water content, loss on drying, residual solvents, limit tests. Other tests are per pharmacopeial monograph or supplier method
	Identification	HPLC (UV-VIS, RI, DAD detection), GC, TLC, UV-	HPLC (UV-VIS, RI, DAD detection), GC, TLC, UV-

		VIS spectrophotometry, FTIR, basic tests.	VIS spectrophotometry, IR, basic tests.
	Assay, impurities and related substances	(U)HPLC (UV-VIS, RI, DAD detection), GC (FID), UV-VIS spectrophotometry, volumetric titrations, dissolution. Determination of related substances/impurities and degradation products	HPLC (UV-VIS, RI, DAD detection), GC (FID), UV-VIS spectrophotometry, volumetric titrations
	Stability testing	ICH conditions/ WHO conditions	N/A

General information

The site was opened in April 2000.

Adcock Ingram Healthcare (Pty) Limited - Research and Development provided services to all Adcock Ingram manufacturing/corporate sites, namely:

- Adcock Ingram Healthcare (Pty) Limited - Wadeville (South Africa)
- Adcock Ingram Healthcare (Pty) Limited - Clayville (South Africa)
- Adcock Ingram Critical Care (Pty) Ltd – Critical Care (South Africa)
- Adcock Ingram Healthcare (Pty) Limited - Bangalore (India)
- Adcock Ingram Limited - Corporate (South Africa)

The Laboratory carried out the following activities:

- Final Product Release Control (FPRC) of products manufactured by the local and international manufacturing sites belonging to Adcock Ingram Limited, as well as other third-party contract manufacturers under license to Adcock Ingram Limited.
- Analysis of samples for commercial product investigations including customer complaints, when required.
- Development and validation of analytical methods (and related specifications, where appropriate) for application in QC testing (release and stability), cleaning validation and comparative dissolution.
- Verification of analytical methods.
- Analytical method transfers to Adcock sites and other third-party contract manufacturers.
- Analysis of product development samples (laboratory- and pilot-scale batches) for new and reformulated products.
- Analysis of pilot batches for pilot stability purposes and selected commercial products.

	• Analysis and release of raw materials for use in pilot-scale batches of products. • Comparative Dissolution testing for new and reformulated products. • Storage and management of pilot and commercial stability samples for Adcock Ingram Limited. • Final Product Release Responsibility (FPRR) for Adcock Ingram Limited products.
History	The Laboratory was accepted through the WHO pre-qualification program on 15 Jan 2008, and the most recent WHO inspection took place during December 2016. The facility was inspected by SAHPRA on August 2019.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Quality Management System Personnel Training and Safety Documentation and Records Premises and Equipment Validation – Qualification –Calibration Laboratory Practices Reference standards – Reagents – including water qualification used in Laboratory activities.
Restrictions	The COVID-19 restrictions and the respective safety measurements applied.
Out of Scope	At the time of inspection, the AA spectrophotometry was out of service, awaiting the defect part from overseas. Hence, the equipment performance could not be verified. The activity was removed from the list of Testing activities, as per the Laboratory's request.
Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
CAPA	Corrective action & Preventive action
DQ	Design qualification
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GC	Gas chromatography or Gas chromatography equipment
GMP	Good manufacturing practices
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
IQ	Installation qualification
IR	Infrared spectrophotometry
KF	Karl Fisher titration
LIMS	Laboratory information management system

MB	Microbiology
MR	Management review
N	Normality
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
OQ	Operation qualification
Ph.Eur.	European Pharmacopoeia
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PT	Proficiency testing
PTS	Proficiency testing scheme
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QM	Quality manual
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
TLC	Thin layer chromatography
TOC	Total organic carbon
URS	User requirements specifications
USP	United Stated Pharmacopoeia
UV	Ultraviolet-visible spectrophotometry or spectrophotometer
VMP	Validation master plan
VS	Volumetric solution

Part 2	Summary of findings and recommendations

1. Organization and management

The organization and management structure of the Laboratory; including responsibility, authority and interrelationship of the personnel were specified in the organizational chart approved on 7 Oct 2021 by RD&I Manager. The Laboratory was headed by Dr Adrienne Müller and comprised of the following sections:

- QA department
- Formulation department
- Analytical department

The Laboratory had arrangements to ensure that its management and personnel were not subject to commercial, political, financial and other pressures or conflicts of interest that might adversely affect the quality of their work. A form for Ethics and Data Integrity and a form for Declaration of conflicts of interests were signed and dated by staff to ensure confidentiality appraisal and the absence of conflict of interests in accordance with the applicable SOPs.

2. Quality management system

A quality manual (QM) defining the quality management system was available and authorized on 9 Feb 2021. Laboratory's documentation system with an overview of the Quality System was described in the QM. The QMS was supported by corporate and divisional standard operating procedures (SOPs), as the second level. The third level of the documentation system consisted of testing documents, forms and specifications developed by each operating unit.

The organization applied an electronic system to supervise and manage the following elements of the QMS.

- Change control
- CAPA
- Deviation

Register control reports could be extracted from the QMS system for performance assessment purposes and notifications could be generated through the system if the incorporated timeframes were not met.

Internal audit

The activities of the Laboratory were systematically and periodically audited internally in accordance with the respective SOP. QA was responsible to prepare and maintain the self-inspection schedule, follow up and ensure closure of inspection findings and that periodic review of self-inspection findings was carried out. Self-inspection was performed annually and included documentation on audits and walkabouts for each department. The schedule was approved by the QA manager. Department specific aid-memoires were used for self-inspection. On completion of inspection, inspection report was prepared specifying observations/non-conformances. Observations were classified as:

- Critical
- Major
- Minor

Selection and qualification criteria for auditors were specified. The selection was based on:

- Educational qualifications
- Experience in pharmaceutical industry
- Knowledge and skills

Auditors' certificates, self-inspection schedules for 2020 and 2021, and a randomly selected self-inspection report were reviewed and discussed. The respective CAPAs were logged and followed-up in the applicable system.

Management Review (MR)

SOP for Quality management Review was discussed. The SOP was applicable to the MR of the Quality System at RD&I. According to the SOP, MR meetings should be conducted biannually. The meeting would be chaired by the QA Department and meeting should focus on data generated for the last six months. The MR agenda's content was specified.

MR minutes of meeting consolidated all actions items generated and if required, items were routed through CAPA system. QA was responsible to consolidate the minutes of the meeting and circulate it to the management for review. Signed and approved MR minutes were kept by QA.

QM review Jan to Jun 2021 (H1), dated 06 Aug 2021 was discussed during the inspection.

Change Control

Well managed procedures were established and implemented for making, documenting and controlling changes in accordance with SOP for Change management which was applicable to permanent changes. Change management was managed and monitored through QA Management System.

If the target date could not be met, the person responsible for the action must initiate a request for extension, providing a reason for the postponement was acceptable. The Head of QA department was responsible to review and complete all action plans to be authorized for final closure.

Handling of deviation / CAPA plans

Handling deviations and CAPA plans were managed in accordance with SOP for Deviation management, and SOP for Corrective action and preventive action.

The Deviation management procedure was used for any incident resulted in a non-conformity with a direct or potential impact on product quality and/or patient safety and maybe related to raw and or packaging materials, process equipment, process environment, method of production or testing or any other incident that might influence product quality and therefore applicable to all current/future (new) systems and related item including (but not limited to) facilities , utilities, equipment, processes and documentation in use.

Deviations were classified as:

- Critical
- Major
- Minor

Randomly selected deviations and the respective CAPAs were discussed.

Risk management

Work instruction for Quality Risk management was available and discussed. The purpose of the document was to identify various potential risks to ensure quality and to assess and reduce or remove the quality risk for products. According to the SOP, FMEA methodology was used for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that were most in need of change. Risk register for 2021 was available with 8 risk assessments.

Randomly selected Risk assessments were discussed.

Deficiencies identified concerning the Quality Management system were adequately addressed in the respective CAPA Plan.

3. Control of documentation

The Laboratory established and maintained a system of procedures to control all documents (preparation, revision, distribution, return, archiving). A master list identifying the current version status and distribution of documents was available which was regularly monitored. Each controlled document had a unique identifier, version number, date of implementation, reference to the previous version, together with a revision history. The documents were authorized and released by the QA manager and available at the relevant location. SOP for Control and numbering of documentation, implemented on 6 May 2020 was in place comprising the authorization for copying and the identification of copies from official and controlled documents. Relevant staff was trained on new and revised SOPs in accordance with the distribution list attached to each SOP; the personnel acknowledged by signature that they were aware of applicable changes. Usage logbooks were generated, supervised and filed by QA annually. The QA department had also procedure for issuance of forms in accordance with an issuance registry.

The logbook for OOS register was reviewed.

The following SOPs were also applicable:

- SOP for Creating, updating and control of Standard Operating Procedures and Work Instruction
- WI for Introduction of a new procedure, system, equipment, utility to RD&I

4. Records

A manual system was used for recording of data. Data generated was recorded in a laboratory notebook issued by QA to the analyst. Electronic data generated was printed out and attached to the notebook. The notebook was reviewed by QC/QA. Electronic reviews/sign-offs were performed for generated data. Approval was performed by QA.

Records were made of analytical tests, including calculation and derived data, method validations/ verifications, instrument use, calibrations and maintenance and sample receipt in logbooks containing consecutively numbered pages. The records were complete and signed, alterations were commented, and references were made to appendices containing the relevant recordings, e.g. chromatograms and spectra. Records were kept in an archive for a period of shelf-life plus one year. Access to the archive was restricted to authorized personnel.

The history of randomly selected samples was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, archive). For details refer to section 18.

5. Data processing equipment

All computerized systems were appropriately qualified as per GAMP 5 guidance and PIC/S GMP guide, Annexure 11 - Computerized systems. An inventory of all computerized systems was available with information about unique identification, purpose, physical location of the software and RDI no.

Records on hardware configuration, installation and changes (incl. software updates) were kept for computerized systems which were components of test equipment. Electronic data was adequately protected from unauthorized access. Each user has a unique account login and appropriate access privileges. These were described in the respective procedure of each equipment/ system. Passwords were changed on a regular basis, based on group policy.

Procedures were established and implemented for making, documenting and controlling changes to information stored in computerized systems. Computer generated, time-stamped audit trails for electronic records were maintained and reviewed as part of the quality control review for each tested product.

Electronic data was backed up at appropriate regular intervals on VEEAM, which was a backup server. The backup was automated, and snapshot of the software was regularly transferred to the applicable server. SOP for data backup and retention, approved on 24 Jun 21 was reviewed and discussed.

Concerning spreadsheets (e.g. Excel®), all cells including calculations were locked so that formulas could not accidentally overwritten. Free access was only given to cells to be filled in with data. Calculation algorithms were tested with another validated software or by a pocket calculator. The sheets were made available only on a secured standalone computer with limited access.

During validation of computerized systems, the frequency, roles and responsibilities regarding the review of original records (including audit trails) was established based upon a documented and justified risk assessment.

The restoring process was managed through SOP for Disaster recovery of the Adcock system. The process was completed once a year. The last documentation was available from September 2020, checking the backed-up data in accordance with applicable SOP. There was also a schedule for year 2021 to perform a new restoring for 2021.

The following applicable procedures were also available:

- SOP for Management of Empower Data
- SOP for Creation and Operation of Excel Sheets
- SOP for Data Integrity
- SOP for Access control management for the BMS
- SOP for Audit Trail Management for the BMS
- Validation Master Plan

6. Personnel

The Laboratory had sufficient personnel with the necessary education, training, technical knowledge and experiences for their assigned functions. Staff undergoing training was assessed on completion of the training. The Laboratory maintained current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The Laboratory maintained also records of all technical personnel, describing their qualifications, training and experience.

Training in good data and record management in evaluating the configuration settings and reviewing electronic data and metadata, such as audit trails, for individual computerized systems used in the generation, processing and reporting of data was performed.

SOP for Induction and training at RD&I, effective 30 Sep 2021 and SOP for Training and qualification of laboratory analysts, implemented on 16 Oct 2019 provided guidelines for induction and training of employees. Based on assessments (written and practical), audit findings, CAPA and deviations, retraining needs were identified by the department manager and the identified trainings were accordingly conducted either internally or externally. Training records were kept in the individual training files. Individual training records were filed by QA.

Randomly selected job descriptions, CVs and training documentation of supervisors and analysts were reviewed and confirmed.

PT testing

The laboratory had only participated in one PT-scheme provided by WHO in 2019.

Deficiencies identified concerning the Personnel were adequately addressed in the respective CAPA plan.

7. Premises

A facility tour was carried out during the inspection.

The total under-roof area of the facility was 2600 m^2 and it was designed to suit the functions and to perform the operations to be conducted. The facility consisted of:

- An administration block,
- Analytical laboratory,
- Formulation laboratory (with manufacture area for development trials) and
- Walk-in stability chambers for sample storage

Separate storage facilities were maintained for the secure storage of samples, retained samples, reagents, laboratory accessories and reference substances, if necessary, under refrigeration (2-8°C) and frozen. The temperature of these rooms was monitored and controlled by a digital system. In case of temperature excursion, a notification would be sent to the QA staff via SMS.

The pest control invoice was provided to verify that the action was completed by a contracted service provider every month.

Gases were stored in a dedicated store, isolated from the main building. The Laboratory provided separate rooms for storing flammable substances, fuming and concentrated acids and bases.

SOP (WI) for Filing and storage of documents by QA was implemented on 31 May 2021. Provisions for retrieval and return of documentation were applied. The archiving facility was fireproof.

Deficiencies identified concerning the Premises were rectified as per the respective CAPA plan.

8. Equipment, instrument and other devices

A list of equipment used in the laboratory, with information about brand and model was available in Appendix 6 of LIF. Validation schedule of analytical equipment 2021, dated 1 Oct 2021 with information about validation date and review date was reviewed.

For more details, refer to section 12.

9. Contracts

The following contract laboratories were used for selected analysis as below. Technical agreements were in place to ensure compliance with standards for activities contracted out.

- Pharma-Q (Pty) Ltd; for Microbiological analysis, Preservative Effectiveness Testing (PET)
- North-West University, Potchefstroom Campus Research Institute for Industrial Pharmacy (RIIP); for Analysis of raw materials & FFP and performing comparative dissolution studies as defined in appendix D to the contract.

The signed contracts defined the contracted work and established duties and responsibilities for each party. The competence of the contracted organizations was periodically assessed, and records of these assessments were kept.

SOP for Management of Vendors of Critical Laboratory Consumables was applicable to:

- New vendors/brokers
- Alternative vendors/brokers

Risk assessments should be performed based on the questionnaire and quality documents obtained and if required on-site audits should be carried out and frequency of re-audit should be specified. Audits should be carried out by QA, using a check list.

Group Quality Assurance (corporate) SOP for Selection and approving contract manufacturers, contract packers, Contract Laboratories and Contract distributors was available and discussed. The Laboratory was not involved in the abovementioned procedure. This was done by corporate Group Quality Assurance.

A deficiency identified concerning the Contracts was adequately addressed in the respective CAPA plan.

10. Reagents

SOP for Control of chemicals in the analytical laboratory was available and discussed. The procedures defined the receipt, labelling, storage, usage and inspection of chemicals. The analyst should verify the following information prior to usage of reagents:

- Validity period of all chemicals – external and internal expiry date
- Physical nature of the chemical before use

The chemicals were electronically registered and contained information about

- Reagent number
- Name
- Storage location
- Batch No
- Supplier
- CN number
- Date received
- Supplier expiry date
- R&D expiry date

The opening date of container and expiry date was recorded on all containers. Expired chemicals were identified and removed from the Laboratory by the responsible person. Allocation of expiry dates were defined in the respective SOP.

According to the SOP, chemicals were purchased from approved vendors as per the applicable SOP. Safety data sheets were available electronically and in paper form.

Entrance to the chemical store was biometrically controlled.

SOP for Reagent solutions and SOP for Volumetric solutions were discussed. Shelf life expectancy and labelling of solution, including volumetric solution were adequately described. Volumetric solutions were re-standardized weekly.

The labels contained:
- Name
- Concentration
- Analyst who prepared the solution
- Date of preparation
- Expiry date
- Reference to unique solution No
- Balance No

The Elix 70 system produced purified water from portable tap water by combining several purification technologies i.e. removal of particles and free chlorine; Reverse Osmosis; Electro-Deionization followed by exposure to UV light to reduce bacterial levels. It was fitted with an in-line conductivity meter.

The final product water was tested for ionic, organic, bacterial and particulate contaminants. The purified water was stored in a reservoir for laboratory applications.

The storage reservoir fed a distribution loop around the laboratory allowing distribution of purified water to several points of use. In addition, the Elix 70 product water was fed to two Milli-Q systems for further purification to ultra-pure water quality.

Conductivity (in-line meter readings) of the purified water was performed daily. Weekly testing included conductivity testing, microbiological analysis, and Total organic Carbon (TOC) analysis.

The applicable procedures were:
- SOP for Elix 70 and Milli Q water purification system
- SOP for Chemical analysis and microbiological testing of purified and ultra-purified water

11. Reference substances and reference materials

Reference substances were managed and monitored in accordance with SOP for Reference and working standards. Working standards were prepared by the Laboratory and they were stored and used in a manner that did not adversely affect their quality. Reconciliation of the reference standards was well recorded. The following information was kept on the labels of reference substances and/or the accompanying documentation (as appropriate):

- Name
- Standard No
- Re-standardization date
- Purity
- Expiry
- Storage conditions
- Water/LOD
- Vial opened
- Vial valid up to
- Vial No

Testing results (CoA) and safety data sheets were also provided. The identification number was quoted on the analytical worksheets whenever the reference substance was used. A register of all reference substances was also available.

SOP for HPLC, UPLC and GC columns was discussed to verify proper handling of chromatography columns. UPLC column RDIU132 (manufacturer Waters) was randomly checked to confirm the implementation of the applicable procedures. Columns were stored in the laboratory cupboards in manufacturers packaging.

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

Each item of equipment, instrument or other devices used for testing, verification and/or calibration were uniquely identified, when applicable. The status of calibration and the date when recalibration was due was indicated on the instrument label.

The performance of equipment, including measuring devices was generally verified at appropriate intervals according to a plan established by the laboratory. Specific procedures were established for each type of measuring equipment, considering the type of equipment, the extent of use and supplier's recommendations.

The pH meter and balances were connected to printers with date and time options. The uncertainty measurement was implemented in their practice. pH meters were verified with standard certified buffer solutions before use. Balances were checked daily using internal calibration and regularly using suitable test weights, and requalification was performed annually using certified reference weights.

Records were kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. Defective equipment was taken out of service and they were clearly labelled.

Randomly selected Laboratory's equipment IQ, OQ and PQ evidence, as well their periodic performance verification and maintenance documentation were reviewed to verify the equipment suitable design and proper functionality.

A deficiency identified concerning the Equipment was adequately addressed in the respective CAPA plan.

13. Traceability

Test results were traceable, were appropriate, ultimately to primary reference substances.

All calibrations or qualification of instruments were traceable to certified reference materials and to SI units (metrological traceability).

14. Incoming samples

The laboratory was not responsible for sampling of materials/product.

A delivery document, original CoA, check sheet and datalogger were accompanied each sample submitted to the laboratory and contained the following information:

- Description of the sample,
- Specification to be used for testing,
- Required storage conditions as stated on the sample packaging.
- Transport condition

The blank form for Certificate of Analysis with information about the samples specifications and analytical notebook were issued by the QA and sent to the laboratory, together with the samples for analyst allocation.

All delivered samples and accompanying documents were assigned a registration number. A logbook as a register was kept in which the following information was recorded:

- Registration number of the sample,
- Date of receipts,
- Unit to which the sample was forwarded.

Prior to testing, the samples were stored safely, considering the storage conditions for the sample. The samples were received at the laboratory unit for testing together with the test request by the responsible person to be allocated to the available qualified analyst. Test requests were provided based on post-importation CoAs.

Visual inspection of samples was carried out by the laboratory staff to ensure that labelling conformed with the information contained in the test request.

All samples were sent to the laboratory unit. The samples were stored safely in designated cabinets in the laboratory. After completion of the test, the remaining samples were returned to QA-unit to be stored in a separate room. The environmental conditions were required to be monitored. Retained samples were logged in a logbook and were kept until one-year post expiry.

All tests were performed after receipt of test request.

Deficiencies with regard to the Incoming samples were sufficiently addressed in the organization's CAPA plan.

15. Analytical worksheet

The analysts recorded information about samples, test procedures, calculations and results in analytical notebooks issued by QA as controlled document for each sample, which were completed by raw data.

The records contained the following information:

- The date on which the analysis was started and completed;
- Reference to specifications and full description of the test methods, by which the sample were tested, including the limits; identification of test equipment used; reference substances, reagents and solvents employed;
- Interpretation of the results and
- The conclusion whether the sample was found to comply with the specifications;
- Any deviation from the prescribed procedures (which were approved and reported).

All values obtained from each test, including blank results, were immediately entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, were attached or were traceable to the electronic record file or document where the data was available.

The completed analytical worksheets were signed by the responsible analyst and verified, approved and signed by the supervisor. For corrections the old information was deleted by putting a single line through it; it should not be erased or made illegible. Alterations were signed by the person making the corrections the date for the changes inserted. The reason for the change was given, when applicable.

16. Validation of analytical procedures

SOP for Validation of analytical methods, SOP for Analytical method verification and SOP for Transfer of analytical procedures – Method transfer were available and reviewed. The applicable criteria and parameters to be considered during method validation / verification / method transfer were predefined in the respective SOP. A logbook was available to record the validation / verification / method transfer methods that were provided in the Laboratory. Appropriate system suitability tests were employed prior to the analytical tests for verification of pharmacopeial methods and/or validated analytical procedures.

17. Testing

Test procedures were described in detail and allowed analysts to perform the analysis in a reliable manner. Specific tests were carried out by specialized external laboratory.

18. Evaluation of test results and OOS investigation

SOP for Investigation of OOS and OOT and the respective flow chart were in place describing the conduct of investigations of OOS test results. When a doubtful result (suspected OOS result) was identified, a review of the procedures applied during the testing process was undertaken by the supervisor and the analyst.

Doubtful results were rejected only if an error could clearly be identified.

If the investigation was inconclusive, the SOP gave clear guidance on the number of retests allowed (based on statistical principles). Once an error was identified, corrective and preventive measures were recorded and implemented. All individual results (all test data) with acceptance criteria were reported. The repeat of tests was done by a second analyst, as experienced and competent as the first one.

Analytical test reports were issued by the Laboratory based on information recorded in analytical worksheets.

The test reports further included the following information:
- The background and the purpose of the testing;
- Reference to the specifications and methods used;
- The results of all tests performed (or numerical result with the SD of all tests performed);
- The statement whether the sample complies with the requirements, through a checklist.

The OOS investigation of randomly selected samples were reviewed to verify the correctness of analytical worksheets, the respective records and OOS investigation procedure, including the CoAs.

19. Certificate of analysis

A certificate of analysis was prepared for each sample/batch of a substance or product and contained series of information, among others:
- The results of the tests performed with the prescribed limits and
- A conclusion as to whether the sample was found to be within the limits of the specification.
- The date on which the tests were completed.

20. Retained samples

Retained samples were kept in their final pack and retained as required, i.e. one-year post expiry date, in a locked designated room. The samples were logged in a respective logbook.

21. Safety

Staff was wearing laboratory coats, including eye protection. Special care was taken in handling highly potent, infectious or volatile substances. Highly toxic and/or genotoxic samples were handled in safety cabinets. Safety showers were installed. Safety data sheets were available before testing was carried out. Eye wash stations were installed and regularly monitored.

Miscellaneous	
Assessment of the Laboratory Information File	The LIF was provided with implementation date 27 Jul 2021.
Annexes attached	N/A

Part 3	Conclusion / Inspection outcome

Based on the areas inspected, the people met, and the documents reviewed, including the CAPA plan provided for the observations listed in the Inspection Report, ***Adcock Ingram Healthcare (Pty) Ltd - Research & Development,*** located at ***1 Sabax Road, Cnr. Adcock Ingram Avenue and Sabax Road Aeroton Johannesburg, 2013 South Africa*** is considered to be operating at an acceptable level of compliance with WHO GPPQCL Guidelines.

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.

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
   Short name: WHO TRS No. 961, Annex 2
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
   Short name: WHO TRS No. 1033, Annex 4
   https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

6. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO GMP guidelines*** or ***TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

7. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6
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