World Health Organization

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WHO Prequalification Unit – Inspection Services Team (INS)
WHO PUBLIC INSPECTION REPORT
of the Quality Control Laboratory
WHOPIR

Part 1	**General information**
Laboratory Details	
Name of the Laboratory	M&L Laboratory Services (Pty) Ltd. (Mérieux NutriSciences - *MXNS*)
Address of the inspected Laboratory	40 Modulus Road, Ormonde Gauteng, RSA 2135 Johannesburg South Africa
GPS Coordinates	Latitude: S 26°14'12.3" Longitude: E 028°00'25.0"
Address of corporate office, telephone number, and fax number	Same as above
Dates of inspection	From 7 to 9 July 2025
Type of inspection	Routine inspection
Inspection record number	INSP-QCL-2023-0001
Introduction	

Brief description of testing activities

Type of analysis	*Finished products*	*Active pharmaceutical ingredients*
Physical/ Chemical analysis	pH, water content, loss on drying, water content (Karl Fischer), friability, disintegration, tablet hardness, dissolution, viscosity, density, uniformity of dosage units	pH, water content, loss on drying, water content (Karl Fischer), melting point, conductivity
Identification	IR, TLC, HPLC, UPLC, UV, spectrophotometry, and basic tests	IR, TLC, HPLC, UPLC, UV, spectrophotometry, and basic tests
Assay, impurities, and related substances	HPLC (UV, fluorescence, RI, conductivity, PDA), UPLC (PDA), GC, UV,	HPLC (UV, fluorescence, RI, conductivity, PDA), UPLC (PDA), GC,

		potentiometric, and volumetric titrations	UV, potentiometric, and volumetric titrations
General information	M&L Laboratory Services operated as a contract testing laboratory based in Johannesburg, South Africa, with two sites. The laboratory was originally established in 1930 by two private individuals, initially functioning as a geochemical exploration facility. Over the years, multiple changes in shareholding have been observed, and the scope of operations has been expanded. At the time of this inspection, the laboratory was functioning as a division of Mérieux NutriSciences. <u>Regarding Mérieux NutriSciences:</u> Mérieux NutriSciences South Africa has 34 years of experience in addressing the food industry's needs. The company was originally established in 1991 under the name Swift Micro Laboratories. Following a period of ownership by a para-statal entity, the company underwent a management buy-out. Subsequently, it entered into a joint venture with Mérieux NutriSciences, marking the beginning of its integration into the global network. The entity has since transitioned to operating under the Mérieux NutriSciences name. Further strategic development included the acquisition of Hortec (Pty) Ltd, strengthening the organization's capabilities within South Africa. In 2024, Mérieux NutriSciences entered into an agreement to acquire Bureau Veritas' global food testing business. This initiative aimed to expand the company's global footprint, enhance its service capabilities, and reinforce its leadership in the food testing, inspection, and certification (TIC) sector across all continents.		
History	The same organizational structure has been maintained throughout the various acquisitions. Food testing activities had been discontinued at this site, and the site was designated solely for agrochemical and pharmaceutical testing. The Pharmaceutical and Microbiological laboratories were licensed by the South African Health Products Regulatory Authority (SAHPRA). The laboratory was prequalified by WHO on 18 July 2017 and had undergone several WHO inspections, the most recent of which was conducted from 18 to 20 October 2021.		
Brief report of inspection activities undertaken – Scope and limitations			
Areas inspected	Organization and management, including: - Structure - QMS - Documentation and records - Computerized systems Planning and strategic management, including: - Service providers and suppliers - Performance management - Quality Risk management		

	Resources including: - Personnel - Premises - Equipment qualification - Reagents, RS Technical activities including - Handling of samples - Verification, and transfer of analytical methods - Testing, evaluation, and reporting of results & OOS Safety
Restrictions	Not applicable
Out of Scope	The Microbiology Laboratory was excluded from the scope of this inspection because it was relocating to new premises at the time of the inspection. Additionally, the laboratory requested that the stability studies be excluded from the scope of prequalification activities.
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
ERS	Electronic recognition system
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 Fischer 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
QHSE	Quality, Health, Safety, and Environment
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 system

1.1. Structural and general requirements

The laboratory, or the organisation of which it formed a part, was legally authorised by SAHPRA to operate and to assume responsibility for the test results, certificates of analysis, and all other types of work performed.

Since the 2021 WHO PQ inspection, several significant updates had been implemented at M&L Laboratory Services. Equipment and software enhancements included the upgrade of software systems, as well as the installation of a new UV spectrophotometer with updated software. Personnel developments involved key appointments and promotions in pharmaceutical operations, QA, and reference standard coordination. Infrastructure improvements included the installation of a borehole and a JoJo tank (water tank), the construction of a new chemical store, the establishment of an archiving facility, the implementation of biometric fingerprint readers, and the setup of a reference standard bank. Additional changes included a shift in company ownership and the introduction of a logbook tagging system.

Analysts reported to their respective supervisors, who in turn reported to the Pharmaceutical Business Lead. The quality department was comprised of two Pharmaceutical QA Managers: one primarily

responsible for OOS investigations, and another primarily responsible for the maintenance of the QMS. Both QA Managers reported to the QHSE Manager.

Senior management, including managers, business leads, and directors, was responsible for the establishment, implementation, and control of the quality system and data governance system by ensuring that appropriate policies, training, and technical systems were in place.

A procedure was established to mitigate any potential influences that could compromise impartiality, including the declaration of conflicts of interest and the safeguarding of all laboratory information, such as marketing authorizations, analytical methods, and the transfer of results and reports.

Organizational charts were established as part of the LIF to define the Laboratory's organizational and management structure, its position within the parent organization (Mérieux NutriSciences), and the interrelationships among management, technical operations, support services, and the QMS.

The responsibility, authority, and interrelationships of all personnel who managed, performed, verified, reviewed, or approved work impacting the results of laboratory activities were specified in job descriptions.

Trained substitutes or deputies were nominated for key management and specialized scientific personnel. A member of staff (QHSE Manager) was designated as the quality manager, responsible for ensuring compliance with the QMS and granted direct access to the M&L Managing Director. Adequate information flow and communication had been maintained among staff at all levels to ensure awareness of the relevance of activities and the Laboratory's mission.

1.2. Quality management system

The quality manager was responsible for ensuring the establishment, implementation, and maintenance of a QMS appropriate to the Laboratory's activities. Prior to implementation, the QMS was communicated to and understood by the appropriate personnel. All elements of the system were required to be documented either electronically or on paper.

For more details, refer to the relevant subsections under Section 1.

1.3. Control of documentation

An electronically available master list was established to identify the current version of the quality system documentation. The distribution of documents, including record forms, was controlled and reconciled in the event of revisions.

An applicable SOP was implemented for the control and review of documents. The procedure ensured that:

- Each document had a unique identifier, version number, and implementation date.
- Authorized standard operating procedures were readily accessible.
- Documents were regularly reviewed and updated as necessary.
- Invalid documents were promptly replaced with authorized, revised versions.

- Revised documents referenced previous versions, which were retained in archives to ensure traceability.
- Staff received training on new and revised procedures.
- Documentation, including records, was retained in accordance with national legislation for a period of ten years.

Staff were informed of new and revised procedures upon their entry into force. The QMS ensured that:

- Revised documents were prepared, reviewed, and approved at the same level as the original versions.
- Staff acknowledged awareness of the changes and implementation dates through signatures or alternative mechanisms.

Observations related to controlled documentation have been adequately addressed in the respective CAPA plan.

1.4. Change Control

The Laboratory implemented SOP for managing changes, providing a systematic method for assessing the impact of any change on activities that could affect the Company's procedures, outputs, and services. The scope of the procedure covered all corrective, preventive, and continuous improvement actions. This Change Control procedure applied to all changes impacting any activity with potential effects on the Company's procedures, outputs, and services.

When changes were required, such as improvements to existing procedures or the introduction of new methods, they were approved and monitored by the Business Lead Manager. Change processes were also addressed during management reviews, allowing oversight by senior management.

The laboratory authorized, documented, and validated all changes prior to implementation, including laboratory software configurations and modifications to commercial off-the-shelf software. Validation reports were available. The related observation was adequately addressed in the respective CAPA plan.

The quality manager ensured that changes were documented, assessed for impact, approved, planned, implemented, and reviewed. Staff acknowledged awareness of the changes and their implementation dates through signatures.

Selected Change Control requests were reviewed during the inspection.

1.5. Control of Records

The applicable SOPs described the identification, collection, indexing, retrieval, storage, backup, access, maintenance, and disposal of all quality and technical or scientific records, whether in paper, electronic, or hybrid format. The organization continued to use the an offsite archiving facility in accordance with an existing agreement. The most recent audit of the facility was performed in January 2020.

Original documentation, including calculations and derived data, calibration, verification records, and final results, was retained for approximately ten years, as required by the applicable SOP.

Records included data entered in analytical worksheets on consecutively numbered pages, with references to relevant records in appendices, on paper. In addition, samples were registered in LIMS upon receipt.

SOP for Control of Management System Documents was in place to control the issuance of blank paper templates for data recording.

Records for each test contained information to allow repetition or recalculation, including the identification of the personnel involved.

The LIMS ensured traceability. Access to stored electronic data was restricted to authorized personnel. Traceability was maintained by documenting the name and lot number of the reference substance. The test report also included the serial number of the HPLC column used for the analysis. Additionally, a certificate of analysis for the reference substance was available.

Quality and technical records were legible, retrievable, stored, and retained in a secure environment to prevent damage, deterioration, or loss.

Original records were stored under secure and confidential conditions, with access restricted to authorized personnel. Electronic storage and signatures were used in conformance with the requirements.

Quality management records included reports from internal and external audits, inspections, management reviews, risk assessments, and records of complaints and their investigations, as well as records of corrective and preventive actions.

It was noted that the laboratory registries of QMS parameters—such as OOS, CC, complaints, deviations, and logbooks—were documented using an application under the Mérieux domain. The application was equipped with a version history feature, allowing visibility of user access and changes made. However, it was also noted that the organization was in the process of validating the system for compliance with CFR Part 11, and this activity was ongoing as part of the recent acquisition by Mérieux NutriSciences.

The facilities' logbooks were wire-bound and sealed with a marker bearing a specific identification number.

Observations related to Controlled records have been adequately addressed in the respective CAPA plan.

1.6. Control of Data / Computerized Systems

A list of software systems was provided prior to the inspection.

SOP for Computer System Validation was available. According to this SOP, upon successful completion of a computer system's validation, the system was required to be maintained in its validated state. Any changes made to the system had to be documented and reviewed through a formal change control procedure. Each proposed change was to be evaluated to determine its potential impact on the validation status, ensuring that the system remained in a validated and compliant state.

It was noted that the laboratory did not have a documented process for the periodic review of computer systems, despite this requirement being defined in the Master Qualification Plan (MQP). Nevertheless, changes to computer systems were managed through the established Change Control system. Changes to the chromatography software system had been reviewed and discussed, and the need for changes or modifications had been identified during internal audits.

As stated in the relevant procedure, a periodic review of the qualified status was required every five years unless otherwise stipulated in the applicable equipment SOP. This process had to be formalised, and all available documentation was to be reviewed for completeness and current validity. Additionally, all operating ranges, limits, and calibration ranges were required to be verified against the actual used values.

A Master Qualification Plan was prepared as the primary planning document outlining the rationale for defining the scope of systems to be qualified and the resulting qualification activities. The plan also described the organisation and responsibilities for executing the required tasks.

SOP for Data Integrity, issued on 31 May 2023, defined the IT security policy for data integrity at M&L Laboratory. The procedure addressed the current backup practices in place at the laboratory. The objectives of the IT security policies were to limit access to information and information processing facilities, ensure that only authorised users had access to systems and services, hold users accountable for safeguarding information, and prevent unauthorised access to systems and applications.

To ensure the proper backup and security of all on-site M&L servers, the IT department was responsible for managing and maintaining the backup processes. Shared network data was stored on a cloud system, where it was protected using versioning. The backup process included several key components, such as the selection list defining the data to be backed up and the backup frequency specifying how often backups were performed. M&L operated servers both on-site and in the cloud, including one cloud server. Details of these servers were provided in the table included in the SOP.

Commercial off-the-shelf software, when used within its designed application range, was considered validated.

Computerized systems were operated in compliance with provider and/or laboratory specifications, and could be capable of recording system failures along with corresponding corrective actions, where applicable. The audit trail of the selected chromatography software application was thoroughly investigated during the inspection, with respect to administrative rights, the ability to remove audit trails, and the modification of user types and integration parameters.

The administrative rights for the chromatography software system were assigned to the QA Manager based on a documented risk assessment. The QA Manager was not involved in the day-to-day activities of the laboratory. The Empower software systems were networked and capable of communicating with each other.

For test data managed in computerized systems, electronic data was protected from unauthorized access through the implementation of an enabled audit trail, which was periodically reviewed. Additionally, electronic data were regularly backed up, remained retrievable, and were properly stored.

The electronic LIMS system remained under the ownership of the previous owner, and it was noted that a new system, supplied and supported by MXNS, was in the process of being implemented for use in the laboratory.

Observations related to the Computerized systems were adequately addressed in the respective CAPA plan.

1.7. Corrective and preventive actions

CAPAs triggered by OOS, deviations, customer complaints, external audit results, and other deviations were handled under their respective procedures, unless the duration exceeded 30 calendar days. In such cases, they were managed in accordance with the respective SOP.

1.8. Internal audits

The Quality Manager was responsible for organizing internal audits, including the planning, establishment, implementation, and maintenance of an audit program. Provisions were made to take into account the results of previous audits. The respective SOP was established to govern these activities:

- Planning and performing audits periodically by the Quality Manager (at least once a year) to enable systematic assessments.
- Defining the scope of each audit using risk-based criteria, including critical activities. The follow-up of the implementation of corrective and preventive actions was tracked but not formally documented.
- Reporting audit results to relevant management, discussing during management review, and communicating to staff.
- Implementing appropriate corrections and corrective actions promptly upon identifying nonconformities.

- Monitoring the effectiveness of implemented corrective actions. The effectiveness of CAPAs triggered in response to major NCs was to be followed within three months. This might be too short a timeframe for some rare activities.
- Retaining records as evidence of the audit program implementation and results.

The observation related to Internal audit was adequately addressed in the respective CAPA plan.

1.9. Complaints

Complaints were managed in accordance with the respective SOP.

The Laboratory Director was informed of the received complaints and ensured the coordination of the complaint handling process, including:

- A description of the process for receiving, verifying, investigating, tracking submitted complaints, and determining necessary actions.
- Assurance that appropriate action was taken within predefined timelines to resolve complaints.
- Verification that the entire process was documented and fully traceable.
- Informing the complainant of the investigation outcome, if possible, and upon request.

Where possible, a staff member not directly involved in the subject of the complaint was engaged in the handling process. The Quality Manager ensured the collection, verification, and recording of all necessary information, while the Operations Manager informed the complainant of the outcome of the process, provided the complainant's identity was available.

1.10. Management Review

Laboratory management reviews were convened every 12 months to monitor the effectiveness of the management system in accordance with the applicable SOP.

Senior management, including the Laboratory Director (or equivalent) and the Quality Manager, ensured that previous decisions had the intended impact on laboratory activities and resources. Planning for the subsequent period was also undertaken to maintain the suitability, adequacy, and effectiveness of the laboratory QMS.

Outcomes of management reviews were recorded, documenting all decisions and actions related to the effectiveness of the QMS, the improvement of laboratory activities, the allocation of required resources, and necessary enhancements.

Records of management reviews included information on:

- Suitability of policies and procedures.
- Performance management.
- Status of actions from previous reviews.
- Changes in internal and external factors impacting the laboratory.
- Results of internal and external audits or inspections and any required follow-up actions.
- Changes in laboratory activities.
- Adequacy of resources.
- Training programs.

- Feedback from customers and staff.
- Outcome of received complaints.
- Corrective and preventive actions.
- Effectiveness of implemented improvements.
- Follow-up and monitoring of identified risks and opportunities.
- Results of external quality control.
- Trend analysis results.
- Atypical and out-of-specification results.

1.11. Improvement

The laboratory identified and selected opportunities for improvement and implemented the necessary actions. These opportunities were identified through:

- Review of policies, procedures, and objectives.
- Audit and inspection results.
- Corrective and preventive actions.
- Risk assessment.
- Management review.
- Staff suggestions.
- Analysis of data, trends, and proficiency testing results.

Data analysis was conducted on the monthly numbers of OOS and deviations over the course of a calendar year. The application of a rolling 12-month window, consideration of the workload for each month, and the use of statistical analysis tools were discussed.

Additionally, the laboratory collected feedback from customers through methods such as customer satisfaction surveys, communication records, and the review of reports. This feedback was used as a tool for continuous improvement.

Samples were generally managed on a “First in – First out” basis; however, priority lists were also taken into consideration. These lists were discussed weekly with the client to establish the work schedule for the upcoming week.

Requirements for handling and evaluating proficiency test results were established in SOP for Handling of Proficiency Test Samples and Control of Out-of-Specification Proficiency Test Work, issued on 5 April 2024. A Proficiency Testing plan was provided annually, outlining the types of PT required for the following ten years. A table was available demonstrating the plan for the period 2025–2035.

The laboratory used LGC Axio, represented in South Africa by Industrial Analytical, as the service provider for proficiency testing samples in the pharmaceutical sector. The analyses could be verified through the service provider’s online portal.

The observation related to the Improvement was adequately addressed in the respective CAPA plan.

2. Planning and strategic management

2.1. Externally-provided services and supplies

The process for selecting and purchasing the products and services required by the laboratory was described in the respective SOP. This included measurement materials—such as reference materials and certified reference materials, as well as chemical and biological reference substances—equipment, reagents, and services, including calibration, qualification, sampling, testing, maintenance, proficiency testing schemes, and assessment and auditing.

The company indicated that they were in the process of transitioning to supplier control under Mérieux NutriSciences, which would result in the current process, as described above, being superseded.

Observations related to Service providers and suppliers were adequately addressed in the respective CAPA plan.

2.2. Quality Risk Management

The laboratory adopted a formal, well-established approach to risk management in accordance with the applicable SOP. This approach encompassed the identification, assessment, treatment, prioritization, continuous monitoring, and review of risks. A total of 47 risks were identified as part of the process-based risk assessment conducted for the pharmaceutical laboratory. Various types of risks associated with processes, activities, and products were considered. Procedures and methodologies were defined to minimize, monitor, and control the probability or impact of adverse events and potential failures; however, these procedures and methodologies were not referenced in the risk file.

Two primary principles of quality risk management were:

- Evaluation of the risk to quality based on scientific knowledge and ultimately linked to the protection of the patient. However, the company indicated that it had no direct contact with patients, and risks to patients were therefore not explicitly considered.
- The level of effort, formality, and documentation of the quality risk management process was commensurate with the level of risk.

An interdisciplinary team, led by the Quality Manager and including experts from various areas, was established to coordinate and facilitate risk-related decision-making. This process was carried out during annual management review meetings. The initiation and planning of the quality risk management process included defining the risk, assembling background information, and determining the appropriate decision-making levels. No documented timeline was associated with the process.

Observations related to the Quality risk management were adequately addressed in the respective CAPA plan.

3. Resources

3.1. Personnel

The competence requirements for personnel for each function were documented in job descriptions. The laboratory had established procedures and criteria for the selection and assessment of personnel competence in accordance with the QMS.

Staff undergoing training were supervised and assessed upon completion, with documented assessments. Competency re-assessments were conducted every two years. The Laboratory Director or a designated person authorized personnel to perform specific laboratory activities, ensuring that only sufficiently qualified and trained individuals were permitted to carry them out.

Procedures and criteria for the continuous assessment of personnel competence were documented, and training or requalification of personnel was provided as appropriate.

A training matrix of the competencies of each position was maintained.

The Pharmaceutical business lead was responsible for consigning samples to specific units and approving analytical test reports and certificates of analysis.

Designated qualified personnel were responsible for reviewing all analytical data to ensure the validity of test results and executing specific tests or analytical techniques requiring advanced technical training and knowledge.

Observations related to Personnel and their training were adequately addressed in the respective CAPA plan.

3.2. Premises

The laboratory's layout was available, and the facility was of suitable size, construction, and location. The premises adequately accommodated the requirements of a pharmaceutical testing laboratory and minimized risks to both staff health and the quality of analytical results. Emergency exits were present and accessible. Rest and refreshment rooms, as well as toilets, were separated from the laboratory areas. Changing areas were easily accessible for high-risk zones and were appropriate for the number of users. For general areas, staff changed in the corridor at the back of the facility and used laboratory shoes.

The sample reception area was designated for staff responsible for receiving samples upon handover by the client's courier.

Storage facilities were organized for the storage of samples, reagents, and equipment. Separate storage areas were maintained to ensure secure storage under appropriate temperature and humidity conditions, with access secured by locks. Controlled substances were marked, stored separately, and access to the sample storage area was restricted to designated personnel. Safety procedures were implemented for the handling and storage of toxic or flammable reagents.

Temperature and humidity were monitored through a digital monitoring system, which was also linked to an alarm system. Email notifications were generated in the event of temperature or humidity excursions. This system was used for monitoring refrigerators storing reference substances and samples, as well as the sample storage room. The monitoring system was connected to the system for

the sample storage room. A separate system was used to monitor the laboratory environment. The corresponding alarm logs and audit trail were reviewed, and the recorded excursions were discussed.

Access to restricted areas was controlled through biometric authentication (fingerprint) and key access.

Archive facilities were provided to ensure the secure storage and retrieval of all documents. Physical records were kept in secure rooms, while electronic records were retained with duplicate copies at an external facility. Document boxes designated for archiving were labelled using stickers supplied by offsite facility. The Laboratory maintained an index of each box's contents, along with a record of the movement of boxes to and from the offsite facility.

Procedures, such as SOP for Waste Disposal, were in place to ensure that all waste materials were managed in a procedurally correct manner, with due consideration for safety and environmental aspects, and in compliance with the requirements of Good Laboratory Practice. The procedure defined practices for the neutralization of solutions with specific characteristics. The scope of the procedure covered the handling and removal of waste other than classified poisons, solid non-toxic waste materials, biohazardous waste, and pharmaceutical excess sample waste, as well as the general principles of waste disposal.

The facility was equipped with two diesel generators and an uninterruptible power supply (UPS) system to ensure operational continuity during electrical power outages. The maintenance of emergency backup generators was governed by SOP for Operational and Maintenance Procedure for the Emergency Backup Generator. A logbook containing weekly check record sheets was available and was reviewed. The UPS system was maintained in accordance with SOP for Use and Maintenance of the UPS System.

The temperature mapping of the sample storage room, conducted on 16 May 2025, was available and reviewed. The purpose of this mapping exercise was to evaluate the ability of the Pharmaceutical Sample Storage Room and the Reference Standard Bank Room to consistently maintain the required temperature range of 15°C to 25°C under operational conditions over a five-day period. Additionally, the assessment aimed to verify the storage room's capability to maintain humidity levels at or below 60% RH, ensuring compliance with the required acceptance criteria throughout the mapping period under operational conditions.

Observations related to the Premises were adequately addressed in the respective CAPA plan.

3.3. Equipment, instruments, and other devices

The laboratory was required to have the necessary apparatus, equipment, instruments, or instrument systems used in pharmacopeial analyses to ensure the correct performance of tests and related activities.

All equipment, modules, and accessories were uniquely identified.

The documentation of selected equipment was reviewed to verify whether the analytical equipment had been adequately qualified, demonstrated fitness for its intended purpose, complied with pharmacopeial requirements, and/or followed manufacturer recommendations. The laboratory retained ultimate responsibility for equipment qualification.

A preventive maintenance schedule and equipment qualification plan were established for analytical equipment. These activities were carried out either by the laboratory or by a competent external service provider.

Observations related to the Equipment were adequately addressed in the respective CAPA plan.

3.4. Reagents and materials

Reagents and chemicals, including solvents and materials used in tests and assays, were required to meet appropriate quality standards and be suitable for their intended use. Commercial reagents were sourced from verified and approved qualified providers and were accompanied by certificates of analysis and material safety data sheets. Reagent management covered the entire life cycle—from purchasing and preparation to use and disposal—in accordance with SOPs. A requisition form was used to request chemicals from stock, and a register was maintained by the chemical storage custodian. The supplier supervised the stock, and new supplies were provided to the laboratory as needed. The laboratory had relocated chemical storage to two ventilated rooms, which had been inspected by the service provider (Fire Safety).

3.5. Reference substances

Reference substances from reputable commercial sources or those supplied by the pharmaceutical product manufacturer, approved by the national medicines licensing authority, were used.

The control of reference substances and materials was overseen by a designated staff member.

All reference substances and materials were assigned an identification number. Each batch received a new identification number, marked on individual vials, and referenced in analytical worksheets.

A register was maintained for all reference substances and materials, containing detailed information such as identification number, description, source, receipt date, batch designation, storage location, expiry or retest date, certificates, and material safety data sheets.

4. Technical activities

4.1. Sampling

The laboratory was not performing any sampling.

4.2. Incoming samples

Samples were received and handled following the SOP for Control of Pharmaceutical Products Received for Testing.

A standard test request form was required to be completed for every sample submitted to the laboratory.

Once the Analyst was assigned, the Laboratory Administrator issued the HPLC column and reference substances to the analyst. This issuance was documented in a column register sheet and a reference substance receipt and usage register sheet for each item.

Each sample and its accompanying documentation were assigned/labelled with a unique registration number (Job Number and Sample ID) through the LIMS software system, with labels generated by the same system. The laboratory began using this system in 2019. In cases where the label printer was out of service, labels were produced manually. Separate registration numbers were assigned for requests relating to different medicines, dosage forms, batches, or sources. A sample acknowledgment form was completed and submitted to the laboratory along with the samples for analyst assignment.

The laboratory was in the process of implementing a new LIMS system. The system validation was ongoing and being conducted by the supplier. The supplier had been evaluated through a questionnaire, and the corresponding User Requirements Specification was available.

The register (LIMS) and the corresponding acknowledgment form recorded the details of samples, including:
- Sample registration number.
- Receipt date.

Upon receipt, the sample was required to undergo visual inspection by laboratory staff to ensure conformity with the test request information. Any discrepancies or damages were promptly recorded, and queries were referred back to the sample provider.

Samples, both before testing and after the completion of required tests, were stored appropriately.

The Laboratory Administrator or a designated person determined the specific unit responsible for testing.

All documentation accompanying each numbered sample sent to the specific unit was verified to ensure it bore the correct identification number.

Observations related to the Incoming samples were adequately addressed in the respective CAPA plan.

4.3. Selection, validation, and verification of analytical procedures

SOP for Analytical Method Transfer described the procedure for conducting analytical method transfers within the Pharmaceutical Laboratory at M&L Laboratory. It outlined the process and requirements for transferring validated analytical test methods from an originating laboratory (Transferring Unit) to a receiving laboratory (Receiving Unit), which would adopt the methods for routine analytical testing. The SOP detailed the steps for method evaluation, preparation, execution of transfer testing, and compilation of final reports.

The method transfer applied to both quantitative and semi-quantitative analytical methods, such as limit tests, used in the analysis of pharmaceutical materials—including raw materials, drug substances, intermediates, ingredients, and products—critical to determining the quality of the finished dosage form. The SOP generally covered in-house test methods based on specialized techniques such as, but not limited to, HPLC, UV, TLC, titrimetric methods, microbiological assay methods, and IR.

The laboratory maintained a list of clients, each governed by a Service Level Agreement (SLA) specifying the products to be tested and the applicable specifications. One selected SLA was reviewed, including the list of products and agreed terms. Test methods were provided by the clients in the form of validated methods, and the laboratory was responsible for verifying these methods through the method transfer process, as described in the SOP.

Once samples were received, the Laboratory Supervisor assigned an analyst, who was also responsible for carrying out the respective method transfer.

The procedure ensured that the Receiving Unit could successfully perform the transferred analytical method. It included method evaluation, confirmation of equipment availability, and training provided by the Sending Unit. Approved samples were tested by the Receiving Unit according to an agreed protocol. All results were documented in a Method Transfer Report, and any deviations were managed in accordance with internal SOPs. Final qualification of the Receiving Unit was determined by the customer based on the transfer results. If acceptance criteria were not met, an OOS investigation was initiated.

The laboratory did not perform any method development or method validation; instead, the transfer of the method was considered as verification of the method. In general, the laboratory used validated methods provided by clients or manufacturers and only rarely applied pharmacopeial methods. However, the laboratory was to start analyzing samples for SAHPRA and WHO products, which might necessitate the use of pharmacopeial procedures.

System suitability tests were performed prior to and throughout the analysis of samples to ensure that the complete analytical system—including instrument, reagents, columns, and analysts—was suitable for the intended application, in accordance with the SOP for Use of the HPLC Systems. Trial injections, performed solely for system suitability purposes, were carried out only on the standard and resolution standard. Printouts of these injections were generated and attached to the analytical record.

Retention times were compared to confirm consistency, and resolution was verified to be within acceptable limits. Additionally, peak areas or heights were required to be comparable to those obtained in the previous analysis. If these criteria were met—i.e., retention times were consistent, resolution was acceptable, and peak areas or heights were within expected ranges—the system and column were deemed suitable for analysis.

The laboratory provided an additional SOP for Injection Procedure and System Suitability Criteria for Routine HPLC and UPLC Analyses, which detailed the requirements for system suitability tests. These tests were designed to ensure adequate performance of the chromatographic system, thereby supporting the accuracy and precision of results during routine analyses.

Observations related to the Method verification were adequately addressed in the respective CAPA plan.

4.4. Technical records

The analytical worksheet, or any suitable alternative document, was an internal record used by the analyst to document information related to the sample, test procedure, reagents, standards, materials, calculations, and test results. It included all raw data generated during the analysis and served as documentary evidence to confirm whether the sample under examination complied with the specified requirements.

A unique analytical worksheet was used for each numbered sample or group of samples. Completed analytical worksheets from different units relating to the same sample were consolidated to form a complete record.

The following information was verified to be recorded in the analytical worksheet:

- Registration number of the sample
- Page numbering, including the total number of pages (including annexes)
- Date of the test request
- Dates on which the analysis was started and completed
- Name and signature of the analyst
- Description of the sample received
- Identification of the test equipment used
- Reference substances used, including the provider, lot number, and potency or content
- Results of the system suitability test, if applicable, along with any analytical acceptance criteria
- Identification of reagents, solvents, and columns (if applicable) employed
- Results obtained, including those from other internal analytical sections or external laboratories, if applicable
- All values obtained from each test, including blank results, were entered immediately on the analytical worksheet
- All graphical data, whether obtained from recording instruments or plotted manually, were attached or traceable to an electronic record file or document.

It was noted that the process of sample preparation was not recorded step by step; instead, reference was made to the respective test method for documentation. Mobile phase solution preparation was documented using a dedicated form for Mobile Phase Solution Preparation. The completed analytical worksheet was signed by the responsible analyst and subsequently reviewed and approved by designated qualified personnel, either in paper format or electronically. Calculations and data transfers were checked in an appropriate and systematic manner or were controlled by a validated electronic system.

The analytical worksheet and any attachments, including calculations and recordings of instrumental analyses, were archived together with the specification.

4.5. Testing

Testing methods were made available by customers. The monograph of the appropriate pharmacopoeia was used in rare cases when testing for compliance with specifications, as the laboratory primarily operated under client-specific Service Level Agreements.

Test methods should provide the information necessary to enable trained analysts to perform the analysis in a reliable and reproducible manner. The system suitability criteria defined in the method were fulfilled.

Samples were randomly selected for review of their respective documentation, covering the entire process from receipt of the sample to the issuance of the Certificate of Analysis, including sample retention. If applicable, the investigation of any OOS results was also reviewed.

Observations related to the Testing were adequately addressed in the respective CAPA plan.

4.6. Evaluation of test results

For compliance testing, the product was required to meet all acceptance criteria outlined in the approved specification. Test results were compared with the specification limits to determine whether the sample met the requirements, and a conclusion was drawn regarding the conformity of the test results with the specification.

Each test result was traceable to an appropriate primary reference substance, sourced either from a pharmacopoeia or a manufacturer, or, where applicable, to a certified reference material.

4.7. Out-of-specification results

When a suspected OOS result was identified, a review of the procedures applied during the testing process was conducted by the supervisor together with the analyst or technician, using a checklist prior to performing any retesting. In accordance with SOP for Nonconforming Work, the investigation ensured that:

- If stable, original sample preparations were not discarded until the investigation was completed.
- Raw data were examined to identify any possible discrepancies.
- All calculations were checked.
- The equipment used was verified to be qualified and calibrated, and acceptable system suitability tests had been performed.
- The appropriate reagents, solvents, and reference substances were used.
- The correct glassware was used.

The identification of an error that caused an aberrant result invalidated the result, and a retest of the sample, to be conducted by the same technician or analyst, was required.

Suspected OOS results could only be rejected if they were attributed to an identified error. In cases where the investigation was inconclusive, a confirmatory determination was required to be performed by another trained analyst. Where applicable, hypothesis testing was considered to better define the root cause.

All investigations and their conclusions were recorded. If an error was identified, a root cause analysis was conducted, and any corrective actions were documented, implemented, and recognized as risks and opportunities for improvement.

4.8. Reporting of results

The Operational Supervisor compiled the analytical test report in hard copy, containing the analytical test results for approval by the Pharmaceutical Business Lead or the designated deputy. Subsequently, the dossier containing all relevant information pertaining to the sample—including its origin, chain of custody, and analytical data—was archived.

Any amendments or changes to the original analytical test report required the issuance of a new document, in which:

- Any change of information was identified and dated.
- The reason for the change was included in the new corrected document.
- The new report was uniquely identified and contained a reference to the original document it replaced.

In cases of OOS results, the initial CoA reflected the OOS finding prior to the issuance of a new and final CoA. Both versions were shared with the client.

The analytical test report provided the following information:

- A title.
- The laboratory registration number of the sample.
- The laboratory test report number.
- The name and address of the laboratory testing the sample.
- The name and address of the originator of the request for analysis.
- The name, description, and batch number of the sample, where appropriate.
- An introduction giving the background to and the purpose of the investigation, if applicable.
- A reference to the specifications used for testing.
- The results of all the tests performed.
- A conclusion as to whether or not the samples were found to be within the limits of the specifications used.
- A statement to the effect that the results relate only to the items tested, calibrated, or sampled.
- The date on which the tests were completed.
- The signature of the authorized person reviewing and authorizing the report.
- The name and address of the original manufacturer.
- The date on which the sample was received.
- The expiry date or retest date, if applicable.

A Certificate of Analysis, containing the same information as the analytical test report, was prepared for each batch of a substance or product.

The laboratory was responsible for the accuracy and completeness of all information provided in the report.

4.9. Retained samples

The Laboratory did not retain any samples. For more details, refer to the respective observation for incoming samples.

5. Safety rules

Environmental health and safety policies were followed in the Quality Control Laboratory to protect staff, the public, and the environment. Safety rules also included proper handling of compressed gas cylinders with adherence to color identification codes. Appropriate protective clothing—such as eye protection, masks, and gloves—was available and suitable for use. The facility was properly signed.

It was recommended that a dedicated area specifically for the removal of broken glass be made available in the laboratory. Using a designated tool helps prevent cross-contamination, minimizes the risk of injury to personnel, and ensures that glass fragments are handled and disposed of safely and appropriately, in line with good laboratory safety and housekeeping practices.

Miscellaneous	
Assessment of the Laboratory Information File	The Laboratory Information File was submitted and reviewed.
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 ***M&L Laboratory Services (Pty) Ltd.-(Mérieux NutriSciences - MXNS)***, located at ***40 Modulus Road, Ormonde, Gauteng, RSA 2135, Johannesburg; 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. 1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report, Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
   Short name: WHO GPPQCL Guidelines, TRS No 1052, Annex 4
   https://www.who.int/publications/i/item/9789240091030

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
   https://www.who.int/publications/m/item/trs961-annex2

3. 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
   https://www.who.int/publications/m/item/annex-4-trs-929

4. 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/m/item/annex-4-trs-

5. 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***
   https://www.who.int/publications/m/item/trs986-

6. 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
   https://www.who.int/publications/m/item/annex-2-trs-957

7. 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
   https://www.who.int/publications/m/item/trs957-annex3

8. 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
   https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex6-gmp-sterile-pharmaceutical-products.pdf

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
   Short name: WHO TRS No. 961, Annex 7
   https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex7-transfer-technology-pharmaceutical-manufacturing.pdf?sfvrsn=2e302838_0

10. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 96, Annex 9)
    ***Short name: WHO TRS No. 961, Annex* 9**
    https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

11. General guidelines for the establishment, maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report, Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    https://www.who.int/publications/m/item/trs943-annex3

12. Guidelines on heating, chelation, and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report, Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex
    Short name: WHO TRS No. 1010, Annex 8
    https://www.who.int/publications/m/item/Annex-8-trs-1010

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report, Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.
    Short name: WHO TRS No. 981, Annex 2
    https://www.who.int/publications/m/item/trs981-annex2

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report, Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3.
Short name: WHO TRS No. 981, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-981

15. WHO guidelines for preparing a laboratory information file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva. WHO Technical Report Series, No. 961, 2011, Annex 13.
Short name: WHO TRS No. 961, Annex 13
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs961-annex13-guidelines-preparing-laboratory-information-file.pdf?sfvrsn=54d1f397_2https://www.who.int/publications/i/item/9789241209922

16. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report, Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4.
Short name: WHO TRS No. 992, Annex 4
https://www.who.int/publications/m/item/trs992-annex4

17. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature–sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report, Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5.
Short name: WHO TRS No. 992, Annex 5
https://www.who.int/publications/m/item/trs992-annex5

18. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report, Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
https://www.who.int/publications/m/item/trs1010-annex10

19. Good chromatography practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report, Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO Good chromatography practices
https://www.who.int/publications/m/item/trs1025-annex4

20. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report, Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

21. WHO model certificate of analysis. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second report, Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 4.
Short name: WHO TRS No. 1010, Annex 4
https://www.who.int/publications/m/item/trs1010-annex4

22. Good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth report, Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3
Short name: WHO TRS No 1033, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-1033

23. Guidelines on pre-approval inspections. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report, Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 7
Short name: WHO TRS No 902, Annex 7
https://www.who.int/publications/m/item/trs902-annex7

24. Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first report, Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 3
Short name: WHO TRS No 1003, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-1003