Nelson Labs®
A Sotera Health company

Quality Manual / Site Master File

Combined document

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Revision History:

Rev. No.	Date Revised	Revision Summary	Author
13	18 APR 2019	- Addition of revision history - Complete rearrangement of the quality manual in line with the requirements of ISO 17025:2017 - Update of organizational structure - Change of procedural references to new MasterControl references - Upgrade to multi-use document Quality Manual / Site Master File (incorporation of site master file). - General upgrade of outdated information - Including definition of GxP criticality	BB
14	10JUL2020	- Replacement of Jos Bollen by Bart Boerjan as 24-hour contact. - Addition of cleaning, disinfection and steam sterilization validation of reusable devices to scope of services. - Clarification on mutual acceptance of data (MAD) for GLP studies and mutual recognition agreement between US FDA and EU GMP for GMP studies - Introduction of HCM for direct reporting lines and responsibilities. - Split of Health, Safety and Environment management and maintenance of facility. - Replacement IT Manager by IT Director EMEAA - Clarifying note on replacement QP and end responsibility Qualified Person. - Alignment of processes and referenced procedures - Clarifying note added on job aids - Use of Kaizen cards for bottom-up continuous improvement - Use of LIMS for equipment status introduced - Involvement of QP in management review process clarified. - Included new GLP website of Sciensano	BB

TABLE OF CONTENTS:

1 SCOPE

This document and related Standard Operating Procedures (SOPs) are applicable to the ISO 17025, GLP and GMP requirements needed for our third party laboratory participation services (§1.2).
Throughout this document, paragraph 4, 5, 6, 7 and 8 are aligned with the ISO 17025:2017 requirements.

This document is reviewed yearly. Illustrations from underlying documents are to be evaluated on the latest revision of the respective documents.

1.1 BRIEF HISTORY OF THE LABORATORY

The European Laboratory was started in 1991 with the opening of a new facility in Leuven, Belgium. The laboratory was named Toxikon Europe NV and was part of the Toxikon Corporation with headquarters in Boston, US. This laboratory was initially specialized in environmental chemistry and pollutant testing, for which it was officially accredited. Toxikon Europe gradually expanded into a contract laboratory specializing in Analytical Chemistry Studies, *in vitro* Toxicology, and Microbiology Studies, servicing the Life Science Industry.

In 2007, Toxikon Europe moved into a brand-new state of the art facility at the research park in Leuven. During the past 10 years, the laboratory has constantly developed its business by becoming a world-leading lab in the field of container-closure interaction studies (Extractables and Leachables).

Toxikon Europe was acquired by Sotera Health (formerly Sterigenics International LLC) on October 31, 2017. Following the acquisition, the name of the company changed to Nelson Labs NV and became part of the business unit of Nelson Laboratories within Sotera Health. Sotera Health goes to market through its three companies: Nelson Labs™, Nordion® and Sterigenics®:

Figure 1: Illustration of Nelson Labs as one of the 3 business units under the Sotera Health umbrella

Nelson Labs is a global provider of laboratory testing and consulting services and performs over 400 microbiological and analytical laboratory tests across the medical device, pharmaceutical and tissue industries.

Nordion is a global provider of mission-critical radioisotopes used for the prevention, diagnosis and treatment of disease. Nordion ensures the reliable supply of Cobalt-60, the primary input to the gamma sterilization process, to the leaders in healthcare, including sister company Sterigenics.

Sterigenics is a global provider of comprehensive sterilization solutions that eliminate potential health threats, using the most advanced and reliable medical sterilization techniques available. Sterigenics has deep expertise across Gamma, Ethylene Oxide (EO), Electron Beam (E-beam) and X-ray sterilization.

In November 2017, the parent company name changed from Sterigenics International LLC to Sotera Health LLC. Its three operating companies – Nelson Labs™, Nordion® and Sterigenics® – continue to maintain their current names.

The business activities of Toxikon Europe are from November 2017 embedded in the laboratory services of Nelson Labs. As from April 24th, 2018 the laboratory is branded as Nelson Labs and no longer uses the Toxikon reference. Legally "Nelson Labs NV" and commercially "Nelson Labs Europe" are used.

Further references to Nelson Labs in this document apply to the Leuven laboratory facility only.

1.2 TESTING SERVICES IN SCOPE

Nelson Labs is a service based company and its success in the contract testing area has been through a demonstrated ability to provide testing services of high scientific quality, in a cost-effective manner, and in conformance with projected schedules. Nelson Labs mainly serves the medical device, pharmaceutical and biotechnology industries.

Testing services provided by Nelson Labs include:

- General Analytical Chemistry – Extractables/Leachables – Compendial testing
- Product/Special Chemistry/Impurities
- *In Vitro* Toxicology Testing
- Microbiology Testing
- Drug Release and Stability Testing
- Cleaning, disinfection and steam sterilization validation of reusable devices

This document is designed to register the Quality Management System and Technical Competencies of Nelson Labs' facility. Services are mainly focussed on the following industry segments:

- Medical Device
- Biotech
- Pharmaceutical
- Other (Miscellaneous)

1.3 PREDICATE RULES AND APPLICABLE REGULATIONS FOR THE QUALITY SYSTEM

The laboratory has the ability to develop, validate and conduct methodologies in a wide variety of scientific disciplines and support research and development efforts in compliance with different regulations (see §10).

Depending on the predicate regulation to which the test should comply, three regulations are incorporated into the laboratory quality system.
The ISO/IEC 17025 for testing laboratories is used as a backbone to which requirements of EudraLex Good Manufacturing Practices (GMP) and OECD Good Laboratory Practices (GLP) are added where applicable.

It remains the responsibility of our sponsors to request and qualify Nelson Labs NV as supplier for the appropriate regulation in relation to the testing service (§1.2) requested.

Nelson Labs continues to monitor all regulatory changes for appropriate updates to all of its quality and regulatory programs.

Nelson Labs maintains its quality system and management procedures compliant with the requirements of the above regulations. As a consequence, most quality and management procedures are covered by all three regulations. For the technical procedures, the applicable regulation is indicated in section 0.

1.3.1 Licensing, certification and accreditation by notified bodies

All SOPs are prone to inspection by competent authorities (§1.3.1.1, 1.3.1.2, 1.3.1.3 and 1.3.1.4).

1.3.1.1 *ISO/IEC 17025 accreditation of the laboratory by BELAC*

ISO/IEC 17025 compliance is monitored by BELAC, a Belgian government institution. BELAC is a signatory of all existing MLAs (multilateral agreements) and MRAs (multilateral recognition agreements) of EA (European co-operation for Accreditation), ILAC (International Laboratory Accreditation Cooperation) and FALB (Forum of Accreditation and Licensing Bodies).

In this way, reports and certificates issued by BELAC accredited bodies are internationally recognized.

1.3.1.2 *GLP compliance monitoring of the laboratory by Sciensano*

Sciensano represents Belgium in various international networks and assures compliance of good laboratory practices for activities on behalf of international clients such as the Organisation for Economic Cooperation and Development (OECD).

Nelson Labs NV and its national GLP authority Sciensano fulfil the requirements defined in the Mutual Acceptance of Data (MAD) system which allows OECD member countries to mutually accept Study Data generated according to Good Laboratory Practice regulations. These data can thus be accepted in regulatory filing requiring compliance to 21CFR58.
Refence: http://www.oecd.org/env/ehs/mutualacceptanceofdatamad.htm

1.3.1.3 *GMP compliance monitoring of the laboratory by FAHMP*

The FAHMP is the Belgian competent authority which grants authorisations and checks that medicines and health products conform to current regulations concerning manufacture, distribution, delivery and import. Only QC-testing on medicinal products as manufacturing

activity is applicable for Nelson Labs.
Nelson Labs NV holds a valid EU GMP manufacturing and import authorization for QC testing and hence Study Data generated by Nelson Labs NV in accordance with Good Manufacturing Practice regulations can be accepted in regulatory filing requiring compliance to 21CFR210 and 21CFR211.
Reference:
https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra

1.3.1.4 *FDA registration and compliance with 21 CFR Part 11, 210 & 211*

Next to the official European certification, the laboratory is also FDA registered and prone to inspection by this US Authority. As stated in §1.3.1.3, the Belgian FAHMP is allowed to conduct inspections on behalf of FDA under the mutual recognition agreement concluded on 16 November 2018 between the European Union (EU) and the United States (USA).
Principles from 21 CFR part 11 on e-records and e-signatures are implemented where applicable.

2 REGULATORY QMS REFERENCES

- ISO/IEC 17025, General Requirements for the Competence of Testing and Calibration Laboratories, with respect to the technical and quality system requirements applying to test laboratories
- EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice (Medicinal Products for Human and Veterinary Use) and Annexes
- OECD Principles of Good Laboratory Practice N°1 to 19
- 21 CFR Guidance for Industry Part 11, Electronic Records; Electronic Signatures

Note: guidelines are referenced throughout this document where applicable (e.g. ICH Q2(R1))

3 TERMS AND DEFINITIONS

For the purpose of Nelson Labs' quality management system, general definitions are provided in ISO 9000. ISO/IEC 17000 is preferred, when related to certification and laboratory accreditation.

Depending on the predicate regulation, terminology used, especially for roles and responsibilities, can be different and is based on:

1. ISO/IEC 17000 Conformity Assessment – Vocabulary and General Principles
2. ISO 9000 Quality management systems - Fundamentals and vocabulary
3. VIM, International Vocabulary of Metrology, issued by BIPM, IEC, IFCC, ILAC, ISO, IUPAC, IUPAP, and OIML
4. OECD Principles of Good Laboratory Practice N°1 to 19.
5. EudraLex The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

4 GENERAL REQUIREMENTS

4.1 IMPARTIALITY

Nelson Labs' personnel are free from any commercial, financial or other pressures, which might influence their technical judgment. Influence on the results of examinations and tests by external persons are excluded. The remuneration of analysts is independent of the number of tests carried out and of the results of the tests. All employees sign agreements related to their independence.

Given the nature of the testing services which Nelson Labs provides, the risk of personal benefit and impartiality is considered low. For release testing on medicinal products, release of testing results is the sole responsibility of the qualified person (EudraLex Vol 4 Annex 16).

Being embedded in a Sotera Health corporate organisation, every employee of the laboratory has to take a course on anti-bribery and corruption and sign approval with the Sotera Health Ethics and code of conduct.

4.2 CONFIDENTIALITY

Nelson Labs has policies and procedures in place to ensure the protection of its clients' confidential information and proprietary rights, including procedures for protecting the electronic storage and transmission of results.

If required by the sponsor, confidentiality and non-disclosure agreements are put in place.

5 STRUCTURAL REQUIREMENTS

5.1 LEGAL ENTITY

Nelson Labs is a Limited Liability Company (Société Anonyme – Naamloze Vennootschap), according to Belgian Company Law since 28th December 1990 (founded as Toxikon Europe), with a capital of 125.000 €, fully subscribed and paid up. Nelson Labs is located at Romeinsestraat 12, 3001 Leuven, Belgium and delivers analytical and microbiological laboratory services to support the medical device, biotech and pharmaceutical industry. The company number (Ondernemingsnummer) is 0442.395.719.

When required during regulatory inspection, more information can be requested from management and is to be found in the coordinated statutes (Document in Dutch) dated on April 24th, 2018 and signed by Isabelle Mostaert (associated notary).

5.2 RESPONSIBLE MANAGEMENT

This section describes the responsibility, authority, and management structure of the facility. Top Management has ultimate responsibility for the laboratory testing services and quality programs. Together with the Quality Manager Top Management is also responsible for setting the laboratory quality policy and meeting the expectations and needs of clients and Regulatory-Monitoring authorities. The Managing Director ensures that all staff are trained to understand, implement and maintain the quality objectives outlined in this document, at all levels.

Study Directors, Department Supervisors and Directors are responsible for implementing the quality programs described in this document. They, together with technicians and all designated staff members, are responsible for the quality of services under their control.

The organization of Nelson Labs is described as follows: the hierarchical structure is defined through the organizational charts (§5.3) Responsibilities are departmentalized by functional area (technical areas). The responsibilities of the different functions are described in detail within the "function descriptions" (AUX1815) as well as the authority and interrelationships of all personnel who manage, perform or verify work. Named organizational charts and direct reporting lines can be found in an oracle cloud Human Capital Management system (HCM).

The Managing Director has the final responsibility for the European Operations and reports to the Vice President EMEAA of Nelson Laboratories.

Top Management: Managing Director and VP EMEAA Operations holding final business-related responsibilities. This means providing adequate facilities, equipment, personnel and knowledge in order to assure testing services in a compliant and timely manner.

The following Key Managerial personnel reports directly to the VP EMEAA but has a "dotted" reporting line to the Managing Director:

Technical Management: The Director of Lab Operations to which the Department Supervisors (Physico-Chemistry, Micro-Tox and Pharma) report to, holds final responsibility for all commercial laboratory related activities and corresponding technical release of results under ISO 17025, and commercial R&D. The Head of QC holds the final technical responsibility related to QC testing activities on medicinal products, under GMP. Together with the Scientific Director for non-commercial R&D and business development related items, they hold the final technical responsibility.
Project Management: Interfacing with clients and coordination of the reporting process by Study Directors, which contain results released by Technical Management. Project Management and Study Directors are the internal clients who order a specific analysis (under the scope of the laboratory) from the Department Supervisors.
Quality Assurance Management: Ensuring compliance with the applicable international standards, functioning independently from laboratory operations and reporting directly to Top Management by the QA Manager.
Health, Safety and Environmental Management: Responsible for activities and processes related to Health, Safety and Environment.
Facility Maintenance: Responsible for all infrastructural related activities, (Facility engineer).

The following Key Managerial personnel reports directly into the corporate Sotera Health structure but has a "dotted" reporting line to the VP EMEAA and Managing Director:

Support Management: Holding overall responsibilities:
- with respect to all IT related activities (IT Director, EMEAA)
- related to the Sales services of the company (Sales & Business Development Manager)
- related to Marketing (Marketing Manager)
- related to Finance (FP&A Manager)
- related to HR (HR Officer)

The Qualified Person operates in close collaboration with the Quality Assurance unit but holds final responsibility as per EudraLex volume 4 Annex 16:

Qualified Person: Holding final responsibility for all quality decisions (GMP) related to the QC testing of medicinal products and holding final responsibility to issue Certificates of Analysis and GMP study reports. Nelson Labs QP never holds the final certifying responsibility but supports the sponsor's certifying QP with a confirmation statement indicating that Nelson Labs testing is performed according to GMP.

There is substitute arrangement for the key management tasks and responsibilities of the Managing Director, Scientific Director, Director of Lab Operations, QA Manager, Department Supervisors, Director E&L Services and all Study Directors, in order to maintain a continuity of the management system.
The only exception is the Qualified Person, who can only be replaced by another Qualified Person, entitled as registered industrial pharmacist after formal cumul acceptance by the Belgian Federal Agency for Health and Medicinal Products.

According to GMP, the overall organisational procedure is initiated by the Study Director, who, after Sponsor communication, orders a study from the Department Supervisor. According to ISO, the latter organises the planning and follow-up of the study, and based on the obtained results, releases a test report (containing results). The raw data is passed to the Study Director, who, based on the test report and raw data, writes either a test result report or a study report, which is communicated to the Sponsor after QA approval. For the QC testing of medicinal products, the only difference implicates the final responsibility of the Qualified Person for the release of a certificate of analysis.

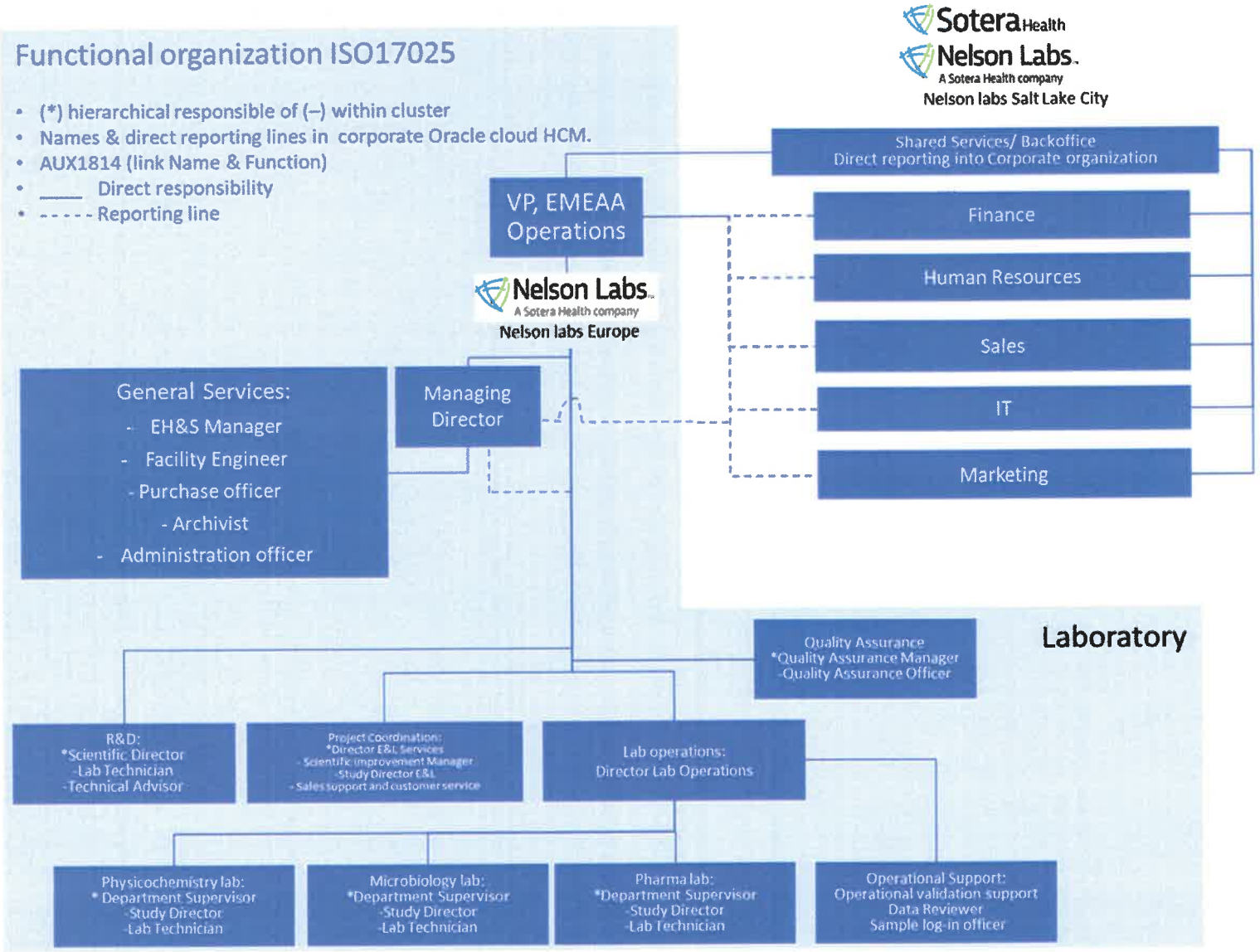
For GLP studies, the overall organisational procedure is initiated, conducted and reported by the Study Director GLP, in collaboration with QAU.

Site Leadership Team meetings, study director meetings, lab meetings and quality meetings are held on regular basis as to discuss operational matters and monitor the effectiveness of the general operation and quality system within Nelson Labs.
Quarterly (during Site Leadership Team meetings) the status of yearly management review imperatives is evaluated. Monthly, during Site Leadership Team meetings, a dashboard containing Quality Performance Indicators is discussed in order to track the implementation of goals, continuous improvement, objectives and specific actions.

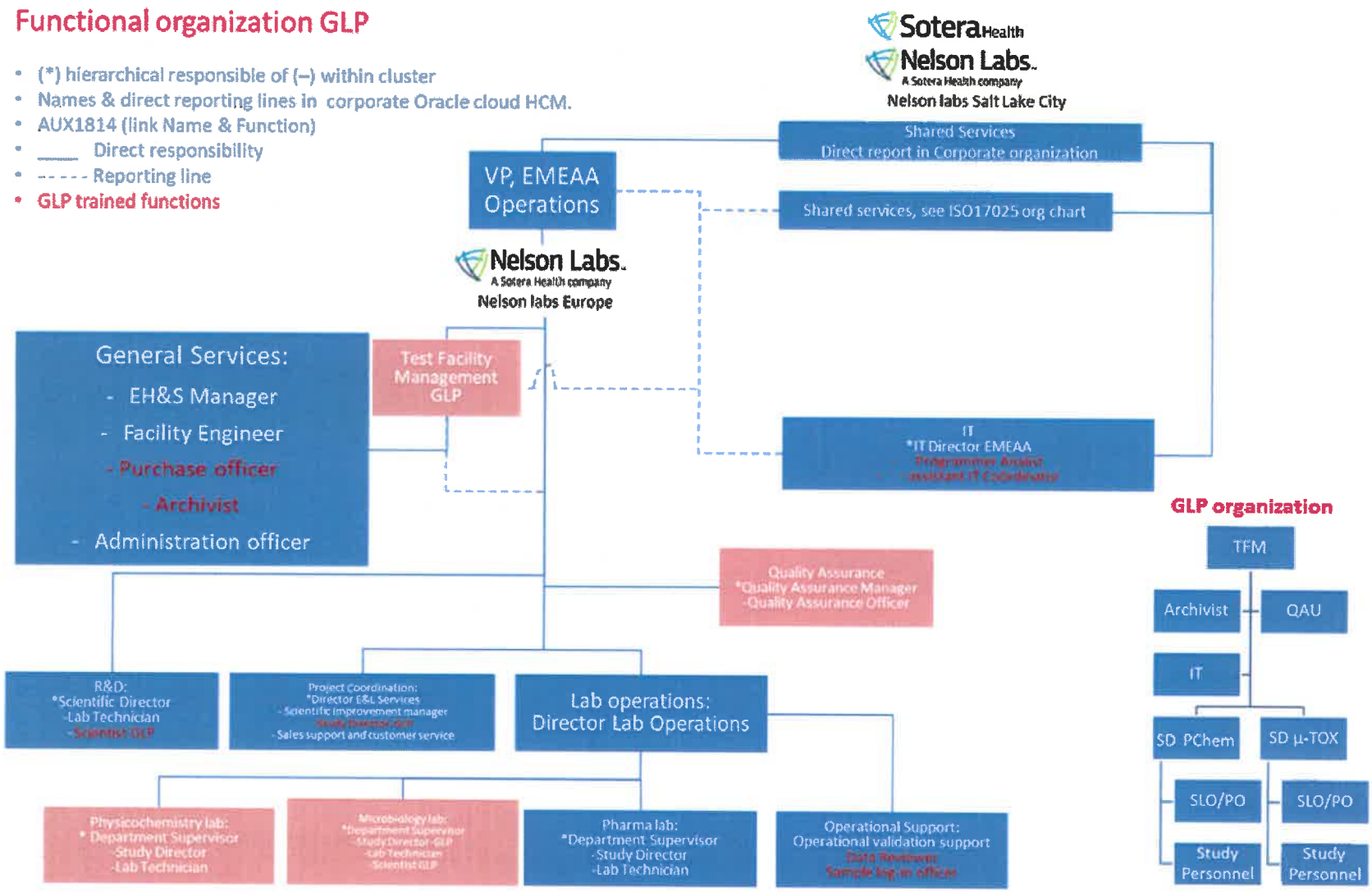
5.3 ORGANIZATIONAL CHARTS

In the following sections the hierarchical relationships for every predicate regulation are indicated thereby using the nomenclature from those regulations (ISO 17025: AUX1800; GMP: AUX1801 and GLP: AUX 1803).

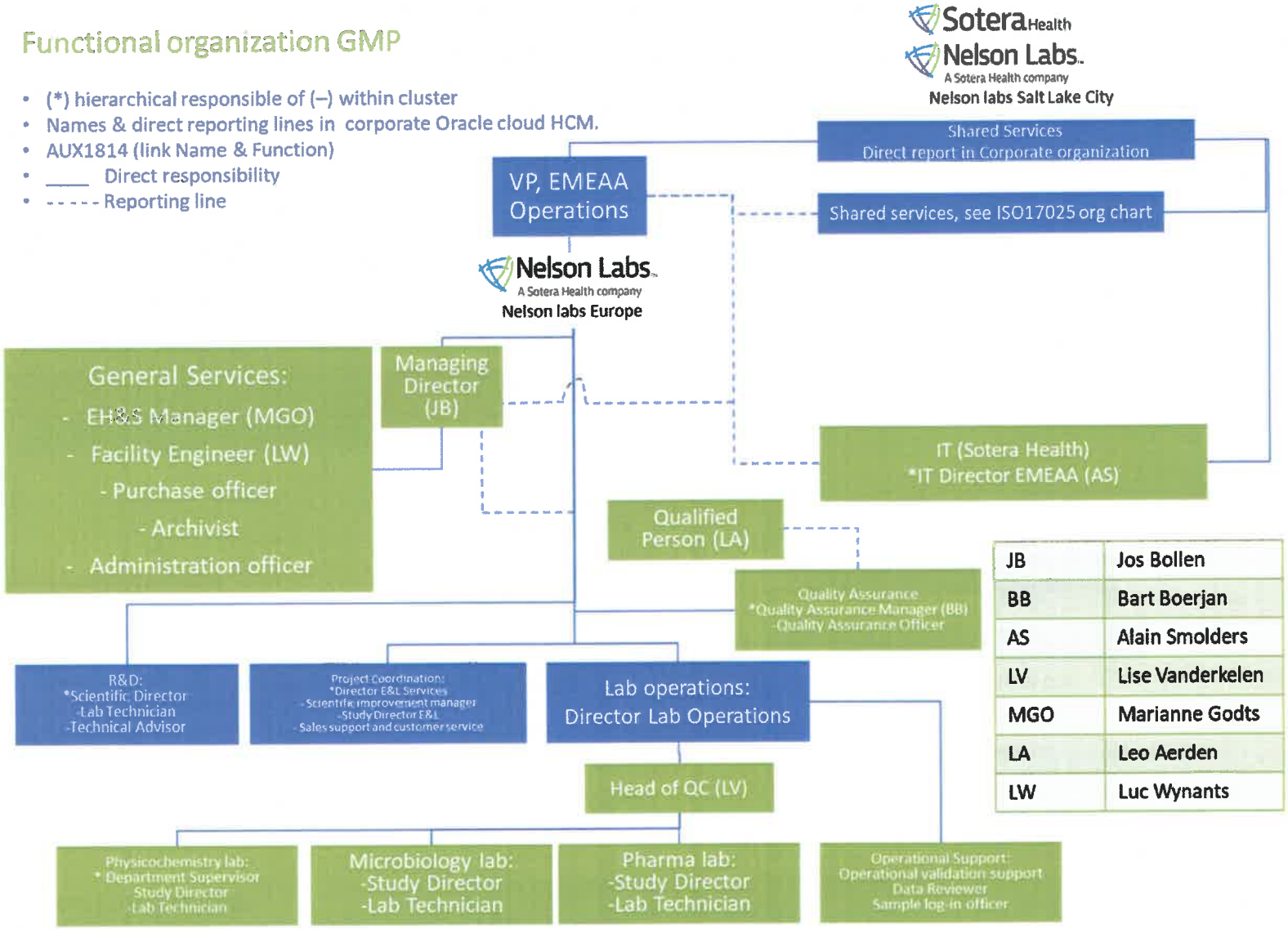
5.3.1 Organizational chart ISO 17025



5.3.2 Organizational chart GLP



5.3.3 Organizational chart GMP



5.4 RELATED DOCUMENTATION

These procedures are fully documented in the following Standard Operating Procedures (SOPs):

SOP0448	Company Organization Table
SOP0420	Job descriptions
SOP0440	Personnel and Organization
SOP0445	Conduct of Site Leadership Team, Quality, Lab and SD Meetings
SOP0199	Matrix of Technical Competence

6 RESOURCE REQUIREMENTS

6.1 GENERAL

Nelson Labs's strategy for resource management always returns to "fit for purpose" or "suited for intended use" and "maintaining the validated state".

6.2 PERSONNEL

Nelson Labs' Management ensures the competency of all who operate specific equipment, who perform tests, evaluate results, and sign test reports.

Nelson Labs' Management formulates the goals with respect to the education and the skills of the laboratory personnel. Nelson Labs has a policy and procedures for identifying training needs and providing initial and ongoing training of personnel. The training program is relevant to present and anticipated tasks of the laboratory, on a retrospective, ongoing, and prospective basis.

Nelson Labs Management authorizes specific personnel to perform particular types of tests, to issue test reports, to give opinions and interpretations, and to operate particular types of equipment. The laboratory ensures that such personnel work in accordance with the laboratory's quality management system. Job descriptions are maintained for managerial, technical, and all support personnel involved in testing, the generation of data, and any other support role related to the testing services provided. The laboratory maintains records of the relevant competence, educational and professional qualifications, training, skills, and experience of all technical personnel.

6.2.1 Related Documentation

These procedures are fully documented in the following SOPs:

MAN0015	Training Policy
SOP0441	Personnel, Recruitment and Evaluations
SOP0432	Personnel, Medical Controls, Hygiene and Working conditions
SOP0419	Personnel and Training
SOP0420	Job Descriptions
SOP0199	Matrix of Technical Competence
SOP0475	Training in MasterControl - User guide for Document Management team

6.3 FACILITIES AND ENVIRONMENTAL CONDITIONS

Nelson Labs Management ensures that the physical laboratory and non-laboratory environment of the building do not invalidate the results or adversely affect the required quality of any measurement. Contamination is prevented by effective separation of adjacent areas with incompatible activities. Good housekeeping rules and standard laboratory hygiene and safety procedures are employed by all personnel.
To avoid the presence and development of pests in the laboratories and offices, a pest prevention and control program has been developed in collaboration with a specialised company. The pest control and prevention program will focus on rodents (rats and mice), cockroaches and flying insects.

Nelson Labs monitors critical environmental conditions as required by relevant specifications or where they may influence the quality of the results. Tests are suspended when the environmental conditions, which may affect the tests, are in question. Specialized test areas are monitored and maintained to specific technical/condition requirements specific to the type of work. Examples include cell and tissue culture and sterility rooms and other conditioned environments. Nelson Labs has a Thermoguard monitoring system in place for controlled storage rooms, such as refrigerators and climatic chambers, which generates alarm messages to Nelson Labs personnel, in case an Out-Of-Specification signal occurred.

6.3.1 Related Documentation

These procedures are fully documented in the following SOPs:

MAN0013	Risk assessment for "mixed use" of premises, resources and systems
SOP0442	Facilities Description
SOP0443	Visitor Registration at Nelson Labs Premises
SOP0224	Use and Maintenance of cell and tissue culture room
SOP0278	Monitoring of controlled storage for temperature and humidity
SOP0198	Use and Maintenance of sterility room
SOP0444	Use and Maintenance of emergency generator

6.4 EQUIPMENT

Nelson Labs is equipped with appropriate instrumentation for conducting the tests within its scope of application. The equipment is operated by authorized/trained personnel. All instruments are qualified by means of calibration wherever applicable. Nelson Labs has a Validation Master Plan in place, which provides a framework and practices for validation and qualification of equipment, computer systems and networked systems for Nelson Labs' laboratory processes based on GAMP 5 (Good Automated Manufacturing Practices published by ISPE, 2008). It is also applicable to the validation of Macros and Spreadsheet applications. The Validation Master Plan aims to ensure that validations and qualifications are done efficiently and consistently throughout the organization and meet regulatory, quality and business requirements. The plan should ensure that the company's validation procedures are followed. The company Validation Master Plan is the basis of individual project Validation Plans.
The process of new equipment to be qualified (based on EudraLex Volume 4, Annex 15) is initiated by an assessment for criticality. Hereby, GxP-critical systems are established and monitored through an IQ (initial qualification), OQ (operational qualification) and PQ (performance qualification) program. DQ (design qualification) procedures are also utilized as required for appropriate selection procedure for acquisition of equipment. All changes to qualified equipment shall be made traceable to a risk assessment and are validated accordingly

in order to *Maintain a Validated State*. In addition, an Event and Error Log is kept, and formal change control applies when critical changes are made to a GxP-controlled system.

6.4.1 Related Documentation

These procedures are fully documented in the following SOPs:

MAN0012	Validation Policy
SOP0277	Equipment Use and Maintenance
SOP0383	Equipment General Procedures
SOP0386	System Validation
SOP0387	Operational Change Control for Lab- and IT Systems

6.5 METROLOGICAL TRACEABILITY

6.5.1 General

All equipment used for tests, having a potential or significant effect on the accuracy or validity of the test result, are calibrated (and/or qualified) before being put into service, and recalibrated (and/or requalified) on a routinely basis. The equipment is labelled to indicate its status with a physical label either indicating the qualified state directly or a scannable label for the LIMS system.

6.5.2 Specific Requirements

Nelson Labs has full traceability for all related standards/materials in use to the International System of Units (SI). Nelson Labs also employs the use of certified reference materials to provide reliable chemical characterization and utilizes consensus standards wherever applicable. Nelson Labs performs interlaboratory and/or proficiency testing wherever required and available.

6.5.3 Reference Standards and Reference Materials

Nelson Labs has procedures for safe handling, transport, storage and use of reference standards and materials in order to prevent contamination or deterioration, and in order to protect their integrity.

Reference standards and materials are purchased with certificates, to facilitate tracking to international standards. Certified weights and thermometers are available for internal verification purposes and are periodically calibrated by an external ISO17025 calibration service supplier. These materials are used for no other purpose within the laboratory.

Internal reference standards are to be used for calibration only and for no other purpose, unless it can be shown that their performance as reference standards is not impacted. Reference materials can be used for quality control purposes. Checks needed to maintain confidence in the calibration status of reference standards materials may be carried out according to defined procedures and schedules, as required. All materials are tracked and their proper storage and integrity maintained.

6.5.4 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0391	Calibration Weights for Balances
SOP0367	Use and Calibration of Thermometers
SOP0390	Control of Reference Standards and Materials

SOP0377	Chemical Lab Inventory: Preparation, Traceability, Labeling, Acceptability and Usage
SOP0378	Determination of the purity of qualitative and quantitative standards
SOP0215	Characterization of test, control and reference items
SOP0227	Culture and maintenance of reference micro-organisms

6.6 EXTERNALLY PROVIDED PRODUCTS AND SERVICES

Nelson Labs has procedures for selecting suppliers of materials and services, and to assure the conformance of purchased items. The Department Supervisors are responsible for providing specific order information and release of materials from designated vendors in case of absence of a certificate of analysis. They select and manage contract service providers from a qualified supplier list. Criteria for supplier acceptability include providing acceptable levels of performance in terms of quality, cost, delivery, and service.

6.6.1 Externally provided Products

Requests for the purchase of routine materials or services are processed through the Purchase Officer. For non-routine purchases, the Department Supervisor appoints specifications, which should be purchased by the Purchase Officer using qualified suppliers.

After arrival of the materials, the product is logged in using Nelson Labs' LOMS or LIMS system and calibration or reference standards are verified before release into the laboratory.

6.6.2 Externally provided Services

Nelson Labs uses subcontractors in a limited way. Nelson Labs' business strategy is to only work in areas where Nelson Labs has the expertise and control over the scientific test data, and does not have to rely on outside sources to provide this information. In the event Nelson Labs does require subcontracting of tests, all subcontractors must be qualified through vendor qualification procedures under ISO 17025. Only qualified, accredited and licensed subcontractors who comply with the ISO standard may be utilized as per the contract requirements between Nelson Labs and the Sponsor, and for the work in question, within the testing scope of Nelson Labs.

Concerning QC testing of medicinal products, intended for the generation of a certificate of analysis, subcontracting laboratories should be certified according the GMP in the European Union, and in Belgium according to the accreditation by the Belgian authorities, represented by the Federal Agency for Medicines and Health Products (FAMHP).

6.6.3 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0381	Vendor and subcontractor Qualification and Monitoring Procedures
SOP0380	Purchasing Services, Equipment and Supplies
SOP0384	Notification and Inspection Procedures of Material and Equipment Receipt – Lab Inventory
SOP0208	Conduct of a GMP study
SOP0382	Communication and sample flow between Nelson Labs NV/Toxikon US and Nelson LLC

7 PROCESS REQUIREMENTS

Many factors collectively determine the correctness and reliability of tests and/or calibrations as performed by the laboratory. The extent to which these factors contribute to total uncertainty may differ from test to test, and in the calibration performed. Nelson Labs takes all relevant factors like human factors; accommodation and environmental conditions; test and calibration methods and method validation; equipment; metrological traceability; sampling; the handling of test and calibration items; into account in developing test and/or calibration methods.

7.1 REVIEW OF REQUESTS, TENDERS AND CONTRACTS

Nelson Labs has procedures for contract or project review available to ensure that project requirements are clearly and adequately defined and understood; the laboratory has the capability and resources to meet the requirements; and the appropriate test methodology is selected and capable of meeting the Sponsors' requirements. To facilitate the project review, the author of a quotation (and/or protocol) stipulates which methodology is applicable on the samples by means of a reference to the SOP, Sponsor Specified Procedure (SSP) and/or by specifying additional project specific requirements in a protocol (if applicable). Any differences between the test request forms, purchase orders (POs), or any other contract review documentation and instructions are resolved prior to beginning any work, and the project is logged as "non-conforming". Each contract must be acceptable both to the laboratory and the Sponsor.

The same contract review process is repeated whenever amendments or other post delivery requests are made or required after work has started, and any requested procedural changes or deviations are communicated to the Sponsor and finally approved and documented using Nelson Labs' LOMS system.

7.1.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0200	Study Logging Procedures, Sample Receipt, Storage and Contamination Control Practices Using LOMS System
SOP0446	Quotation Procedures
SOP0202	Communication with Sponsors
SOP0211	Assignment of Study Responsibles – GLP
SOP0213	Study Plan for a GLP Study

7.2 SELECTION, VERIFICATION AND VALIDATION OF METHODS

Nelson Labs has Standard Operating Procedures (SOPs) for all tests within its scope, as well as for the use and operation of all relevant equipment, and on the handling and preparation of items for testing. All instructions, standards, manuals and reference data relevant to the work of the laboratory is maintained in an updated and current status and is made readily available to all personnel through the laboratory computer network, MasterControl, or through certified hard copies.

7.2.1 Selection of Methods

Nelson Labs uses test methods that meet the needs of the Customer and which are appropriate for the tests it performs, preferably those published as international, national, or regional standards. Nelson Labs ensures that it uses the latest edition of a standard unless it is not

appropriate or possible to do so. When necessary, the standard is supplemented with additional details to ensure consistent application, and incorporated into company SOPs and protocols, wherever required and applicable.

When the Customer does not specify the method to be used, the laboratory selects appropriate methods that have been published either in international, national, or regional standards, by reputable technical organizations, or in relevant scientific texts or journals, compendia methods, or as specified by the manufacturer. Laboratory-developed methods or methods adopted by the laboratory are also used if they are appropriate for the intended use and if they are appropriately validated. The Customer is informed as to the method chosen and works collaboratively with the laboratory to reach consensus on method selection. The laboratory first confirms that it can properly perform the new methods before introducing the tests. If the standardized method changes, the confirmation/validation is repeated. Nelson Labs will inform the Customer when the method proposed by the Customer is considered to be inappropriate or out of date.

7.2.2 Laboratory Developed Methods

When it is necessary to employ methods not covered by standardized methods, these are subject to agreement with the Customer and include a clear specification of the Customer's requirements and the purpose of the test. Laboratory developed methods are planned activities and assigned to qualified individuals equipped with adequate resources to develop the method. Effective communication among all related departments is conducted for proper implementation.

7.2.3 Non-Standard Methods

Deviations from approved test methods have to be documented, technically justified, authorized and when having potential impact, accepted by the Customer. For new test methods, procedures are developed prior to the tests and calibrations being performed, and must include all applicable technical SOP/SSP required content.

7.2.4 Validation of Methods

Nelson Labs validates all non-standardized methods, laboratory designed methods, methods used outside their original scope, and modifications to methods to confirm that they are fit for the intended use. The validation is as extensive as necessary to meet the needs in the given application or field of application. Extensive validations of analytical methods are performed based on the ICH Q2(R1) guideline.

When validated methods are transferred between laboratories and sites, their validated state should be maintained to ensure the same reliable results in the receiving laboratory.
Nelson Labs uses an 'analytical method transfer' process that establishes documented evidence that the analytical method works as well in the receiving laboratory as in the originator's laboratory, or the transferring laboratory.

7.2.5 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0204	Method Validation
SOP0216	Reporting and Rounding off Results
SOP0205	Measurement of Uncertainty and Validation for Microbiological Methods
SOP0426	Non-conformances/Deviations (including retest)

SOP0202	Communication with Sponsors
SOP0206	Estimation for Measurement of Uncertainty
SOP0429	Out-Of-Specification Procedure

7.3 SAMPLING

Nelson Labs has material selection procedures in place as required by each specific test preparation standard or test method. Nelson Labs is provided test material by the customer and does not implement sampling plans or statistical sampling techniques based on its scope of business. The customer provides to Nelson Labs the appropriate sample or subsection of a sample for testing purpose.

The laboratory records describe, or make traceable, the sample condition, amounts received, amounts utilized, and sample preparation procedures for testing. No other specific sampling plans are part of the scope of services provided by Nelson Labs, or its management system.

7.4 HANDLING OF TEST OR CALIBRATION ITEMS

Nelson Labs has procedures for the receipt, handling, protection, retention and/or disposal of test items, including all provisions necessary to protect the integrity of the test item. Upon receipt, the test item is uniquely identified. Any non-conforming samples or projects are logged and testing will not be initiated until all requirements, based on stated paper work or other specified conditions, as described in the relevant test method, are met. When there is any doubt as to the suitability of a test item, or when an item does not conform to the description provided, or the test requirements are not specified in sufficient details, the Study Director consults the Sponsor for further instructions before proceeding. In this case, samples are indicated as "non-conforming", and are put on hold. All relevant discussions between Study Directors and Sponsor are recorded.

Nelson Labs has procedures and appropriate facilities for avoiding deterioration, loss or damage to the test item during storage, handling and preparation; instructions provided with the item shall be followed.

7.4.1 **Related Documentation**

These procedures are fully documented in the following SOPs:

SOP0200	Study Logging Procedures, Sample Receipt, Storage and Contamination Control Practices using LOMS System
SOP0278	Monitoring of controlled storage for temperature and humidity
SOP0203	Subsampling of aqueous and organic solvent based extracts/test solutions for extractables and leachables studies
SOP0221	Sample Return and Sample Destruction procedures
SOP0207	Conduct of a leachable study
SOP0201	Management of specially regulated substances
SOP0454	Aseptic Techniques

7.5 TECHNICAL RECORDS

Nelson Labs retains original observations, derived data, calibration records, and a copy of each test report for a defined period. The records for each study contain sufficient information

- to establish an audit trail,
- to facilitate, if possible, identification of factors affecting the uncertainty and
- to enable the study to be repeated under conditions as close as possible to the original.

The records include the identity of personnel responsible for performance of each test, and data auditing personnel involved.

Nelson Labs has no control over sampling uncertainty, as test materials and products are sampled by the Sponsor and provided to Nelson Labs (see also §7.3).

7.5.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0417	Development, review, reconciliation and archiving of forms and raw data
SOP0430	Good Documentation Practice (GDP) and Signature policy
SOP0220	Contents and Final Review of a Completed Project File

7.6 EVALUATION OF MEASUREMENT UNCERTAINTY

Nelson Labs has procedures in place for estimating uncertainty for all calibrations and types of calibrations. Nelson Labs validates its methods taking predefined criteria for accuracy and precision, and as a consequence maximum uncertainty, into account. By doing so Nelson Labs guarantees appropriate accuracy in reporting and interpretation of uncertainty upon Sponsor's request.

7.6.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0204	Method Validation
SOP0216	Reporting and Rounding off Results
SOP0205	Measurement of Uncertainty and Validation for Microbiological Methods
SOP0202	Communication with Sponsors
SOP0206	Estimation for Measurement of Uncertainty

7.7 ENSURING THE VALIDITY OF RESULTS

Nelson Labs ensures the quality of its test results by QC verification prior to issuing results. All reported results are double checked by reviewing raw data sheets, instrument print-outs, draft reports, and all other relevant documentation to guarantee the traceability of the reported results. Finally, QAU reviews all projects.

The controls can be divided in three categories: first line controls (e.g. QC verification and application of control charting (where applicable)), second line controls (e.g. blind sample analysis) and third line controls (e.g. participation in interlaboratory comparison and/or proficiency testing programs).

7.7.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0220	Contents and Final Review of a Completed Project File
SOP0425	Quality Assurance and Quality Control
SOP0210	Assuring the Quality of test results
SOP0208	Conduct of a GMP study
SOP0214	Conduct of a GLP Study
SOP0424	QA program GLP
SOP0209	Conduct of a commercial R&D study

7.8 REPORTING OF RESULTS

7.8.1 General

Results for all studies carried out by Nelson Labs are reported in a Test Report. This report includes all the information requested by the Customer and necessary for the interpretation of the test results and all information required by the method used.

Depending upon the type of study and in agreement with the Customer, results are represented in the form of a Test Result Report or a Study Report.

7.8.2 Test Report

This type of report is released by the (assistant) Department Supervisor under ISO 17025.

7.8.3 Test Result Report

This is a short report form, with summarized procedures and results. The results may be presented in tabular form.

7.8.4 Study Report

A test result report may be expanded into a full study report if required by the Customer to provide a detailed description of the applied procedures and of the obtained results, per ISO 17025 requirements.

7.8.5 Calibration Reports

Nelson Labs can provide certificates and calibration information with respect to instrumentation utilized during study conduct, either internal or external certificates, upon Sponsor's request. Nelson Labs does not provide independent calibration certification services for customers. It is an internal program for Nelson Labs' equipment only.

7.8.6 Certificate of Analysis

Under GMP, a Certificate of Analysis is issued by the Qualified Person in case of QC testing on medicinal products.

7.8.7 Conclusions, Statement of Conformity, Opinions, and Interpretations

Conclusions and statements of conformity can only be made based on a predetermined and on the report documented decision rule (e.g. specification). Opinions and interpretations shall be clearly marked and may include recommendations, guidance, or other statements interpreted to be subjective.

7.8.8 Test and Calibration Results Obtained from Subcontractors

Results for tests/calibrations performed by subcontractors are clearly identified in the test report.
Only qualified subcontractors through appropriate supplier qualification procedures are utilized.

7.8.9 Electronic Transmission of Results

In the case of transmission of test and calibration results by phone, fax, or other electronic means, copies of these transmissions are retained by the laboratory to assure delivery. PDF files are typically utilized.

7.8.10 Amendments

Any corrections and/or additions to the signed final report are in the form of an amended report. An amended report is clearly identified as such on the cover page and the header of each subsequent page. All changes made to the amended report are listed within a section "Amendments" together with the reason (and a rationale whenever applicable) for changes, and signed and dated by the Study Director and QAU.

7.8.11 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0217	Reporting of a GLP study
SOP0218	Test Report, Test Result Report and Study Report Generating Procedures
SOP0219	Certificate of Analysis Generating Procedures

7.9 COMPLAINTS

Nelson Labs has procedures for the resolution of complaints received from Sponsors or other parties, and to file complaints towards her suppliers.

Considering customer complaints, three categories are attributed: Level 1, Level 2, and Level 3, depending on the gravity of the issue.

Records are maintained of all complaints, investigations and corrective and preventive actions taken by the laboratory.

7.9.1 Related Documents

SOP0428	Dealing with Complaints

7.10 NON-CONFORMING WORK

Nelson Labs has procedures in place to monitor for actual or potential non-conformances to the Management System or Sponsor contracts, including all testing and/or related calibration work. The following procedures are in place:

- responsibilities and authorities for the management of non-conforming work are designated and actions (including halting of work and withholding of test reports as necessary) are defined and taken when non-conforming work is identified;
- an evaluation of the significance of the non-conforming work is made, including a full technical and quality review;

- remedial actions are taken timely, together with any decision about the acceptability of the non-conforming work;
- the responsibility for authorizing the resumption or retesting of work is defined prior to data release;
- Customers are notified of deviations where potential impact on results of tested products cannot be excluded.
- Customers are contacted for corrective actions and/or retesting when non-conformances are noted after data is reported and potential impact on reported results cannot be excluded (see also §7.8.10).

Deviations from SOPs, protocols, SSPs and quotations might occur during a study, and can lead to remedial actions such as retests. Retests can also originate when Out-of-Specifications (OOS) results were obtained.

Based on the criticality of the non-conformance (grade A (=critical), grade B (=major) or reoccurring grade +* (=minor)) and when a significant risk exists for the integrity of the results or for the effectiveness of the Quality Management System, corrective actions are to be considered.

7.10.1 **Related Documentation**

These procedures are fully documented in the following SOPs:

SOP0426	Non-Conformances/Deviations (including Retest)
SOP0429	Out-Of-Specification Procedure

7.11 CONTROL OF DATA AND INFORMATION MANAGEMENT

Calculations and data transfers are subject to appropriate checks in a systematic manner. Where computers or automated equipment are used for the acquisition, processing, recording, reporting, storage or retrieval of study data, the laboratory ensures that the integrity of the results is protected. For GxP critical systems, requirements from EudraLex Volume 4 annex 11 and/or OECD N°17 and 21CFR11 are implemented whenever appropriate.

7.11.1 **Related documentation**

Management system documentation:

MAN0014	Data Integrity Policy
SOP0220	Contents and Final Review of a Completed Project File
SOP0425	Quality Assurance and Quality Control
SOP0481	Audit trail review
SOP0208	Conduct of a GMP Study
SOP0214	Conduct of a GLP Study
SOP0408	Open lab ECM User Procedure
SOP0409	Open lab ECM System Procedure

8 MANAGEMENT SYSTEM REQUIREMENTS

8.1 MANAGEMENT SYSTEM OPTION ACCORDING TO ISO/IEC 17025:2017

Nelson Labs maintains a Management system according to option A of the ISO 17025:2017 standard.

8.2 MANAGEMENT SYSTEM (MS) DOCUMENTATION

Nelson Labs has established, documented and implemented a MS, and maintains and continually improves its suitability and effectiveness in accordance with the requirements of ISO 17025:2017.
The basic elements of Nelson Labs' MS are the Quality Manual / Site Master File, standard operating procedures (SOPs), protocols, sponsor specified procedures (SSPs), instructions, and any other documentation or instructions provided to Nelson Labs by its Customer or study Sponsor.

Note: Job aids can be generated and managed in the same document management system as the documents described above, but they are not in scope of the QMS.

Study Directors, Department Supervisors, technicians, and other employees are obligated to work in accordance with the specific requirements of the documented MS. All internal quality-related activities are governed by procedures and written instructions. The document structure consists of a Quality Manual / Site Master File, policies and procedures (management, operations, Quality management system and supporting flows).

Nelson Labs manages these processes in accordance with the requirements of ISO/IEC 17025:2017.

8.2.1 Quality Manual / Site Master File

The Quality Manual / Site Master File includes the scope of the management system. This document outlines and refers to documented procedures established for the MS and their interrelationship to other processes of the MS.

8.2.2 Quality Policy Statement

This statement and the implementation and adherence to the principles of ISO 17025:2017, EudraLex GMP and OECD GLP, reflects management's commitment to provide assurances of the highest level for managing quality and focusing on meeting customer requirements and satisfaction.

8.2.3 Quality Objectives

Nelson Labs' management ensures that quality and management system objectives are established at relevant functions and levels within the company. Nelson Labs demonstrates this through this Mission Statement:

Mission statement: We help the best companies in the world improve the quality of life by providing the highest standard in laboratory testing, partnering to bring life-enhancing innovative products to market.

This commitment of continuous improvement is monitored on a monthly (MMR, monthly management review) and yearly (YMR, yearly management review) basis and decided upon in EMEAA leadership meetings and assured by Nelson Labs training policy, based on Plan-Do-Check-Act cycle.

8.2.4 Nelson Labs Values

SAFETY, PEOPLE, INTEGRITY, CUSTOMER FOCUS and EXCELLENCE

8.2.5 Nelson Labs Goals and Management Commitment

Based on the corporate Sotera Health goals, Nelson Labs employees strive towards achieving the following goals with the highest respect of the company values:

- Expand Global Network
- Deliver Profitable Volume Growth
- Create One Company Capabilities
- Maximize Investment Returns

The entire Nelson Labs staff team must adhere to the spirit and letter of the firm's quality policy as well as the directives outlined in the Quality Manual / Site Master File and its subordinate documents, and maintain impartiality and independence of testing activities. I have continuously supported these objectives and plan to continue to be actively involved through personal commitment, active participation, and financial support in meeting the goals and objectives outlined in this document. I will continually be available to address all management system issues either directly or through directives to Quality Assurance Unit and Laboratory Management.

With regard to our GLP compliance program, the Test Facility Management will provide all necessary means (qualified and sufficient personnel, appropriate infrastructure and dedicated instrumentation) that are indispensable for the proper conduct of a GLP compliant study.
The GLP qualified personnel will be specifically assigned, and will receive appropriate tools and time for the proper conduct of a GLP study.

Top and Quality management approves this document by electronic approval.

Jos Bollen	Eric Meyers	Bart Boerjan
Managing Director	Vice President EMEAA	Quality Assurance Manager

8.3 CONTROL OF MANAGEMENT SYSTEM DOCUMENTS

8.3.1 General

Nelson Labs has procedures to control all documents that comprise the quality documentation system. Documents are circulated for use by management and technical staff as required. All documents issued to personnel in the laboratory are reviewed and approved prior to issue.

All document management related processes are under control of a document management team which resides at QAU.

The Quality System of Nelson Labs is based on and often refers to 'external' documents, such as regulations, standards, normative documents and guidelines.

Three levels of (internal) documentation define the Quality System of Nelson Labs:

- The first level is the Quality Manual / Site Master File, which include or make reference to established policies and supporting procedures including technical procedures.

- The second level is comprised of SOPs and SSPs (Sponsor Specified Procedures), which are written documents to describe an operation, analysis or action that could influence data quality.
- The third level consists of data recording forms in support of SOPs: documents / templates to record raw data, log equipment activities or to describe the actual organizational / technical situation of Nelson Labs (or a department thereof).

8.3.2 Internal Documents

Internal documents can be of different types: Standard Operating Procedures (SOPs), Sponsor Specific Procedures (SSPs), Protocols, Logs, Instructions, Forms, or other Nelson Labs generated documents.
All internal documents are uniquely identifiable and revisioning and changes thereof are traceable.
Nelson Labs has processes in place which guarantee review, approval and training of internal documents prior to issue.
All documents are accessible to staff by logging into the corporate document management tool called MasterControl. Access is managed in cooperation with document management.

8.3.2.1 *SOP, SSP and forms*

The respective overview Matrices for Standard Operating Procedures, Sponsor Specific Procedures and forms can be found on the local network and are accessible through MasterControl:

T:\Quality\Quality Public\MasterControl

SOPs are periodically evaluated for their suitability and completeness.

8.3.2.2 *Protocols*

Study and test specific protocols are, on request of the sponsor, generated and, at least, approved by Study Director, QAU and Sponsor prior to initiation of a test.

An overview can be found on the local network:

T:\Quality\Quality Public\Protocols Nelson Labs (Pdf)

8.3.3 External Documents

External documents, such as books, regulations, standards, reference articles, etc. are indexed and contained in a database of secured Office® documents on the laboratory computer network. The use of external document control ensures that only current external information is utilized and updated on a periodic and/or scheduled basis.

8.3.4 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0416	External Document Control – Library Management
SOP0413	Development, Change Control, Periodic Review and Archiving of a Standard Operating Procedure
SOP0414	Development, Review and Archiving of Sponsor Specified Procedures (SSP)
SOP0151	Document Management using MasterControl
SOP0179	MasterControl Document Management – User guide for general staff

SOP0189	MasterControl Document Management – User guide for Document Owners and Management
SOP0417	Development, review, reconciliation and archiving of forms and raw data
SOP0430	Good Documentation Practice (GDP) and Signature policy
SOP0194	MasterControl Document Management - User guide for Document Management team
SOP0475	Training in MasterControl - User guide for Document Management team

8.4 CONTROL OF RECORDS

8.4.1 General

Nelson Labs has procedures for identification, collection, indexing, access, storage, maintenance and disposal of quality and technical records.

8.4.2 Technical Records

Nelson Labs retains original observations, derived data, calibration records, and a copy of each test report, for a defined period. The records for each study contain sufficient information

- to establish an audit trail,
- to facilitate, if possible, identification of factors affecting the uncertainty and
- to enable the study to be repeated under conditions as close as possible to the original.

The records include the identity of personnel responsible for performance of each test, and data auditing personnel involved.

Nelson Labs has no control over sampling uncertainty, as test materials and products are sampled by the Sponsor and provided to Nelson Labs.

8.4.3 Quality Records

Quality records are generated and maintained by Nelson Labs to demonstrate the successful operation of the facility's quality and management system.

8.4.4 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0417	Development, review, reconciliation and archiving of forms and raw data
SOP0430	Good Documentation Practice (GDP) and Signature policy
SOP0392	Archive Procedures
SOP0220	Contents and Final Review of a Completed Project File
SOP0447	Billing procedures
SOP0393	Back-up and Restore of Software and Data

8.5 ACTIONS TO ADDRESS RISKS AND OPPORTUNITIES

Nelson Labs addresses risks and opportunities by built in impact analysis in the quality management flows of deviation handling, corrective and preventive actions, dealing with complaints, lab and IT system validation, change control and management review.

Periodical trending analysis and KPI evaluations might bring forth new imperatives which are evaluated in a risk based manner.

Ad hoc risk assessments are preferably done by a failure mode and effects analysis by taking probability, severity and detectability of the risk into account.

8.5.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0426	Non-conformances/Deviations (including retest)
SOP0427	Corrective / Preventive Action Procedures
SOP0428	Dealing with Complaints
SOP0386	System Validation
SOP0387	Operational Change Control for Lab- and IT Systems
SOP0449	Management Review Procedures
SOP0431	Quality Risk Management

8.6 IMPROVEMENT

Nelson Labs continually measures goal setting and the effectiveness of its management system through the use of the quality policy, quality objectives, audit results, quality system data analysis, corrective and preventative actions, Quality metrics and Quality management review status reports. In addition, a training policy was created, including the qualification of personnel by education, experience and training. An internal training program was designed to adequately train the personnel.
Opportunities for improvement are identified as output from the Quality Management system (see 8.5) or bottom-up using Kaizen cards.

8.6.1 Related Documentation

Management System documentation:

SOP0449	Management Review Procedures
SOP0445	Conduct of Site Leadership Team, Quality, Lab and SD Meetings
MAN0015	Nelson Labs Training Policy

8.7 CORRECTIVE ACTIONS

8.7.1 General

Nelson Labs has procedures to implement corrective and/or preventive actions to eliminate the causes of existing non-conformances in order to prevent re-occurrence. Furthermore, Nelson Labs evaluates the need for improvement to prevent occurrence of non-conformances, either technical or within the quality management system.
Corrective/Preventive actions are initiated with a cause analysis, followed by a selection and implementation of corrective/preventive actions and finally monitoring of the planned actions. Additional audits are also possible.

8.7.2 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0426	Non-conformances/Deviations (including retest)
SOP0427	Corrective / Preventive Action Procedures

8.8 INTERNAL AUDITS

Nelson Labs conducts process and facility based audits to verify the compliance, implementation and suitability of Nelson Labs' quality activities with the requirements of the management system and to gain evidence of full traceability. The internal audit program addresses all elements of the quality system covering both the management system and testing activities with respect to the ISO/IEC 17025, GLP and GMP. The QAU is responsible for planning and organizing audits.

The QAU or an authorized and qualified external auditor carries out all technical audits. Audits of Nelson Labs' QAU are performed on an ongoing basis by Sponsor audits or other external auditors or Nelson Labs' management.

Results of internal quality audits are recorded, agreed upon corrective/preventive actions, individuals responsible, and time schedules for completion are defined.

Process and facility based inspections are performed at least every 2 years according an Internal Audit Schedule and the results are incorporated in the Management Review.
These internal audits are used for ISO/IEC 17025, GLP and GMP.
Additional auditing activities are required for GMP and GLP:

- for GMP, a periodic review is established on computerized systems
- for GLP, critical phase audits are planned. Audits concerning the archive and computerised system are already part of the internal audit program

8.8.1 Related Documentation

These procedures are fully documented in the following SOPs:

SOP0421	Internal audit: process and facility based inspections
SOP0422	Sponsor Inspections
SOP0423	Periodic Review of (critical GxP) computerized systems
SOP0424	QA program GLP

8.9 MANAGEMENT REVIEW

Quality Meetings, Study Directors Meetings, Site Leadership Team Meetings and Lab Meetings are held regularly to discuss operational matters and monitor the effectiveness of the general quality and management system. Also, an evaluation and planning of the personnel and investment is established every year, and incorporated in the Management Review.

Yearly, typically near the end of the first quarter of the year, the Management Review is organized in order to assess the effectiveness of the Quality Management System, the suitability of the company Quality policy and testing activities, concluding with decisions regarding necessary process changes or improvements versus the prior year.
The Quality Manager will draft a presentation, including the required elements to be reviewed by ISO 17025, which will be discussed during a dedicated Site Leadership Meeting.
All responsible management will evaluate and discuss the hits and misses of the actionables of prior management review, and based on the review of the presentation set forth new imperatives for the year to come.

A Management Review report is generated by the QA Manager and approved by the Managing Director summarizing the review and evaluation of the Quality Management System of the past

year and goal setting for the subsequent year, including needed changes or improvements to the Quality Management System.
The findings of the Management Review and objectives for the subsequent year are translated into actionables which are tracked and evaluated quarterly during Site Leadership Team meetings. The qualified person is notified of the report and the status of actionable follow-up.

8.9.1 **Related Documentation**

This procedure is fully documented in the following SOPs:

SOP0445	Conduct of Site Leadership Team, Quality, Lab and SD Meetings
SOP0449	Management Review Procedures
SOP0428	Dealing with Complaints
SOP0450	Customer Survey
SOP0422	Sponsor inspections
SOP0421	Internal audit: process and facility based inspections
SOP0423	Periodic Review of (critical GxP) computerized systems
SOP0426	Non-conformances/Deviations (including retest)
SOP0427	Corrective / Preventive Action Procedures

9 APPENDIX A: QUALITY ASSURANCE AT NELSON LABS NV, DETAILED OVERVIEW OF ROLES AND RESPONSIBILITIES

9.1 QUALITY ASSURANCE

The Quality Assurance Management is committed to dedicated and independent Quality Assurance (QA) and Quality Control (QC).

The basic outline of the functional units responsible for data generation and review is as follows:

- Lab Technician
- Data Reviewer
- Department Supervisor / Head of QC
- Study Director
- Quality Assurance Unit (QAU)
- Qualified Person

The first level of QC lies with the trained bench *technicians* conducting the analyses. Proper documentation and peer and data review are important aspects of laboratory quality management at this level.

Key Managerial Personnel (VP EMEAA Operations, Managing Director, Scientific Director, QA Manager, Department Supervisors and Director E&L Services) is responsible for ensuring that adequate facilities and equipment are available to the analysts to ensure the production of scientifically and technically valid data. The Department Supervisor interacts closely with the analysts and provides them with adequate supervision in order to ensure that the laboratory- and QC-procedures are strictly adhered to.

The *Quality Assurance Unit* is responsible for auditing the laboratory facilities, procedures, processes, equipment and raw data. The results of these audits are presented to the responsible management and may be used, when required, to decide upon preventive and corrective action. By doing so, the QAU assists in maintaining and continuously improving the management systems and technical procedures in the laboratory.

The responsibility of the Qualified Person applies to the quality decisions (GMP) related to QC testing on medicinal products and to the issue of Certificates of Analysis for the QC testing on medicinal products and related GMP study reports.

According to ISO, more detailed, the function descriptions of the Technical Management and Quality Management are described below:

The function description of the Technical Management: the Department Supervisors or Head of QC responsibilities are, but not limited to:

- *final responsibility for the performance of the analyses in his/her department*
- *final and unique responsibility for the release and reporting of test results generated in his/her department. The results of each test or series of tests shall be reported accurately, clearly, unambiguously and objectively, and in accordance with any specific instructions in the test methods. He/she signs and dates the final release to indicate acceptance of the responsibility for the validity and integrity of the data (SOP0218., current revision). This also includes the review and acceptance of results of reported subcontracted work*
- *oversee short/long term scheduling of all tests/analysis and manage day-to day activities in the his/her department*
- *provide adequate supervision of testing staff, including trainees and oversee performance of technicians, including reporting issues to Top Management*

- *authorize specific personnel to perform particular types of tests, to generate test reports and to operate particular types of equipment and ensure that tests are performed and equipment is only operated by authorized personnel (SOP0419 & SOP0199, current revision)*
- *responsible for ensuring that adequate facilities and equipment are available to ensure the production of scientifically and technically valid data, advise on specific department related investments, develop User Requirements Specifications (SOP0386, current revision)*
- *responsible for organizing the set-up, calibration, validation, maintenance and service checks on all chemistry instrumentation and related equipment. Responsible for preventive maintenance logs for all equipment in the department (SOP0277 & SOP0383., current revision)*
- *ensure proper method validation and performance within all required/applicable technical and QA/QC guidelines (e.g. ISO, ICH, GMP, FDA, EMEA, Pharmacopoeia's...) (SOP0204 / SOP0205 /SOP0206 / SOP0429, current revision)*
- *ensure that the latest valid edition of a standard or procedure is used unless it is not appropriate or possible to do so*
- *ensure a proper upstream-downstream communication cycle*

Quality related roles & responsibilities

- *responsible for implementing the quality program as described in the Quality manual and Site Master File and ISO 17025, GMP and/or GLP compliance in their assigned department (Quality manual and Site Master File, current revision)*
- *ensure that environmental conditions are monitored, controlled and recorded as required by the relevant specifications, methods and procedures or where they influence the quality of results.*
- *ensure the competence and training status of all who operate specific equipment, perform tests, evaluate results (SOP0419, current revision)*
- *evaluate and handle Quality Control samples (Test methods SOPs, current revision)*
- *evaluate and handle Out of Specifications (SOP0429, current revision)*
- *evaluate and handle Deviations (SOP0426, current revision)*
- *utilize QA audit information to determine the extent to which the management system objectives are being met (e.g. complaint & CAPA resolution) and responsible for handling and implementation of CAPA's (SOP0427 and SOP0428, current revision)*
- *responsible for development and updating all relevant SOPs and protocols for the assigned department, both technical and non-technical (SOP0413, current revision)*
- *interface with regulatory agencies and QAU on all certification issues for the laboratory*

Other roles & responsibilities

- *ensure the protection of its customers' confidential information, and proprietary rights, impartiality and operational integrity*
- *assist in development of new test procedures and services*
- *provide trouble shooting assistance*
- *ensure proper maintenance of supply inventory (SOP0380, current revision)*
- *compliance and enforcement of general corporate policies in the department including the LSV, CSV and the health and safety policies in the laboratory*
- *productive participation in periodical management meetings*
- *responsible for taking precautions against the loss, contamination, or change of particular reagents and chemicals used for analyses.*
- *interact (on request) on all sales and marketing activities, he can be asked to participate at seminars and congresses, give presentations and or publish scientific articles*

The function description of the Quality Management: the QA Manager responsibilities are, but not limited to:

- *ensure that the management system related to quality is implemented and followed at all times*
- *set up, organize and implement all necessary quality systems appointed by the top management (e.g. ISO 17025 , GMP (EU), GLP (OECD), ICH...), and maintain accreditation status thereof.responsible for establishing a master list identifying the current revisions status and distribution of documents in the management system*
- *ensure that authorized editions of appropriate documents are available and that invalid or obsolete documents are promptly removed from all points of use, or otherwise assured against unintended use (SOP0413, current revision)*
- *responsible for the management of internal audits. Set up periodically, and in accordance with a predetermined schedule and procedure internal audits of the activities to verify that the operations continue to comply with the requirements of the management system and the International guidelines (SOP0421, current revision)*
- *assess overall MS (Management System) and the quality of the data generated within the laboratory*
- *provide a measure of quality for all methods and tests*
- *responsible for all company policies (VMP) and programs related to CSV, LSV, Change Control, Periodic Review and action plans in order to obtain and maintain cGMP compliance.*
- *ensure permanent records are readily available in order to demonstrate instrument performance as a basis for maintaining calibration/verification or validated state for GXP critical equipment*
- *advise and monitor the establishment and implementation of the Quality Manual and ensure continuous improvement*
- *develop and implement all necessary directives and procedures to execute a system of quality assurance and quality control*
- *responsible for the interface with regulatory agencies, sponsor inspections and the follow-up on the outcome of these inspections (SOP0422, current revision)*
- *manage the review of reports including final reports, raw data, batch QA records, and all other QA records including equipment calibration, validation, preventive maintenance, etc on accuracy and completeness*
- *initiate and coordinate all necessary corrective/preventive action procedures (SOP0427, current revision)*
- *assist in the development of annually management Review reports. Provide advice on necessary changes to the MS and new goals to be set for the subsequent year are identified in the report.*
- *handle complaints (SOP0428, current revision)*
- *report all important findings (deviations from the protocol, SOPs, all non compliances) to technical management, the SD and top management, if necessary*

- *lead regular QA meetings and set priorities (SOP0445, current revision)*
- *provide regulatory/quality/GxP advice in the decision making process and report findings which could jeopardize/compromise the integrity of reported Studies and/or results within staff meetings*
- *ensure adequate training- and improvement programs are developed and implemented*
- *provide guidance to the laboratory on quality related issues in order to maintain the overall quality of laboratory performance*
- *advice on software tools to enhance compliance and lab efficiency*
- *develop and/or review Quality Agreements*
- *respond to sponsor questionnaires*

Quality Assurance responsibilities according to the OECD principles of GLP:

- *see to it that copies of all approved study plans and original SOPs in use in the Test Facility are maintained at the QA department and have access to the master schedule*
- *verify that the study plan contains the information required for compliance with the principles of GLP. This verification should be documented*
- *manage and conduct inspections to determine if all studies are conducted in accordance with the principles of GLP. Inspection should also determine that study plans and SOPs have been made available to study personnel and are being followed. Records of such inspections should be retained.*
  Inspections at Nelson Labs are of 3 types:
  - *Study-based inspections*
  - *Process-based inspections*
  - *Facility-based inspections*
- *inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies*
- *promptly report any inspection results in writing to management and to the Study Director*
- *prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director. This statement would also serve to confirm that the final report reflects the raw data*
- *manage the GLP compliance of computerized systems*
- *In case of a **multi-site study***
  Lead Quality Assurance:
  - *should liase with Test Site QA to ensure adequate QA inspection coverage throughout the study. Particular attention should be paid to the operation and documentation relating to communication among sites*
  - *ensure that the study plan is verified and that the final report is inspected for compliance with the principles of GLP. QA inspections of the final report should include verification that the PI(s) have been properly incorporated.*
  - *ensure that a QA statement is prepared relating to the work undertaken by the test facility including or referencing QA statements from all test sites*

  Test site QA:
  - *should review sections of the study plan relating to operations to be conducted at the site*
  - *should maintain a copy of the approved study plan and amendments*
  - *should inspect study-related work at the site according to his/her own SOPs, unless required to do otherwise by the lead QA, reporting any inspection results promptly in writing to the PI, TSM, SD, TFM and Lead QA*
  - *should inspect the PI's contribution to the study according to the test site SOPs and provide a statement relating to the QA activities at the test site.*

9.2 RELATED DOCUMENTATION

Management System documentation:

SOP0425	Quality Assurance and Quality Control
SOP0420	Job descriptions
SOP0419	Personnel and training
SOP0445	Conduct of Site Leadership Team, Quality, Lab and SD Meetings
SOP0220	Contents and Final Review of a Completed Project File
MAN0015	Nelson Labs Training Policy

10 APPENDIX B: SCOPE OF ACCREDITATION AND CERTIFICATION

Actual licenses, certifications and accreditations can be found on the Nelson Labs website:
https://www.nelsonlabs.com/our-company/quality/

Nelson Labs Europe Certifications

Nelson Labs Europe laboratory is:

- GMP inspected and recognized by the Belgian Federal Agency for Medicinal and Healthcare Products (FAMHP)
- GLP certified by Sciensano (ex-Scientific Institute of Public Health (WIV-ISP); Identification number: T02)
- FDA registered (FDA Establishment Identifier (FEI): 3005742674)
- ISO 17025 accredited by BELAC (Identification number: 363-TEST)

The same documents can also be found directly on the website of following notified bodies:

- ISO 17025 by BELAC:
- https://economie.fgov.be/en/themes/quality-and-safety/accreditation-belac/accredited-bodies/testing-laboratories-test

- GMP certificate by FAHMP on EUDRA GMDP:
http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do

- Listed as GLP facility by Sciensano
http://www.glp.be/GLPfacilities.html

- FDA registration:
https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm

11 APPENDIX C: NELSON LABS SOP MATRIX

Nelson Labs' SOP Matrix is kept as a "living document" in electronic format on site.

The overview below is dated July 2020.

11.1 MANAGEMENT SOPS

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		EHS (Hygiene, Med. Control, Fire prevention, evacuation, ...)			
1.2.2	SOP0432	Personnel, Medical Controls, Hygiene and Working conditions	x	x	x
5.1.1	SOP0433	Fire Prevention and Evacuation	x	x	x
5.1.2	SOP0434	Use and care of Personal Protective Equipment	x	x	x
5.1.4	SOP0435	Emergency Response and Notification List	x	x	x
5.1.7	SOP0436	Operation and use of Fire Extinguishers	x	x	x
5.1.8	SOP0437	Use of Fire Blanket	x	x	x
5.1.10	SOP0438	Use of emergency shower and Eye wash station	x	x	x
5.1.11	SOP0439	Bioveiligheidshandleiding van het laboratorium voor Microbiologie	x	x	x
		Human Resources (recruitment, evaluations, ...)			
1.2	SOP0440	Personnel and Organization	x	x	x
1.2.1	SOP0441	Personnel, Recruitment and Evaluations	x	x	x
-	MAN0015	Training Policy	x	x	x
		Facility (Access control, pest control, emergency generator, ...)			
2.1.1	SOP0442	Facilities Description	x	x	x
2.1.3	SOP0443	Visitor Registration at Nelson Labs NV Premises	x	x	x
2.2.7.1	SOP0444	Use and maintenance of the emergency generator	x	x	x
		Sales & Marketing			
4.2.13	SOP0446	Quotation Procedures	x	x	x
		Finance & Administration			
4.2.14	SOP0447	Billing procedures	x	x	x
		Communication			
1.2.6	SOP0445	Conduct of Site Leadership Team, Quality, Lab and SD Meetings	x	x	x
		Strategies			
1.1	SOP0448	Company organisation table	x	x	x
1.2.7	SOP0449	Management Review Procedures	x	x	x
4.2.10	SOP0450	Customer Survey	x	x	x
KHB / SMF	MAN0010	Quality manual Nelson Labs NV	x	x	x
VMP	MAN0012	Validation Policy	x	x	x
-	MAN0013	Risk Assessment for Mixed Use of Premises, Resources and Systems	x	x	x

11.2 QUALITY MANAGEMENT SOPs

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Document management			
4.2.1	SOP0413	Development, Change Control, Periodic Review and Archiving of a Standard Operating Procedure	x	x	x
-	SOP0151	Document management using MasterControl	x	x	x
-	SOP0179	MasterControl Document Management - User guide for general staff	x	x	x
-	SOP0189	MasterControl Document Management - User guide for Document Owners and Management	x	x	x
-	SOP0194	MasterControl Document Management - User guide for Document Management team	x	x	x
-	SOP0475	Training in MasterControl - User guide for Document Management team	x	x	x
4.2.11	SOP0414	Development, Review and Distribution of Sponsor Specified Procedures (SSP)	x	x	x
4.2.9	SOP0416	External Document Control - Library management	x	x	x
4.1.8	SOP0417	Development, review, reconciliation and archiving of forms and raw data	x	x	x
		Training			
1.2.3	SOP0419	Personnel and Training	x	x	x
1.2.4	SOP0420	Job Descriptions	x	x	x
1.2.5	SOP0199	Matrix of Technical Competence	x	x	x
		Sponsor- and Self-Inspections			
4.1.13	SOP0421	Internal Audit: Process and Facility Based Inspections	x	x	x
4.2.22	SOP0422	Sponsor Inspections	x	x	x
4.2.33	SOP0423	Periodic Review of (critical GxP) computerized systems	x	x	x
4.2.35	SOP0424	QA program GLP		x	
4.2.34	SOP0425	Quality Assurance and Quality Control	x		x
		Non-Conformance (NCR)			
4.2.20	SOP0426	Non-conformances/Deviations (including retest)	x	x	x
		Corrective & Preventive Actions (CAPA's)			
4.1.14	SOP0427	Corrective/Preventive Action Procedures	x	x	x
		Complaints			
4.1.19	SOP0428	Dealing with Complaints	x	x	x
		Out-of-Specifications (OOS)			
4.1.36	SOP0429	Out-Of-Specification procedure	x		x
		Data integrity			
-	MAN0014	Data Integrity Policy	x	x	x
4.2.5	SOP0430	Good Documentation Practice (GDP) and Signature Policy	x	x	x
-	SOP0481	Audit Trail Review	x	x	x
		Risk Management			
4.2.31	SOP0431	Quality Risk Management	x	x	x

11.3 SUPPORT MANAGEMENT SOPs

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Purchase			
4.1.12	SOP0380	Purchasing Services, Equipment and Supplies	x	x	x
4.1.16	SOP0381	Vendor and Subcontractor Qualification and Monitoring Procedures	x	x	x
4.1.37	SOP0382	Communication and sample flow between Nelson Labs NV and Toxikon US	x	x	
		Validation			
2.2.2	SOP0383	Equipment General Procedures	x	x	x
4.1.18	SOP0384	Notification and Inspection Procedures of Material and Equipment Receipt – Lab Inventory	x	x	x
4.2.29	SOP0386	System Validation	x	x	x
4.2.30	SOP0387	Operational Change Control for Lab- and IT Systems	x	x	x
4.1.26	SOP0390	Control of Reference Standards and Materials	x	x	x
2.2.6.32	SOP0391	Calibration Weights for Balances	x	x	x
		IT			
		General IT procedures			
6.2	SOP0393	Back-up and Restore of Software and Data	x	x	x
6.2.1	SOP0394	Back-up and Restore Procedures	x	x	x
6.2.2	SOP0395	Restore testing and verification procedures	x	x	x
6.3	SOP0396	User Account Management For Nelson Labs NV Network Systems	x	x	x
6.3.1	SOP0397	Nelson Labs NV User account management Procedure	x	x	x
6.5	SOP0398	Hardware Inventory SOP	x	x	x
6.6	SOP0399	Virus and Malware Code Protection	x	x	x
6.7	SOP0400	Nelson Labs NV-Network Infrastructure Documentation	x	x	x
6.8	SOP0401	Software Usage at Nelson Labs NV	x	x	x
6.19	SOP0402	Workstation Installation and Configuration	x	x	x
		IT Systems: Use & maintenance			
6.10	SOP0403	STARLIMS - System Administration	x	x	x
6.11	SOP0404	STARLIMS - Use of the Purchase Manager	x	x	x
6.12	SOP0405	STARLIMS - Use of the Materials Management Module	x	x	x
6.13	SOP0406	Use of Spreadsheet Tools	x		
6.14	SOP0407	Use of Spreadsheet Tools-Lab	x		x
6.15	SOP0408	Open lab ECM User Procedure	x	x	x
6.16	SOP0409	Open lab ECM System Procedure	x	x	x
6.17	SOP0410	STARLIMS - Use of the electronic batchbook module	x	x	x
6.20	SOP0411	STARLIMS - Equipment Management	x	x	x
6.21	SOP0412	STARLIMS - Storage Location Management	x	x	x
-	SOP0196	STARLIMS - Use of the Inventory Management Module	x	x	x
-	SOP0494	STARLIMS: Use of the Recipe Preparation Module	x	x	x
6.18	SOP0455	Server qualification and maintenance	x	x	x
-	SOP0466	LOMS - System administration	x	x	x
		Archiving			
4.2.8	SOP0392	Archive procedures	x	x	x

11.4 OPERATIONS SOPs

11.4.1 Conduct of a study

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Conduct of a study			
4.1.1	SOP0200	Study Logging Procedures, Sample Receipt, Storage and Contamination Control Practices Using Loms System	x	x	x
4.1.38	SOP0201	Management of specially regulated substances	x	x	x
4.2.21	SOP0202	Communication with sponsors	x	x	x
4.1.40	SOP0203	Subsampling of aqueous and organic solvent based extracts/test solutions for extractables and leachables studies	x		
4.1.6	SOP0204	Method Validation	x		x
4.1.28	SOP0205	Measurement of uncertainty and validation for microbiological methods	x		x
4.2.27	SOP0206	Estimation for Measurement of Uncertainty	x		x
3.2.30	SOP0207	Conduct of a Leachable Study	x		
4.1.32	SOP0208	Conduct of a GMP study			x
4.1.41	SOP0209	Conduct of a commercial R&D study			
4.1.30	SOP0210	Assuring the Quality of test results	x		x
1.2.8	SOP0211	Assignment of Study Responsibles - GLP		x	
4.2.36	SOP0212	Master Schedule GLP		x	
4.1.22	SOP0213	Study Plan for a GLP Study		x	
4.1.23	SOP0214	Conduct of a GLP Study		x	
4.1.31	SOP0215	Characterisation of test, control and reference items		x	
4.1.20	SOP0216	Reporting and Rounding off Results	x	x	x
4.1.24	SOP0217	Reporting of GLP Study		x	
4.1.7	SOP0218	Test Report, Test Result Report and Study Report Generating Procedures	x		x
4.1.33	SOP0219	Certificate of Analysis Generating Procedure			x
4.2.7	SOP0220	Contents and Final Review of a Completed Project File	x		x
4.2.37	SOP0221	Sample Return and Sample Destruction procedures	x	x	x

11.4.2 Conduct of a study performing the test: microbiology and toxicological procedures

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Conduct of a study			
		Conduct of a study - Performing the test(s): Microbiological & Toxicological procedures			
3.1.1.1	SOP0222	Cell Counting using a Hemacytometer	x	x	
3.1.1.2	SOP0223	Growth and maintenance of mammelian cell lines	x	x	
3.1.1.3	SOP0224	Use and Maintenance of cell and tissue culture room	x		x
3.1.1.4	SOP0452	Gram staining	x		
3.1.1.8	SOP0225	Preparation, storage and control of growth media and rinse fluids	x	x	x
3.1.1.9	SOP0226	Basic Surface Area Calculation	x	x	
3.1.1.10	SOP0227	Culture and maintenance of reference micro-organisms	x	x	x
3.1.2.3	SOP0228	MEM Elution Test	x	x	
3.1.2.5	SOP0229	Sterility Test (USP,EP and ISO)	x		x
3.1.2.6	SOP0230	Validation of a sterility test	x		x
3.1.2.8	SOP0231	Total Bioburden	x	x	x
3.1.2.9	SOP0232	Growth Promotion Test	x		x
3.1.2.13	SOP0233	Bacterial Reverse Mutation Test (AMES assay)	x	x	
3.1.2.24	SOP0234	Limulus Amebocyte Lysate (LAL) test for detection and quantitation of endotoxins (Kinetic-QCL Method)	x		x
3.1.2.25	SOP0235	Microbial examination of non-sterile products: Microbial Enumeration Tests	x		x
3.1.2.26	SOP0236	Microbial examination of non sterile products: Tests for specified microorganisms	x		x
3.1.2.29	SOP0237	Culturing and Storage of Mycoplasma	x		
3.1.2.30	SOP0238	Preservative efficacy test	x		
3.1.2.32	SOP0239	Bioanalytical ELISA method validation	x	x	
3.1.2.34	SOP0240	Test for Mycoplasma	x		x
3.1.2.37	SOP0242	Carbohydrate test	x	x	
3.1.2.38	SOP0309	Lowry assay	x	x	
3.1.2.39	SOP0336	Hemoglobin test	x	x	
-	SOP0460	Monocyte activation test (MAT)	x	x	
-	SOP0471	BCA assay for determination of protein content	x		
-	SOP0472	Soiling and extraction methods for cleaning validation for healthcare reprocessing	x	x	
-	SOP0476	Steam sterilization validation	x	x	
-	SOP0477	Disinfection validation procedures for healthcare reprocessing	x	x	

11.4.3 Conduct of a study performing the test: analytical procedures

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Conduct of a study			
		Conduct of a study - Performing the test(s): Analytical procedures			
3.2.4	SOP0243	Manual Conductivity determination	x		x
3.2.7	SOP0244	Determination of elements by ICP-OES	x		
3.2.8	SOP0245	Determination of semi-volatile organic compounds(SVOCs) in extracts of aqueous and solid samples by gaschromatography-mass spectrometry (GC/MS)	x		
3.2.10	SOP0246	FTIR-Analysis	x		
3.2.11	SOP0247	Determination of Anions by Ion chromatography	x		
3.2.24	SOP0248	UV/VIS Scanning	x		
3.2.26	SOP0249	Determination of Turbidity	x		
3.2.29	SOP0250	LC/MS Analysis of Polymer Additives and fatty acids using the Agilent 1100 LCMS Trap SL	x		
3.2.39	SOP0251	Sample preparation prior to the determination of organic compounds in extractable/leachable studies	x		
3.2.40	SOP0252	Manual pH Determination	x		x
3.2.44	SOP0253	Total Organic Carbon (TOC) Analysis	x	x	
3.2.47	SOP0254	Determination of volatile organic compounds (VOCs) in liquid or solid samples by Headspace GC/MS	x		
3.2.55	SOP0256	LC/UV Analysis of SULPHUR in Dichloromethane, Isopropanol and Hexane using the Agilent 1200 LCMSD	x		
3.2.58	SOP0257	Determination and Quantification of ammonium(NH4+) in Water by Ultra Violet-Visible Light Spectrophotometry (UV-VIS)	x		
3.2.60	SOP0258	Determination and Quantification of hydrogen peroxide (H2O2) in Water for Injection by Ultra Violet -Visible Light Spectrophotometry (UV-VIS)	x		
3.2.69	SOP0259	Determination and quantification of Silicon Oil in hexane and in Utra Pure Water (UPW) by Graphite Furnace Atomic Absorption Spectrometry (GF-AAS)	x		
3.2.70	SOP0260	Water determination on medicinal products with Metrohm Karl Fisher Type 870 Titrino Plus	x		x
3.2.72	SOP0261	Determination of osmolality with osmometer Advanced Instruments Model 3250	x		x
3.2.73	SOP0262	Measurement of subvisible particles in solutions with the HIAC 9703+ measurement system	x		x
3.2.75	SOP0263	LC-DAD-FLD-MS measurement	x		x
3.2.76	SOP0264	LC/MS Screening using the Thermo Scientific Exactive Orbitrap	x		
3.2.77	SOP0265	Determination of semi-volatile organic compounds (SVOCs) in extracts of aqueous and solid samples by GC/MS after silylation with BSTFA	x		
3.2.78	SOP0266	Determination of 16 EPA Polynuclear Aromatic Hydrocarbons (PAHS) in extracts of aqueous and solid samples by GC/MS	x		
3.2.81	SOP0267	Quantitative Determination of Irgafos 168, Irganox 168 oxide, Irganox 1010, Irganox 1076 and Bis((2.4-ditert-butylphenyl)phosphate in DCM extracts by LCMSMS	x		
3.2.82	SOP0268	ESI-LC/MS Screening using the Thermo Scientific Q-Exactive Focus Orbitrap	x		
3.2.83	SOP0269	Determination of Mercury (Hg) in aqueous solution by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) Matrix: Ultra Pure Water (UPW)	x		
3.2.84	SOP0270	Determination and quantification of bis(2,4)di-tert-butylphenyl)phosphate using the Thermo Fisher Q-exactive focus instrument	x		
3.2.86	SOP0271	Determination of 16 PAHs in extracts by Gas Chromatography - Triple Quadrupole Mass Spectrometry (GC/MS/MS)	x		
3.2.87	SOP0272	Determination of 11 Nitrosamines in extracts by Liquid Chromatography - Triple Quadrupole Mass Spectrometry (LC/MS/MS)	x		
3.2.88	SOP0273	Non Volatile Residue (NVR) determination	x		
3.2.89	SOP0274	DSC analysis	x		
3.2.90	SOP0275	Determination of acetaldehyde and formaldehyde in aqueous solutions after derivatization wih DNPH by LCUV analysis using the agilent 1260 infinity LC/DAD/FLD	x		
3.2.91	SOP0276	Screening for a selected set of metallic impurities in aqueous extracts and drug products by Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	x		
3.2.92	SOP0451	Determination of volatile organic compounds (VOCs) in liquid or solid samples by Headspace GC/MS using Masshunter	x		
-	SOP0467	Screening of volatile and semi-volatile organic compounds using masshunter	x		
-	SOP0487	Determination of semi-volatile organic compounds(SVOCs) in extracts of aqueous and solid samples by gaschromatography-mass spectrometry (GC/MS) using masshunter	x		
-	SOP0458	Determination and Quantification by means of UV/VIS Spectrophotometry	x		

Conduct of a study: Use and maintenance and reagentia & standards

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Reagentia & Standards			
4.1.2	SOP0377	Chemical Lab Inventory: Preparation, Traceability, Labeling, Acceptability and Usage	x	x	x
4.1.29	SOP0378	Determination of the purity of qualitative and quantitative standards	x		
5.1.6	SOP0379	General Housekeeping and labwaste disposal regulations	x	x	x
		Lab equipment : Use & maintenance			
2.2.1	SOP0277	Equipment Use and Maintenance	x	x	x
4.2.28	SOP0278	Monitoring of controlled storage for temperature and humidity	x	x	x
2.2.3.1	SOP0279	Operation and Maintenance of the Genesis UV/Visible Spectrophotometer	x		
2.2.3.2	SOP0280	Use and Maintenance of Stuart Colony Counter	x		
2.2.3.7	SOP0281	Use and Maintenance of the "MicroFlow" Laminar Flow Cabinet	x		
2.2.3.8	SOP0282	Use and Maintenance of the "CleanAir" Laminar Flow Cabinet	x		
2.2.3.9	SOP0283	CEM MARS 5 Microwave Digestion system	x		
2.2.3.11	SOP0284	Use and Maintenance of Naber Muffle Furnaces	x		
2.2.3.12	SOP0285	Use, Validation and Maintenance of Depyrogenation Oven	x		
2.2.3.19	SOP0287	Operation and Maintenance of Varian 720-ES ICP	x		
2.2.3.23	SOP0289	Operation and maintenance of the Cary 50 UV-Visible Spectrophotometer	x		
2.2.3.24	SOP0290	Use and Maintenance of the HP 1100 HPLC system	x		
2.2.3.30	SOP0291	Operation and Maintenance of the Agilent 1100 series LC/MSD Trap Mass Spectrometer	x		x
2.2.3.35	SOP0293	Operation and Maintenance of the Agilent 1200 series HPLC VWD.	x		x
2.2.3.38	SOP0295	Use and Maintenance of the BIO-TEK Automated Microplate Reader	x	x	x
2.2.3.39	SOP0296	Operation and Maintenance of the Agilent 6410 and 6460 LC/MS Triple Quad Mass Spectrometer and Agilent 1200 and 1290 series HPLC	x		x
2.2.3.40	SOP0297	Operation and Maintenance of the Shimadzu Prominence LC-DAD	x		x
2.2.3.42	SOP0298	Use and maintanance of the HACH 2100AN turbidimeter	x		
2.2.3.43	SOP0299	Operation and Maintenance of Perkin Elmer THGA Graphite Furnace AA-600	x		
2.2.3.44	SOP0300	Use and Maintenance of Metrohm Karl Fischer Type 870 Titrino plus	x		x
2.2.3.45	SOP0301	Use and Maintenance of the Agilent (HS)-GC with FID and NPD detector	x		x
2.2.3.46	SOP0302	Use and Maintenance of Osmometer Advanced Instruments Model 3250	x		x
2.2.3.48	SOP0303	Use and maintenance of ProLAB 4000 pH/CONDUCTIVITY meter	x		x
2.2.3.49	SOP0304	Operation and Maintenance of the Agilent 1260 Infinity LC/DAD/FLD	x		
2.2.3.50	SOP0305	Operation and maintenance of the Agilent 6120 Quadrupole LC/MS and 1200 LC/DAD/FLD	x		x
2.2.3.51	SOP0306	Operation and maintenance of the thermo fisher scientific UHPLC, Photodiode array(PDA) detector and mass spectrometer exactive incl. HCD	x		
2.2.3.54	SOP0307	Operation and Maintenance of the Perkin Elmer NEXION 300XX	x		x
2.2.3.56	SOP0308	Use and Maintenance of the Agilent 7890A/7000B EI/CI-GC-QQQ	x		x
2.2.3.58	SOP0310	Use and maintenance of the Perkin Elmer Titan MPS Microwave Digestion system	x		x
2.2.3.60	SOP0311	Use and maintenance of Perkin Elmer DSC 4000	x		
2.2.3.65	SOP0312	Use and maintenance of Sievers M9 Laboratory TOC Analyzer	x	x	
2.2.3.66	SOP0313	Operation and Maintenance of the Agilent 7697A static Headspace Sampler/Agilent 6890N or 7890B Gas Chromatograph / 5975 inert or 5977A or 5977B Mass Selective Detector (HS-GC/MS)	x		
2.2.3.67	SOP0314	Operation and maintenance of the Dionex ICS-2100 Ion Chromatograph	x		
2.2.3.68	SOP0315	Use and maintenance of the "Tecniplast BS48" Biosafety cabinet	x		
2.2.3.69	SOP0316	Operation and maintenance of the Agilent 7890B/7200A EI/CI-GC-QTOF	x		
2.2.3.70	SOP0317	Operation and maintenance of the Agilent single quad GC/MS systems	x		
2.2.3.71	SOP0318	Operation, maintenance and usage of the Brookfield DV3TRV Cone Plate Rheometer	x		x
2.2.3.72	SOP0319	Operation and maintenance of the Thermo Fisher Scientific UHPLC, Photodiode Array (PDA) detector and Hybrid Quadrupole Orbitrap high resolution Mass Spectrometer Q-Exactive incl. HCD	x		
2.2.3.73	SOP0320	Operation and maintenance of the Cary 630 FTIR	x		
2.2.3.74	SOP0321	Operation and maintenance of the Gerstel Dual Head Multipurpose Sampler – Agilent 7980B/5977B GC-MS	x		
2.2.3.75	SOP0322	Operation and maintenance of the Thermo Fisher Scientific UHPLC, Photodiode Array (PDA) detector and Hybrid Quadrupole Orbitrap high resolution Mass Spectrometer Q-Exactive Focus incl. HCD	x		
2.2.3.76	SOP0323	Use and maintenance of HIAC 9703+ Liquid particle counter	x		x
2.2.3.77	SOP0324	Use and maintenance of the "faster BH-EN-2000" biosafety cabinet	x		

11.4.3 Continued

Cross-reference		SOP's per (sub)cluster	Quality Level		
Old number	MC number		ISO	GLP	GMP
		Lab equipment : Use & maintenance			
2.2.6.1	SOP0325	Use and Maintenance of Refrigerators and Freezers	x	x	x
2.2.6.3	SOP0326	Use and maintenance of water baths	x	x	x
2.2.6.4	SOP0327	Use and Maintanance of drying ovens	x		
2.2.6.6	SOP0328	Use and maintenance of Mettler Top Load Balance	x		
2.2.6.7	SOP0329	Use and maintenance of syringes and automatic pipettes	x		
2.2.6.10	SOP0330	Use and Maintenance of Integra Pipetboy	x		
2.2.6.11	SOP0331	Operation and Maintenance of Centrifuges	x		
2.2.6.12	SOP0332	Use and maintenance of Elix and Milli-Q Advantage A10 water purification system	x		x
2.2.6.15	SOP0333	Heating and Stir Plate	x		
2.2.6.16	SOP0334	Operation and Maintenance of Incubators	x		x
2.2.6.17	SOP0335	Use and Maintenance of Inverted Microscope	x		
2.2.6.19	SOP0337	Use and Maintenance of Vortex	x		
2.2.6.21	SOP0339	Use and maintenance of Mechanical Shaker	x		x
2.2.6.25	SOP0340	Use and Maintenance of Motic Light Miscroscope	x		
2.2.6.34	SOP0344	Use and Maintenance of the Lancer Washer	x	x	x
2.2.6.35	SOP0345	Use and Maintenance of TurboVap® II concentration workstation	x		
2.2.6.36	SOP0346	Use and Maintenance of Universal Shaker	x		
2.2.6.37	SOP0347	Use and Maintenance of Grant QBD2 Block Heater	x		
2.2.6.38	SOP0348	Use and Maintenance of binder Climatic Chambers	x		
2.2.6.39	SOP0349	Use and Maintenance of waterbath GD 120	x		x
2.2.6.41	SOP0350	Use and Maintenance of the Steritest Equinox Pump	x		x
2.2.6.43	SOP0351	Use and Maintenance of Mettler Analytical Balance XP 205DR/M	x		
2.2.6.45	SOP0353	Use and maintenance of Reference "TESTO" Datalogger	x		
2.2.6.46	SOP0354	Use and maintenance of Tuttnauer Steam Sterilizer	x		
2.2.6.47	SOP0355	Use and maintenance of the Getinge Isotest Sterility Isolator	x		x
2.2.6.48	SOP0356	Use and Maintenance of Dräger Gasdetection Sytem	x		
2.2.6.50	SOP0357	Use and Maintenance Binder LQC720 Climatic Chamber with ICH compliant Lightfacility and light Quantum control Type II	x		
2.2.6.51	SOP0358	Use and Maintenance of Ultrasonic Waterbaths	x		
2.2.6.55	SOP0360	Use and Maintenance of CO2 Incubator	x	x	
2.2.6.56	SOP0361	Use and maintenance of the Fisher Scientific Accuspin Micro 17 Centrifuge	x		
2.2.6.62	SOP0363	Use and Maintenance of the IKA shaking incubator	x	x	
2.2.6.63	SOP0364	Use and maintenance of the air-monitoring system : SAS super IAQ and 180	x		
2.2.6.65	SOP0365	Use and Maintenance of CISA steam sterilizer	x		x
2.2.6.66	SOP0366	Use and maintenance of the Thermo MaxQ 6000 shaker incubator	x		
2.2.6.67	SOP0367	Use and Calibration of Thermometers	x		
2.2.6.68	SOP0368	Use and maintenance of the Precision Balance Entris 623I-1S	x		
2.2.6.69	SOP0369	Use and maintenance of Climatronix climatic chambers	x		x
2.2.6.70	SOP0370	Use and maintenance of Mettler AL 204 Balance	x		
2.2.6.71	SOP0371	Use and maintenance of the Bioquell QUBE Sterility Isolator	x		x
2.2.6.73	SOP0372	Use and maintenance of the Precision Balance Entris 3202I-1S	x		
2.2.6.74	SOP0373	Use and maintenance of the automated cell counter (nucleocounter)	x		
2.2.6.75	SOP0374	Use and maintenance of the Sartorius Semi-Micro Balance ME215P	x		
2.2.6.76	SOP0375	Use and Maintenance of the Mettler-Toledo XSE 205DU Balance	x		
5.1.5	SOP0376	Cleaning and Preparation of Glassware and Labware	x	x	x
-	SOP0198	Use and maintenance of sterility room	x		x
-	SOP0454	Aseptic Techniques	x	x	x
-	SOP0457	Operation and Maintenance of Perkin Elmer THGA Graphite Furnance AA	x		
-	SOP0459	Operation and maintenance of the Lambda 25 UV/Visible spectrophotometer	x		
-	SOP0464	Use and maintenance of BAGMIXER® 400 W	x		
-	SOP0465	Use and maintenance of the Clariostar microplate reader	x		
-	SOP0469	Use and maintenance of the Washer-Disinfector Belimed WD290 IQ	x		
-	SOP0474	Use and Maintenance of Dynamic Templater Application	x		

12 APPENDIX D: GMP JUSTIFICATION FOR THIS DOCUMENT AS SITE MASTER FILE

The principles of EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice (Medicinal Products for Human and Veterinary Use) are applicable to all processes and systems where GMP is marked in Appendix C of this document (section 0).

12.1 AUTHORIZED PHARMACEUTICAL MANUFACTURING ACTIVITIES OF THE SITE

Nelson Labs has no capability for the manufacture of drug substances and/or drug products. Nelson Labs is a Contract Research Organisation solely engaged to provide QC services to the Pharmaceutical industry, in compliance with EudraLex GMP (§1.1).

Nelson Labs is periodically inspected according to the national inspection program by the Federal Agency for Medicines and Health Products (FAMHP) related to the following Manufacturing Authorisations:

- n° 1844 H, in accordance with Article 40 of Directive '2001/83/EC', for human medicinal products;
- n° 1844 V, in accordance with Article 44 of Directive '2001/82/EC', for veterinary medicinal products;
- n° 1844 IMP, in accordance with Article 13 of Directive '2001/20/EC', for investigational medicinal products.

Nelson Labs holds the following GMP certificates:

- BE/GMP/2017/114 for human medicinal products;
- BE/GMP/2017/115 for veterinary medicinal products;
- BE/GMP/2017/116 for investigational medicinal products.

12.2 QUALITY MANAGEMENT SYSTEM OF NELSON LABS

The Quality Management System of Nelson Labs is described throughout this entire document. Roles and responsibilities of the quality unit are described in detail in section 0.

Additionally, the tasks and responsibilities of the Qualified Person (QP) are described below:

- Final responsibility for all quality decisions directly related to GMP release testing independently from the Top Management
- Final responsibility to issue Certificate of Analysis and, if requested by sponsor, GMP study reports or test result reports. The results of each test or series of tests shall be reported accurately, clearly, unambiguously and objectively, and in accordance with any specific instructions in the test methods and protocols
- Final evaluation of Deviations, Complaints and Out-of-Specifications (OOS)
- Use QA audit information to determine the extent to which the management system objectives are being met (e.g. complaint & CAPA resolution) and responsible for handling and implementation of CAPA's
- Approval for all quality management SOPs related to the GMP release testing

12.3 RELEASE PROCEDURE OF FINISHED PRODUCTS

Nelson Labs QP never holds final certifying/batch release responsibility but supports the sponsor's certifying QP with a confirmation statement indicating that Nelson Labs testing is performed according to GMP.

GMP release testing of drug products / active substances / intermediate products is managed by the Head of QC (technical), the QA department (compliance) and the QP (compliance and release) according to the written monographs, validated test methods and approved specifications from the Contract Giver. After data review and technical release of the data package from the laboratory by the Head of QC, a Certificate of Analysis or other result report (test result report or study report) is generated, which is reviewed by QA. Subsequently, QA informs the QP of all critical aspects with possible impact on the test results. The reviewed results/report are released by the Qualified Person.

12.4 MANAGEMENT OF SUPPLIERS AND CONTRACTORS

See section 6.6 of this document.

12.5 QUALITY RISK MANAGEMENT (QRM)

The approach for Quality Risk Management is based on the general risk management process as outlined in ICH Q9. See section 8.5 of this document.

12.6 PRODUCT QUALITY REVIEWS

Not applicable.

12.7 PERSONNEL

See sections 5.3.3 and 6.2 of this document.

12.8 PREMISES AND EQUIPMENT

12.8.1 Premises

Every room is labelled and the facilities description (floor plan) is available as AUX1802 via the document management system. Nelson Labs' quality system is harmonized to such an extent that every room can be considered for potential GMP activities.

See section 6.3 of this document.

12.8.1.1 *HVAC system*

All laboratories are equipped with individual computer assisted HVAC systems and separated air-handling of each room by means of extraction and pulsing which minimizes the risk of cross-contamination.
Overpressure of rooms and inlet of HEPA-filtered air is installed for critical areas, i.e. Microbiology department.

12.8.1.2 *Water system*

The reversed osmosis water (Water type II) produced by the Elix system can be used for general lab applications and as feed water for the Milli–Q Advantage A10 system. Purified water (Water type I) is used for analysis.

12.8.2 Equipment

See section 6.4 of this document.

12.8.2.1 *GMP Critical computerised systems*

Paper represents the authoritative form of site documentation. In addition to paper, electronic records as generated by computerized lab systems are securely managed. Computerized lab systems comply with the requirements set down in Annex 11 of the EU GMP Guideline.

12.9 DOCUMENTATION

See section 8.3 of this document.
All raw data used for GMP release activities is subject of form reconciliation.

12.10 PRODUCTION

12.10.1 Type of products, Process validation, Material management and warehousing

Not applicable.

12.10.2 Quality Control

As a Contract Laboratory, Nelson Labs performs Quality Control Testing for third parties (Pharmaceutical Industry).
These GMP testing activities include, but are not limited to:

- Method development
- Method validation
- Method transfer
- Pharmacopoeial testing
- Stability study

In view of the different types of analytical activities and studies and their respective quality systems (ISO 17025 & GLP), Nelson Labs has evaluated the 'mixed use' of the Nelson Labs premises, resources, systems and equipment (MAN0013).

The tasks and responsibilities of Head of QC are interchangeable with those of Technical Management as defined in §9.

Nelson Labs ensures the quality of its test results by review prior to issuing results. All reported results are double checked by reviewing raw data sheets, instrument print-outs, draft reports, and all other necessary documentation which guarantees the traceability of the reported results.

All test results that fall outside the established specifications, acceptance criteria or expected result as described in guidelines, test procedures or written agreements between Contract giver and Nelson Labs, are subjected to an Out-of-Specification investigation according to the written procedures.

12.11 DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

12.11.1 Distribution

Distribution is under the responsibility of the Contract Giver.

12.11.2 Complaints

See section 7.9 of this document.

12.11.3 Product defects

Not applicable.

12.11.4 Recalls

Not applicable.

12.12 SELF INSPECTION

See section 0 of this document.

12.13 QUALIFIED PERSON APPROVAL OF SMF JUSTIFICATION

I undersign that the Quality Manual of Nelson Labs in combination with this appendix D related to:

- Management responsibilities
- Process and system audits (processes are clearly defined and systematically reviewed in order to demonstrate the required quality and comply with their specifications)
- Validation of critical steps of the processes and significant changes to those processes
- Qualified and trained personnel
- Adequate premises and space
- Suitable equipment and services
- Correct materials
- Approved procedures and instructions
- Suitable storage
- Documentation (records which enable the complete history of a batch to be traced)
- Test methods (validated and approved for all testing operations described in the marketing authorization)

is in compliance with the GMP principles set forth in EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice (Medicinal Products for Human and Veterinary Use).

Approval by QP of this document

Leo Aerden
Qualified Person
Industrial Pharmacist No. 1253