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Title	Activation I-131 Process and Equipment Proposal Requirements Specification				
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CONTENTS

1. PURPOSE

The purpose of this document is to define the proposed requirements for the production process (technology) and accompanying production and dispensing systems and hot cells, for the production of non-sterile activation I-131 Active Pharmaceutical Ingredient (API) from irradiated Tellurium Dioxide (TeO_2) targets.

The Proposal Requirements Specification includes reference to NECSA and NTP requirements as well as compliance with current Good Manufacturing Practice (cGMP) and GEP (Good Engineering Practice) where relevant.

This document is compiled to facilitate prospective suppliers and/or design engineers in understanding the needs, identifying further requirements, and proposing a suitable production process and equipment design. The Proposal Requirements Specification is not intended as an exclusive approach, the identification of omissions or alternative suggestions by prospective suppliers and/or design engineers are welcome.

The Proposal Requirements Specification is a key document as a point of reference throughout the validation life cycle of the product and equipment i.e. Design specification, Quality Risk Management (QRM), Commissioning, Qualification (C&Q) and Validation activities.

2. SCOPE

This scope of this document applies to the activation I-131 API production process (technology) and accompanying production and dispensing systems and hot cells. This document specifies the requirements associated with the production process and the design, development, and qualification of the production and dispensing systems and accompanying hot cells, which NTP requires to produce non-sterile activation I-131 API from irradiated Tellurium Dioxide (TeO_2) targets.

3. REFERENCES

This document complies with the requirements of:
ISO 9001:2015: Quality Management systems - Requirements, Fifth edition, 2015.
SAHPGL-INSP-02_v8: SAHPRA Guideline on Good Manufacturing Practice for Medicines, Version 8, September 2022
PE-009-16 (Parts I & II): PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I & II, February 2022
ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
ISPE Baseline Guide Commissioning and Qualification, Volume 5, 2nd Edition, 2019
NTP-PRG-0300: Control of Documented Information and Forms
NTP-PRG-0730: Design and Development

NTP-SPE-4140: User Requirements Specification for the Production Process of I-131 from Irradiated TeO_2 Targets
NIL-39: Nuclear Installation License-39
LS-NTP-STR-0002: Licensing Strategy for Activation Iodine Production

The following documents are referenced in this document:
Act 15 of 1973: Hazardous Substances Act 15 of 1973
Act 45 of 1965: National Environmental Management: Atmospheric Pollution Prevention Act 45 of 1965
Act 59 of 2008: National Environmental Management: Waste Act 59 of 2008
Act 85 of 1993: The Occupational Health and Safety Act 85 of 1993
Act 85 of 2008: The Medicines and Related Substances Amendment Act 72 of 2008
Act 85 of 2015: The Medicines and Related Substances Amendment Act 14 of 2015
Act 101 of 1965: The Medicines and Related Substances Act 101 of 1965
ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
ISO 14644: Cleanrooms and associated controlled environments (Part 1 to 4)
ISO 17873 - 2004: Nuclear facilities — Criteria for the design and operation of ventilation systems for nuclear installations other than nuclear reactors
PE-009-16 (Parts I & II): PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part 1 & II, February 2022
PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 3: Manufacture of Radiopharmaceuticals, February 2022
PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 11: Computerised Systems, February 2022
PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 15: Qualification and Validation, February 2022
SAHPGL-INSP-02_v8: SAHPRA Guideline on Good Manufacturing Practice for Medicines, Version 8, September 2022
SAHPGL-RDN-RN-13_v2: SAHPRA Guideline for Management and Disposal of Non-nuclear Radioactive Waste, Version 2, December 2022
SANS 10114-1: 2020 Interior Lighting Part 1: Artificial Lighting of Interiors, 4th Ed
SANS 10142:1 The wiring of Premises - Part 1: Low-voltage installations
SHEQ-INS-0233: Design Control
SHEQ-INS-0234: NECSA QMS Requirement for external Design Organisations
SHEQ-INS-1120: Lighting (Natural and Artificial)
SHEQ-INS-8030: System for the classification and demarcation of radiological areas
SHEQ-INS-8050: Radiological surveillance programme for workplaces
SHEQ-INS-8180: ALARA programme
SHEQ-INS-8230: Management of Radioactive Discharges to the Atmosphere at the Pelindaba
SHEQ-INS-8260: Management of Radioactive Effluent and Discharge at the Pelindaba Site
SHEQ-INS-8310: Requirements in respect of ventilation systems for nuclear facilities
SHEQ-INS-8360: Necsa Solid Radioactive Waste Management System

UNSEAL: Department of Health, Requirements for the Safe Use of Unsealed Radioactive Nuclides, Version 2, February 2001
US Code of Federal Regulations 21 Part 210 – Current Good Manufacturing Practice for Finished Pharmaceuticals
US FDA office of Regulatory Affairs – Guideline for Facilities and Environmental Conditions
21 CFR Part 11: Guidance for Industry, Part 11, Electronic Records; Electronic Signatures — Scope and Application, March 2023
WHO Technical Report Series (TRS) No. 1025, Annex 2: International Atomic Energy Agency and World Health Organization Guideline on Good Manufacturing Practices for Radiopharmaceutical Products
WHO Technical Report Series (TRS) No. 957, Annex 3: WHO Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances, 2010
WHO Technical Report Series (TRS) No. 1010, Annex 8: WHO Guidelines on Heating, Ventilation and Air-conditioning Systems for Non-Sterile Pharmaceutical Products, 2010

4. ABBREVIATIONS AND DEFINITIONS

4.1. The following abbreviations are used in this document:

ACPH	:	Air Changes Per Hour
Al	:	Aluminium Canister
API	:	Active Pharmaceutical Ingredient
CA’s	:	Critical Aspects
CAL	:	Calibration
CDE’s	:	Critical Design Elements
cGMP	:	Current Good Manufacturing Practices
Ci	:	Curries
CNC	:	Controlled Not Classified
CPP’s	:	Critical Process Parameters
CQA’s	:	Critical Quality Attributes
DQ	:	Design Qualification
FAT	:	Factory Acceptance Test
GBq	:	Giga Becquerel
GEP	:	Good Engineering Practice
HEPA	:	High-Efficiency Particulate Arrestance
ID	:	Identification
IQ	:	Installation Qualification
I-131	:	Iodine-131
keV	:	Kiloelectronvolt
L	:	Litres
MBq	:	Mega Becquerel
MeV	:	Megaelectronvolt
MIBG	:	Meta-Iodo-Benzyl-Guanidine

NaOH	:	Sodium Hydroxide
NDA	:	Non-Disclosure Agreement
OQ	:	Operation Qualification
PIC/S	:	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PQ	:	Performance Qualification
QC	:	Quality Control
RAC	:	Radioactivity concentration
SAST	:	South African Standard Time
SAT	:	Site Acceptance Test
TeO_2	:	Tellurium Dioxide
TRS	:	Technical Report Series
UDAF	:	Unidirectional Airflow
WFI	:	Water For Injection
WHO	:	World Health Organization

4.2. The following definitions are provided to ensure a uniform understanding of this document:

Air lock	:	An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.
Controlled Not Classified (CNC)	:	A cGMP manufacturing area designed to produce a consistent and controlled environment, but not necessarily monitored to a given environmental classification.
Qualification	:	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification. Qualification includes Design Qualification (DQ), Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ).
Interim waste storage	:	Interim waste storage area will be used for the collection and interim storage of the waste generated during the production process, before transferring the waste to the long-term waste storage area for decay to the adequate radiological levels for final disposal.
Long term waste storage	:	Long waste storage area will be used for the long-term storage of the waste, to allow the waste to decay to the adequate radiological levels for final disposal.
Centralized Control Room	:	The centralized control room will be centrally located in the facility and used for the monitoring and control of all critical facility, services, systems and equipment parameters and conditions.

5. GENERAL

NTP Radioisotopes SOC Ltd. is one of the leading global producer and supplier of nuclear medicine and radiation-based products and services. NTP would like to establish the manufacturing process of activation I-131 API produced from irradiated Tellurium Dioxide (TeO_2) material at the Necsa site [Located at R104, Pelindaba, Brits Magisterial District]. A process flow diagram indicating the basic process steps of the activation I-131 API production process is provided in Appendix A.

The activation I-131 API is produced by neutron irradiating of TeO_2 material in the SAFARI-1 research reactor for a specified period of time (Up to 21 days). Te-131 is produced by a (n; γ) reaction which decays with a half-life of 25 minutes to I-131 via a beta-minus (β^-) emission. The TeO_2 targets are prepared by encapsulating the TeO_2 material (powder or pellets) into a SAFARI-1 RSC approved aluminium (Al) canister.

Upon completion of the irradiation process, the irradiated TeO_2 targets are transported, via the Lein transfer container, from the SAFARI-1 research reactor to the activation I-131 production facility.

Once in the activation I-131 production facility, the irradiated targets are introduced into the hot cell, for the processing of the TeO_2 targets and the production, activity measurement/ quantification and QC sampling of the I-131 API bulk solution.

Upon completion of the formulation of the I-131 API bulk solution, the customer orders are dispensed as per the customer requirements into a vial.

Upon completion of the dispensing process the customer vials are closed with rubber septum's and aluminium crimp caps and the aluminium vial caps crimped. The activity of each customer vial is measured before being discharged into a shielded container (licensed Type A and Type B(U) transport packaging).

The shielded containers are cleared from any radiological contamination by the safety department before packaging and dispatch.

The activation I-131 production line must be housed in a production area consisting of GMP Grade D (at rest) air quality. The hot cells must be accessible for maintenance purposes from a Controlled Not Classified (CNC) area from a GMP perspective. A facility concept layout of the activation I-131 production line is not yet available and will depend on the recommended production process and equipment layout.

The I-131 production process and accompanying equipment must be designed to ensure compliance with cGMP and radiological requirements and must consist of closed and integrated systems as far as possible.

Due to the nature of the activities and product, all radioactive activities and manipulations shall be performed in shielded hot cells. In addition to the provision of adequate shielding against radiation, operators must also be protected against the inhalation of radioactive substances. The hot cells will therefore operate at negative pressures relative to the atmosphere and surrounding area.

6. RESPONSIBILITIES

N/A

7. PROCESS

The activation I-131 API production process (technology) and accompanying equipment requirements defined in the sections below.

7.1. Compliance Requirements

The activation I-131 API production process and production line must be designed, constructed, installed, commissioned, and qualified in accordance with Good Engineering Practice (GEP), current Good Manufacturing Practice (cGMP) and hazardous (chemical and radiological) material requirements and key focus area stipulated herein:

ID No.	Description
7.1.1.	Act 15 of 1973: Hazardous Substances Act 15 of 1973
7.1.2.	Act 45 of 1965: National Environmental Management: Atmospheric Pollution Prevention Act 45 of 1965
7.1.3.	Act 59 of 2008: National Environmental Management: Waste Act 59 of 2008
7.1.4.	Act 85 of 1993: The Occupational Health and Safety Act 85 of 1993
7.1.5.	Act 85 of 2008: The Medicines and Related Substances Amendment Act 72 of 2008
7.1.6.	Act 85 of 2015: The Medicines and Related Substances Amendment Act 14 of 2015
7.1.7.	Act 101 of 1965: The Medicines and Related Substances Act 101 of 1965
7.1.8.	ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
7.1.9.	ISO 14644: Cleanrooms and associated controlled environments (Part 1 to 4)
7.1.10.	ISO 17873 - 2004: Nuclear facilities — Criteria for the design and operation of ventilation systems for nuclear installations other than nuclear reactors
7.1.11.	NTP-SOP-6204: P1701 Facility Specific Gaseous Radioactive Discharge Control Programme
7.1.12.	PE-009-16 (Parts I & II): PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I & II, February 2022.
7.1.13.	PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 3: Manufacture of Radiopharmaceuticals, February 2022.
7.1.14.	PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 11: Computerised Systems, February 2022.

ID No.	Description
7.1.15.	PE-009-16 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 15: Qualification and Validation, February 2022.
7.1.16.	SAHPGL-INSP-02_v8: SAHPRA Guideline on Good Manufacturing Practice for Medicines, Version 8, September 2022
7.1.17.	SAHPGL-RDN-RN-13_v2: SAHPRA Guideline for Management and Disposal of Non-nuclear Radioactive Waste, Version 2, December 2022
7.1.18.	SANS 10114-1: 2020 Interior Lighting Part 1: Artificial Lighting of Interiors, 4th Ed.
7.1.19.	SANS 10142:1 The wiring of Premises - Part 1: Low-voltage installations
7.1.20.	SHEQ-INS-0233: Design Control
7.1.21.	SHEQ-INS-0234: NECSA QMS Requirement for external Design Organisations
7.1.22.	SHEQ-INS-1120: Lighting (Natural and Artificial)
7.1.23.	SHEQ-INS-8030: System for the classification and demarcation of radiological areas
7.1.24.	SHEQ-INS-8050: Radiological surveillance programme for workplaces
7.1.25.	SHEQ-INS-8180: ALARA programme
7.1.26.	SHEQ-INS-8230: Management of Radioactive Discharges to the Atmosphere at the Pelindaba
7.1.27.	SHEQ-INS-8260: Management of Radioactive Effluent and Discharge at the Pelindaba Site
7.1.28.	SHEQ-INS-8310: Requirements in respect of ventilation systems for nuclear facilities
7.1.29.	SHEQ-INS-8360: Necsa Solid Radioactive Waste Management System
7.1.30.	UNSEAL: Department of Health, Requirements for the Safe Use of Unsealed Radioactive Nuclides, Version 2, February 2001
7.1.31.	US Code of Federal Regulations 21 Part 210 – Current Good Manufacturing Practice for Finished Pharmaceuticals
7.1.32.	US FDA office of Regulatory Affairs – Guideline for Facilities and Environmental Conditions
7.1.33.	21 CFR Part 11: Guidance for Industry, Part 11, Electronic Records; Electronic Signatures — Scope and Application, March 2023.
7.1.34.	WHO Technical Report Series (TRS) No. 1025, Annex 2: International Atomic Energy Agency and World Health Organization Guideline on Good Manufacturing Practices for Radiopharmaceutical Products.
7.1.35.	WHO Technical Report Series (TRS) No. 957, Annex 3: WHO Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances, 2010.
7.1.36.	WHO Technical Report Series (TRS) No. 1010, Annex 8: WHO Guidelines on Heating, Ventilation and Air-conditioning Systems for Non-Sterile Pharmaceutical Products, 2010.

7.2. Process Requirements – Capacity

ID No.	Requirement
7.2.1.	The production process and equipment/ systems must be able to produce a minimum of 200 Ci (7-day calibration) per week.
7.2.2.	The production process must include the basic process steps listed in Appendix A and below:

ID No.	Requirement
	• Introduction and processing of the irradiated TeO_2 targets. • Production and activity measurement/ quantification of the I-131 bulk solution. • QC sampling of the I-131 bulk solution, closing and crimping of the QC vial and discharge into shielded lead pots. • Dispensing of customer orders as per customer requirements. • Closing and crimping of the customer vials. • Activity measurement of customer vials and discharge into shielded lead pots. The detailed process steps and the additional control parameters must be provided by the prospective suppliers and/or design engineers.
7.2.3.	The equipment/ systems must be capable of handling the maximum radioactivity allowed in the hot cells.
7.2.4.	The equipment where radioactive activities/ manipulations are performed shall be adequately shielded to protect the operators against the maximum radioactivity allowed in the hot cells, with a maximum dose rate of 2,5 µSv/h (Contact) in front of the hot cells and 1000 µSv/h (Contact) at the back of the hot cells as per SHEQ-INS-8030. The ALARA principal will apply but the above is the maximum.
7.2.5.	The equipment/ systems must allow for the adequate segregation of the process steps included in ID No. 7.2.2 to avoid mix-ups and cross-contamination.
7.2.6.	Adequate equipment/ systems and in-cell equipment must be provided for the process steps included in ID No. 7.2.2. Closed and integrated systems are preferred. Space requirements for the equipment/ systems must be provided the by prospective suppliers and/or design engineers.
7.2.7.	The prospective suppliers and/or design engineers must provide a facility concept layout that includes the position of the hot cells, operational space constraints around the hot cells (minimum requirements), the material and personnel flows and GMP and radiological area classifications (radiological classifications as per ISO 17873).
7.2.8.	The radioactive processes/ activities listed in ID No. 7.2.2. must be performed in hot cells/ shielded systems, with adequate air cleanliness (Refer to section 7.4 for air cleanliness requirements) and shielding (Refer to ID No. 7.2.4 for shielding requirements).
7.2.9.	Adequate waste management system and waste storage/ handling capacity must be provided for the handling of radioactive solid, liquid, and gaseous waste generated by the production process. A well-documented waste management plan must be provided inclusive of solid, liquid, and gaseous waste management requirements by prospective suppliers and/or design engineers.

7.3. **Process Requirements – Product Physical Properties**

ID No.	Requirement
7.3.1.	The ***TeO_2 (Tellurium Dioxide) target*** used for the manufacturing of activation I-131 API has the following characteristics: • Mass per Target: ≤ 80 g of Tellurium Dioxide (TeO_2) • Packaging: SAFARI-1 RSC approved aluminium canister *(**NOTE**: Drawing will be provided upon request and signing of an NDA)* • Nominal neutron flux = 2e14 neutrons/s/cm^2 • Maximum irradiation time = 21 days
7.3.2.	The I-131 ***bulk solution*** has the following characteristics: • Element: Iodine • Nuclide: I-131 • Chemical Form: Sodium Iodide (I-131) • Half-life: 8.02 days • Decay Mode: Beta and Gamma radiation • Gamma Energies: 364 keV (81% abundance) • Beta Energies: 606 keV (89% abundance) • Volume: < 20 ml • pH: > 10 • Appearance: Clear, colourless solution • Sterility: Non-Sterile • Specific Activity: > 6 Ci (222 GBq)/mg at End of Shelf-life • Radioactive Concentration: > 1 Ci (37 GBq/mg)/ml • Shelf-life: 30 Days from day of manufacture
7.3.3.	The I-131 bulk solution ***QC sample*** has the following characteristics: • Element: Iodine • Nuclide: I-131 • Chemical Form: Sodium Iodide (I-131) • Half-life: 8.02 days • Decay Mode: Beta and Gamma radiation • Gamma Energies: 364 keV (81% abundance) • Beta Energies: 606 keV (89% abundance) • Volume: ≤ 1.3 ml RC sample, Archive sample 1.3 ml • Activity: for RC sample 74 MBq and for Archive sample 148 MBq • Primary Packaging Material: 10 ml vial, with septum and crimping metal cap *(**NOTE**: Drawing will be provided upon request and signing of an NDA)* • Secondary Packaging Material: A40B lead container, *(**NOTE**: Drawing will be provided upon request and signing of an NDA)*

ID No.	Requirement
7.3.4.	The I-131 ***final product*** (customer vials) has the following characteristics: • Element: Iodine • Nuclide: I-131 • Chemical Form: Sodium Iodide (I-131) • Half-life: 8.02 days • Decay Mode: Beta and Gamma radiation • Gamma Energies: 364 keV (81% abundance) • Beta Energies: 606 keV (89% abundance) • Activity: 0.4 Ci to 90 Ci (7 days calibration) • Volume: ≤ 15 ml • pH: ≥ 10 • Radionuclidic Purity: ≥ 99.9 % • Radiochemical Purity: ≥ 95 % (Normal Product) and ≥ 98 % (Extra Pure Product) • Appearance: Clear, colourless solution • Sterility: Non-Sterile • Specific Activity: ≥ 6 Ci (222 GBq) I-131 /mg of Iodine at expiry date • Concentration: ≥ 1 Ci (37 GBq)/ ml at calibration time and date • Primary Packaging: 2ml V-vial, 5ml V-vial, 10 ml-, 20 ml or 30-ml flat bottom vial, rubber septum and aluminium crimp cap. *(**NOTE**: Drawings will be provided upon request and signing of an NDA)* • Secondary Packaging: Type_A and Type_B(U) licensed transport packages *(**NOTE**: Drawing will be provided upon request and signing of an NDA)* • Calibration Date: minimum 3 days after manufacture, specifiable to 12:00 (SAST) • Shelf-life: 30 Days from day of manufacture

7.4. **Process Requirements – Critical Quality Attributes (CQA's) and Critical Process Parameters (CPP's)**

ID No.	Requirement
7.4.1.	The production process must be capable of producing a final product meeting the criteria listed in ID No. 7.3.4. The scientific case for process development (product development data) must be provided by the prospective suppliers and/or design engineers.
7.4.2.	The following processes/ activities (as per ID No. 7.2.2) must be performed in at least a Grade D (at rest) area or higher: • Handling and processing of irradiated TeO_2 targets. • Production and activity measurement/ quantification of the I-131 bulk solution. • QC sampling of the I-131 bulk solution, closing and crimping of the QC vial and discharge into shielded lead pots.

ID No.	Requirement
7.4.3.	The following processes/ activities (as per ID No. 7.2.2) must be performed in at least a Grade C (at rest) area or higher: • Dispensing of customer orders as per customer requirements. • Closing and crimping of the customer vials. • Activity measurement of customer vials and discharge into shielded lead pots.
7.4.4.	The GMP classified areas must comply to the requirements of PIC/S Annex 1, par. 4.27 (total particle concentration) and 4.31 (microbial contamination levels) in the "at-rest" and "in operation" occupancy states, to ensure that the required environmental cleanliness level is achieved and maintained. GMP classified areas shall be classified (total particle concentration) in accordance with ISO 14644 Part 1.
7.4.5.	The air change rate per hour (ACPH) of each GMP classified area shall be adequate to provide a recovery rate of less than 20 minutes to the "at rest state" as per PIC/S Annex 1, par. 4.29.
7.4.6.	The hot cells must operate at a negative pressure relative to the atmosphere and surrounding areas as per ISO 17873 and SHEQ-INS-8310.
7.4.7.	The in-cell equipment (dose calibrator) used for the radioactivity measurement of the I-131 solutions must be able to measure the activity ranges specified in section 7.3 with an overall accuracy ± 5%.
7.4.8.	The in-cell equipment used for the dispensing of the customer orders must be able to accurately dispense I-131 volumes ranging between 0.1 ml – 15 ml with an accuracy of ± 10 % per customer vial.
7.4.9.	The in-cell equipment used for the dispensing of the customer orders must be able to adjust the concentration to ≥ 1 Ci (37 GBq)/ ml (at calibration time and date) with an accuracy of ± 10 % per customer vial.

7.5. Automation and Records

ID No.	Requirement
General	
7.5.1.	Each critical system/ equipment shall be equipped with a user machine interface (HMI) located on the outside of the hot cell allowing the complete management of the machine utilities, data display with recording and reporting parameters, alarms, and controls.
7.5.2.	The possibility of remote monitoring of the critical equipment and process parameters must be provided.
7.5.3.	Each operating software system shall be complaint to 21 CFR Part 11. A certification must be provided, and the system must be tested for compliance as part of equipment qualification.

ID No.	Requirement
Security	
7.5.4.	Access to computerised systems and data storage areas must be restricted to authorised personnel using appropriate controls.
7.5.5.	Each operating software system shall have the capability to provide different user levels, with unique user ID's and passwords.
7.5.6.	Each operating software system must be provided with 3 user types: • ***Type 1:*** Administrator - All rights including exit to windows functionality, change settings, change parameter, use and control the system, access frontend & backend database, can adjust rights for users. • ***Type 2:*** Supervisor - Same rights as user administrator but no exit to windows functionality, no back-end database access. • ***Type 3:*** Standard User - No access to settings and parameters, no exit to windows, no exit back-end database, use and control the system in manual and automatic mode, access to the front-end of the database.
7.5.7.	Each operating software system shall have the capability to record the creation, change, and cancellation of access authorisations.
7.5.8.	Each operating software system shall have the capability to record the identity of personnel entering or changing data, including date and time.
Electronic Signatures	
7.5.9.	Each operating software system should allow for electronic signatures, which should be permanently linked to the respective record and should include the date and time of signing.
Data Storage and Disaster Recovery	
7.5.10.	Each operating software system shall have the capability to record and store all GMP-relevant data at the time of each step and event legibly and contemporaneously. Stored data should be secured against damage.
7.5.11.	Stored data should be accessible (by authorised personnel only), readable, and accurate throughout the data retention period.
7.5.12.	Each operating software system shall have the capability of restoring the stored data, with the same accuracy and integrity, in the case of system failures/ breakdowns.
7.5.13.	Each operating software system shall have the capability of archiving and retrieval of the data in a manner that assures that the archived copy preserves the full content of the original electronic data set, including all metadata needed to fully reconstruct the GMP activity. Archived data should be accessible (by authorised personnel only), readable, and accurate.
7.5.14.	Each operating software system should have the capability of interfacing with a Historian server.

ID No.	Requirement
Time and Date	
7.5.15.	Each operating software system shall have the capability to automatically synchronize the time/ date stamps to the standard reference time.
7.5.16.	Changing of the time and date and time zone must be restricted to authorized personnel only.
Printouts	
7.5.17.	Each operating software system shall have the capability to provide clear copies of the electronically stored data for printing purposes.
Audit Trails	
7.5.18.	Each operating software system shall have the capability to record all the steps that create or modify electronic GMP-relevant data in an audit trail, including the "what" (e.g. original entry), "who" (e.g. user ID), "when" (e.g. time/date stamp) and "why" (e.g. reason) of the action;
7.5.19.	Audit trails must be accessible and convertible to a generally intelligible form for viewing and printing purposes.
Alarms and Events	
7.5.20.	Each operating software system shall provide tools and utilities for configuration, categorizing, prioritizing, logging, annunciating, displaying, acknowledging, disabling, and reporting of alarms and events.
7.5.21.	The operating software system used for the dispensing of the customer vials of must allow for the critical process alarms as a minimum.
Functionality	
7.5.22.	The operating software systems used for the production and dispensing of activation I-131 must consist of the following programmes: • Manual Mode • Automatic Mode • Semi-automatic Mode
7.5.23.	The operating software system used for the dispensing of the customer orders must allow the importing of customer orders from an external order sheet.
7.5.24.	The operating software system used for the dispensing of the customer orders must allow capturing of the following customer order details: • Client – Client Name • Int O/No. – Internal Order Number • Order No. - Client's Order Number • Batch No. - NTP Batch Number • Activity (GBq) – Activity in GBq for the order as on 12 pm Use Date • Production Date • Use Date – Calibration date (12 pm on the day of use)

ID No.	Requirement
	• Collect Date – Day that shipping/ collection from NTP • Expiry Date • Activity Required • Volume Required
7.5.25.	A barcoded system must be provided for the reading of the dispensing recipes and printing of the primary (vial) and secondary (shielded container) packaging labels.
7.5.26.	Label printers for the printing of the primary (vial) and secondary (shielded container) packaging label must be provided. Information to be provided on the labels includes: • Bulk Batch Number • Customer Order Number • Reference Activity (GBq) and Date • Volume • Expiry Date • Contents description and warnings • Product license and registration number • Company name and address
7.5.27.	The method of label printing must be compatible with GMP classified areas and be easy to disinfect and must not fade over time.
7.5.28.	The hot cells/ shielded systems must be equipped with radioactivity detecting monitors inside the cell, integrated with the safety systems of the cell (control opening of the door and airlock door).
7.5.29.	The hot cells radioactivity monitoring system must have the capability to display the dose rates inside the cell and incorporate the alarm limits.

7.6. Design and Consideration

ID No.	Requirement
7.6.1.	Surfaces in contact with product and material must be easy to clean and disinfect and resistant to disinfectants, decontaminants, and sterilizing agents.
7.6.2.	Surfaces in contact with product and material must be resistant to caustic vapours/ liquids.
7.6.3.	Surfaces in contact with product and material must be non-shedding, smooth, impervious, and free from cracks and open joints in order to minimize the shedding or accumulation of particles or micro-organisms.
7.6.4.	Surfaces and transfer medium in contact with product and material must not be reactive, additive, or absorptive so as to alter the quality of the radiopharmaceutical.

ID No.	Requirement
7.6.5.	All in-cell equipment and equipment surfaces must be able to withstand the exposure to radiation and the operating conditions inside the cell on a routine basis.
7.6.6.	Critical working zones must be designed to avoid the creation of recesses which are difficult to clean. Corners/edges shall be rounded in the critical working zones to ease cleaning.
7.6.7.	Lighting levels in the critical work zones must not be less than 500 lux as per SANS 10114-1.
7.6.8.	The equipment/ systems must be equipped with adequate air extraction systems fitted with an impregnated media filter (for I-131 capturing) and HEPA/ ULPA filtration. The exhaust system shall be designed on a redundant basis and shall be connected to the central facility radioactive exhaust system.

7.7. Utilities/ Services/ Systems

ID No.	Requirement
7.7.1.	No utilities are currently available. Supplier to advise on the utilities required.
7.7.2.	A well-documented utilities requirement list (incl. the capacity, pressure, flow, purity/ grade, consumption requirements etc.) must be provided by the by prospective suppliers and/or design engineers.

7.8. Operations and Maintenance

ID No.	Requirement
7.8.1.	NaOH solution shall be preferred for the entrapment of the released I-131 vapour. Alternative entrapment solutions can be proposed.
7.8.2.	The equipment/ system must be capable of interfacing with the Lein transfer container without compromising the containment, product, personnel, and environment from a safety and GMP perspective. ***NOTE:*** *Drawings will be provided on request and upon signing an NDA.*
7.8.3.	The equipment/ systems must be able to handle and process the TeO_2 targets included in section 7.3.1. The TeO_2 targets will be sealed when introduced into the hot cells. ***NOTE:*** *Drawings of the TeO_2 target will be provided on request and upon signing an NDA.*
7.8.4.	The equipment/ systems must be able to produce and measure the activity of the bulk solution included in ID No. 7.3.2.
7.8.5.	The equipment/ systems must be able to dispense, measure (activity) and dispatch the bulk QC sample included in ID No. 7.3.3.

ID No.	Requirement
7.8.6.	The equipment/ systems, used for the dispensing of the final product (customer orders), must be capable of dispensing, measuring (activity) and dispatch the final product (customer orders) included in ID No. 7.3.4.
7.8.7.	The equipment/ systems, used for the dispensing of the QC and final product (customer orders), must be capable of handling the following vial sizes: • 2 ml v-vials • 5 ml v-vials • 10 ml flat bottom • 20 ml flat bottom • 30 ml flat bottom • 30 ml crimp v-vial (septum's and crimp caps different to other vials) ***NOTE:*** *Vial drawings will be provided on request and upon signing an NDA.*
7.8.8.	The equipment/ system must allow for the transfer of the radioactive materials (target materials, I-131 solutions, waste etc.) between the hot cells, using the shortest possible route, without being exposed to the atmosphere, using shielded and airtight transfer systems (Refer to ID No. 7.2.4 for the shielding requirements).
7.8.9.	The equipment/ systems must allow the introduction of the intermediates/ reagents from outside the radioactive environment (hot cells/ shielded systems) into the hot cell/ shielded systems, using the shortest possible route, without being exposed to the atmosphere, using airtight transfer systems to reduce the generation of radioactive waste as far as possible.
7.8.10.	The equipment/ system must allow the introduction of consumables, and primary packaging material into the critical work zones, without compromising the containment, product, personnel and environment from a safety and GMP perspective.
7.8.11.	The system shall allow the radioactive activities and manipulations to be performed inside shielded hot cells which are sealed to the outside environment (isolators).
7.8.12.	Manipulators must be provided for the manipulation of the activities inside the hot cells. Ball-and-tong manipulators (telepliers) are not acceptable.
7.8.13.	An extraction system must be provided for the safe and shielded extraction of the QC samples and product vials into shielded lead pots from the hot cell.
7.8.14.	The extraction system, must be capable of handling the following shielded containers and caps: • Type A • Type B(U) ***NOTE:*** *Drawings will be provided on request and upon signing an NDA.*
7.8.15.	Maintenance of the hot cells/ shielded systems shall be performed from a Controlled Not Classified (CNC) area.

ID No.	Requirement
7.8.16.	Maintenance on all equipment/ systems must be easy to perform, parts that must be replaced or adjusted must be easily accessible and access for calibration must be easy if applicable.
7.8.17.	NTP must ensure that the handling of the solid waste meet the requirements stated in the SHEQ-INS-8360.
7.8.18.	NTP must ensure that the handling of the liquid waste shall meet the requirements stated in SHEQ-INS-8260.
7.8.19.	NTP must ensure that the handling of the gaseous waste shall meet the requirements stated in SHEQ-INS-8230.

7.9. Life-cycle Requirements

ID No.	Description
Design Review	
7.9.1.	During the design phase, and as part of final design approval, design review meetings must be conducted. NTP must be involved with the Design review meetings. The outcomes of these meetings will be recorded and compiled as the design review.
7.9.2.	The design review shall demonstrate that the design meets all relevant user, functional, design, regulatory and compliance requirements.
FAT and SAT Requirements	
7.9.3.	The system shall be Factory Acceptance Tested (FAT) by the service provider and/or subcontractors to the service provider prior to equipment delivery. NTP must be involved with the FAT activities and witness the activities in person. NTP must review and accept the FAT plans/ protocols and reports prior to equipment delivery.
7.9.4.	The system shall be installed and Site Acceptance Tested (SAT) by the service provider and/or subcontractors to the service provider, prior to handover to NTP. NTP must be involved with the SAT activities and witness the activities in person. NTP must review and accept the SAT plans/ protocols, and reports.
7.9.5.	All installation, FAT and SAT documentation must comply with Good Documentation Practices as per GMP requirements.
7.9.6.	All personnel of the service provider performing FAT testing, installation and SAT testing shall supply evidence of accreditation by a relevant testing authority or qualification to perform the activities.
7.9.7.	The service provider shall supply documented evidence that the requirements of this document have been met where appropriate.
7.9.8.	Certificates of compliance with relevant national standards shall be supplied.
Process Commissioning	
7.9.9.	The production process shall be commissioned by the service provider and/or subcontractors to the service provider prior to hand-over to NTP. NTP must be involved with the commissioning activities and witness the activities in person. NTP must review and accept the commissioning plans/ protocols and reports prior to equipment delivery.

ID No.	Description
7.9.10.	All commissioning documentation must comply with Good Documentation Practices as per GMP requirements.
7.9.11.	All personnel of the service provider performing the commissioning activities shall supply evidence of qualification to perform the activities.
7.9.12.	The service provider shall supply documented evidence that the requirements of this document have been met where appropriate.
Qualification Requirements	
7.9.13.	The system shall be qualified by the service provider, prior to handover to NTP. The system shall require Design, Installation and Operational Qualification. NTP must be involved with the qualification activities and witness the activities in person. NTP must review and accept the qualification plans/ protocols, acceptance criteria and reports.
7.9.14.	Performance Qualification/ Process Validation shall be performed by NTP after hand-over of the system to NTP.
7.9.15.	All qualification protocols (DQ, IQ and OQ) must be completed in accordance with Good Documentation Practices as per GMP requirements.
7.9.16.	Qualifications shall be completed prior to hand-over and routine use of the system.
Handover Documentation	
7.9.17.	The service provider shall supply the following equipment/ system documentation as a minimum: • Operating & Maintenance Manuals; • Recommended spare parts list; • All Certificates of Compliance; • FDA 21 CFR Part 11 Compliance certificate (for software systems) • List of alarms and notifications (for software systems) • ISO Certification of Suppliers • Control Philosophy of systems • Equipment specifications (Incl. outsourced subsystems e.g. Manipulators, etc.); • As-built technical drawings [Layout, Electrical, pneumatic, mechanical, and process and instrumentation diagrams (P&ID's)]; • Design Codes and Standards used; • Material data sheets; • Material certificates for Direct Impact Systems (i.e. components in direct contact with the product); • Main equipment data sheets; • Instrument calibration certificates; • Welding process qualification. • Contact details for suppliers and maintenance contractor(s) • Preventative maintenance task list with recommended frequencies • Training records
7.9.18.	The service provider shall supply the following commissioning records as a minimum: • Record of Factory Acceptance Test (FAT) results: - Test Instrument Data (Calibration Certificates of the reference instruments); - System Documentation Verification (documents list for equipment qualification);

ID No.	Description
	- Construction Design Verification ("As-built" documentation); - Main Equipment Specification Verification (evidence of conformance with design); - Functionality/Interlocks Verification (Mechanical as well as software); - Glove Breach Test (if applicable); - Unidirectional Airflow Verification; - Air Change Rate; - Air Velocity Verification; - Filter Integrity Tests; - Leak Tightness Test; - Verification of Air Classification; - Verification of Shielding Integrity; • Record of Site Acceptance Test (SAT) results: - Installation Design Verification ("As-installed" documentation); - Main Equipment Specification Verification (evidence of conformance with design); - Functionality/Interlocks Verification (Mechanical as well as software); - Unidirectional Airflow Verification; - Air Change Rate; - Air Velocity Verification; - Filter Integrity Tests; - Leak Tightness Test; - Verification of Air Classification; - Verification and acceptance of Certificates of Compliance for utilities as compliant with interface specifications (e.g. quality of instrument air, electrical supply, etc.); - Calibrations and associated documentation for all functional performances of the system and subsystems; - Training qualifications for operators and maintenance personnel for agreed to maintenance tasks to be performed by NTP.
7.9.19.	The service provider shall supply the following qualification records as a minimum: • Design qualification protocol and report • Manufacturing qualification report • Installation qualification protocol and report • Operation qualification protocol and report • System risk assessment, including the Critical Process Parameters (CPP's), Critical Aspects (CA's) and Critical Design Elements (CDE's)
7.9.20.	The service provider shall supply the following production process documents as a minimum: • Process Descriptions and/ or Standard Operating Procedures • In-process Checks (IPC), Critical Quality Attributes (CQA's), Critical Process Parameters (CPP's)

ID No.	Description
Maintenance and Service Level Agreement	
7.9.21.	The system shall be installed with a warranty period of no less than 12 months on all parts and labour, from date of handover.
7.9.22.	A Service Level Agreement must be established for 5 consecutive years between the service provider and NTP. The Service Level Agreement must include the following as a minimum: • Spare parts • Preventative maintenance requirements • Ad-hoc/ corrective maintenance requirements • Call-out requirements • Remote assistance requirements
7.9.23.	The routine preventative maintenance schedule shall be included in NTP's ISI&MP.
Life-cycle Testing	
7.9.24.	All controlling and monitoring sensors/displays and measuring instruments shall be added to NTP's ISI&MP and calibrated in accordance with the frequency determined for each item.
Training	
7.9.25.	Training must be provided to NTP personnel (production and maintenance) by the service provider prior to handover to NTP. Training must cover operation, monitoring, cleaning, safety, calibration, and maintenance. Training shall be documented, maintained and training records provided to NTP as part of the hand-over documents.
QMS Documentation	
7.9.26.	NTP shall ensure that the following SOPs have been created and/or updated for the equipment/ system: • Operation • Monitoring • Calibration • Maintenance • Cleaning
Change Management	
7.9.27.	All changes to the Proposal Requirement Specification and equipment/ system design after approval must be performed as per the service provider's quality management system requirements.
7.9.28.	Adequate change management must be performed by the service provider during the design phase as per the service provider's quality management system requirements.

8. RECORDS

Record	Retention Period	By Whom
N/A	None	None

9. TASK HAZARD ASSESSMENT

Task Hazard Assessment is not applicable to this document.

10. LIST OF FORMS

Form Title	Form Number	Exhibit Number
N/A	None	None

11. REVISION HISTORY

Rev.	Date Approved	Nature of Revision	Originated by
1	See title page	First revision.	MM van Vuuren

APPENDIX A: Activation I-131 Production Process Flow