







**RESTRICTED**

Document No.	NTP-SPE-4162	Rev No.	1	Page 1 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

ACTION	NAME & EXPERTISE	SIGNATURE	DATE
Originated By:	M Mukwevho <i>Project Management</i>		2024/06/03
Checked By:	T More <i>Engineering Review</i>		2024/06/03
Checked By:	M Sekgodi <i>Operational Review</i>		2024/06/03
Approved By:	J Selome <i>Project Senior User Review</i>		2024/06/03
Implementation Date:			
DISTRIBUTION LIST (1 = Original, 2 and upwards = Electronic Copy)			
1	QA Records (P1700)	2	Document Centre
<b>Authentication of printed document: This document was printed by:</b>			
NAME		SIGNATURE	DATE


**RESTRICTED**

**RESTRICTED**

Document No.	NTP-SPE-4162	Rev No.	1	Page 2 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

**TABLE OF CONTENTS**

1. PURPOSE.....	3
2. SCOPE .....	3
3. REFERENCES.....	3
4. ABBREVIATIONS AND DEFINITIONS.....	6
5. GENERAL.....	7
6. RESPONSIBILITIES .....	8
7. PROCESS .....	8
8. RECORDS.....	11
9. TASK HAZARD ASSESSMENT .....	11
10. LIST OF FORMS .....	11
11. REVISION HISTORY.....	11

Document No.	NTP-SPE-4162	Rev No.	1	Page 3 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

## 1. PURPOSE

The purpose of this document is to define the high-level proposed manufacturing facility requirements for the production of non-sterile activation Iodine-131 Active Pharmaceutical Ingredient (API) from irradiated Tellurium Dioxide (TeO<sub>2</sub>) targets.

This document includes reference to NECSA and NTP requirements as well as compliance with current Good Manufacturing Practice (cGMP) and Good Engineering Practice (GEP) 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 design. This document is not intended as an exclusive approach, the identification or omissions of alternative suggestions by prospective suppliers and/or design engineers are welcome.

This requirements document is a key document as a point of reference throughout the validation life cycle of the facility i.e. Design specification, Quality Risk Management (QRM), and Commissioning and Qualification (C&Q) activities.

## 2. SCOPE

The scope of this document applies to the Activation Iodine-131 API Manufacturing Facility to be located in Building C2 on the Necsa site [Located at R104, Pelindaba, Brits Magisterial District]. This document specifies the requirements associated with the design Activation Iodine-131 API Manufacturing Facility.


The hot cell production line, i.e. the hot cells and the associated in-cell processes do not form part of the scope of this document, and will be supplied by a third-party specialist supplier. Any and all utilities and or services required for optimal function of the hot cell production line shall be included in the scope of this document.

## 3. REFERENCES

This document complies with the requirements of:

ICH Q7	: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
ISO 9001: 2015	: Quality Management System – Requirements, Fifth edition, 2015.
ISPE Baseline Guide	: Commissioning and Qualification, Volume 5, 2nd Edition, 2019

**RESTRICTED**


Document No.	NTP-SPE-4162	Rev No.	1	Page 4 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

PE-009-17 (Parts I & II)	:	PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I & II, August 2023
SAHPGL-INSP-02_v8	:	SAHPRA Guideline on Good Manufacturing Practice for Medicines, Version 8, September 2022
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 <sub>2</sub> 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 103 of 1977	:	National Building regulations and building standards Act 103 of 1977
ICH Q7	:	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
ISO 8573-1:2010	:	Compressed Air – Part 1: Contaminants and Purity Classes
ISO 9001:2015	:	Quality Management systems - Requirements, Fifth edition, 2015
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-009-17 (Parts I & II):	:	PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part 1 & II, August 2023
PE-009-17 (Annexes)	:	PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 1: Manufacture of Sterile Medicinal Products, August 2023.
PE-009-17 (Annexes)	:	PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 3: Manufacture of Radiopharmaceuticals, August 2023
PE-009-17 (Annexes)	:	PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 15: Qualification and Validation, August 2023.
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

# RESTRICTED

Document No.	NTP-SPE-4162	Rev No.	1	Page 5 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

SANS 7240-16:2008	:	Fire Detection and Alarm Systems Part 16: Sound System Control and Indication
SANS 7240-19:2008	:	Fire detection and alarm systems Part 19: Design, installation, commissioning and service of sound systems for emergency purposes
SANS 10400-O:2011	:	The application of the National Building Regulations Part O: Lighting and ventilation
SANS 10400-T:2011	:	The application of the National Building Regulations Part T: Fire protection
SANS 10114-1: 2020	:	Interior Lighting Part 1: Artificial Lighting of Interiors, 4th Ed.
SANS 10139:2007	:	Fire Detection and Alarm Systems for buildings – System design, installation and servicing, Edition 3.1.
SANS 10142:1	:	The wiring of Premises - Part 1: Low-voltage installations
SHEQ-INS-0234	:	NECSA QMS Requirement for external Design Organisations
SHEQ-INS-1110	:	Housekeeping and demarcation
SHEQ-INS-1120	:	Lighting (Natural and Artificial)
SHEQ-INS-7010	:	Zoning of facilities with hazardous chemical substances
SHEQ-INS-7030	:	Surveillance programme for workplaces containing hazardous chemical substances
SHEQ-INS-7140	:	Management of hazardous chemical waste
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
SHEQ-INS-8920	:	Access Control to Necsa Sites and Its Facilities
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
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

Document No.	NTP-SPE-4162	Rev No.	1	Page 6 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				


## 4. ABBREVIATIONS AND DEFINITIONS

4.1. The following abbreviations are used in this document:

API	:	Active Pharmaceutical Ingredient
cGMP	:	Current Good Manufacturing Practices
DQ	:	Design Qualification
GEP	:	Good Engineering Practice
IQ	:	Installation Qualification
ISO	:	International Organization for Standardization
I-131	:	Iodine 131
NECSA	:	Nuclear Energy Corporation of South Africa
OQ	:	Operational Qualification
PA	:	Public Address
PIC/s	:	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
QC	:	Quality Control
SAHPRA	:	South African Health Product Regulatory Authority
SANS	:	South African National Standards
UPS	:	Uninterrupted Power Supply
WHO	:	World Health Organization

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

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
---------------------------------	---	--

Document No.	NTP-SPE-4162	Rev No.	1	Page 7 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

## 5. GENERAL

NTP Radioisotopes SOC Ltd. (NTP), a subsidiary of the South African Nuclear Energy Corporation SOC Ltd. (NECSA), is a leading global producer and supplier of nuclear medicine and radiation-based products and services. NTP would like to establish a manufacturing facility to produce activation I-131 API from irradiated Tellurium Dioxide ( $\text{TeO}_2$ ) material in Building C2 located on the Necsa site [R104, Pelindaba, Brits Magisterial District].

The Activation I-131 Manufacturing Facility will house the activation I-131 production process together with its support functions and infrastructure to enable continuous and sustainable manufacturing of the activation I-131 API product. A process flow diagram indicating the overall process flows of the activation I-131 API production process and the scope of the facility is provided in Appendix A.


The activation I-131 API is produced by neutron irradiation of  $\text{TeO}_2$  material in the SAFARI-1 research reactor for a specified period of time (Up to 21 days).  $\text{Te-131}$  is produced by a ( $n; \gamma$ ) reaction which decays with a half-life of 25 minutes to I-131 via a beta-minus ( $\beta^-$ ) emission. The  $\text{TeO}_2$  targets are prepared by encapsulating the  $\text{TeO}_2$  material (powder or pellets) into a SAFARI-1 RSC approved aluminium (Al) canister.

Upon completion of the irradiation process, the irradiated  $\text{TeO}_2$  targets are transported, via the Lein transfer container, from the SAFARI-1 research reactor to the Activation I-131 Manufacturing Facility, Building C2.

Once in the Activation I-131 Manufacturing Facility, the irradiated targets are introduced into the hot cell, for the processing of the  $\text{TeO}_2$  targets and the production thereof, activity measurement, quantification, QC sampling, dispensing and packaging of the activation I-131 API bulk solution.

Upon completion of the dispensing process the customer vials are closed with rubber septums 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.

Document No.	NTP-SPE-4162	Rev No.	1	Page 8 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

The activation I-131 production line shall be operated from the front and shall be housed in a controlled and GMP classified area. The hot cells shall be accessed from the back for maintenance purposed and must be housed in a controlled area, but not a classified area from a GMP perspective.

The Activation I-131 Manufacturing Facility shall be designed to ensure compliance with cGMP and radiological requirements.

## 6. RESPONSIBILITIES


N/A

## 7. PROCESS

### 7.1. Requirements

- 7.1.1 Design process flow for Activation I-131 production from Tellurium Oxide inclusive of :
  - 7.1.1.1 Intermediate production and material handling
  - 7.1.1.2 Quality control
  - 7.1.1.3 Waste management,
  - 7.1.1.4 Product packaging and dispatch.
- 7.1.2 cGMP Facility Design inclusive of intermediate production, hot production, material handling, quality control, waste management, product packaging and dispatch.
- 7.1.3 The facility design shall accommodate ancillaries such as,
  - 7.1..1 Maintenance areas
  - 7.1..2 Working space and offices
  - 7.1..3 Rest and refreshment rooms
  - 7.1..4 Kitchen
  - 7.1..5 Amenities and change rooms
  - 7.1..6 Storage space for cleaning equipment and materials
  - 7.1..7 Material and personnel transfer systems.
  - 7.1..8 Server room (Industrial and communication server room)
  - 7.1..9 Control room
- 7.1.4 Define and design utilities to support the Activation I-131 production facility. Utilities design should take account of the entire facility utility structure.




Document No.	NTP-SPE-4162	Rev No.	1	Page 9 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

## 7.2. Compliance Requirements

The Activation I-131 Manufacturing Facility line must be designed, constructed, 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
7.2.1.	Act 15 of 1973: Hazardous Substances Act 15 of 1973
7.2.2.	Act 45 of 1965: National Environmental Management: Atmospheric Pollution Prevention Act 45 of 1965
7.2.3.	Act 59 of 2008: National Environmental Management: Waste Act 59 of 2008
7.2.4.	Act 85 of 1993: The Occupational Health and Safety Act 85 of 1993
7.2.5.	Act 103 of 1977: National Building regulations and building standards Act 103 of 1977
7.2.6.	ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 Version, Nov 2000
7.2.7.	ISO 8573-1:2010 Compressed Air – Part 1: Contaminants and Purity Classes
7.2.8.	ISO 9001:2015: Quality Management systems - Requirements, Fifth edition, 2015
7.2.9.	ISO 14644: Cleanrooms and associated controlled environments (Part 1 to 4).
7.2.10.	ISO 17873 - 2004: Nuclear facilities — Criteria for the design and operation of ventilation systems for nuclear installations other than nuclear reactors
7.2.11.	PE-009-17 (Parts I & II): PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I & II, August 2023.
7.2.12.	PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 1: Manufacture of Sterile Medicinal Products, August 2023.
7.2.13.	PE-009-17 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 3: Manufacture of Radiopharmaceuticals, August 2023.
7.2.14.	PE-009-17 (Annexes): PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Annex 15: Qualification and Validation, August 2023.
7.2.15.	SAHPGL-INSP-02_v8: SAHPRA Guideline on Good Manufacturing Practice for Medicines, Version 8, September 2022
7.2.16.	SAHPGL-RDN-RN-13_v2: SAHPRA Guideline for Management and Disposal of Non-nuclear Radioactive Waste, Version 2, December 2022
7.2.17.	SANS 7240-16:2008 Fire Detection and Alarm Systems Part 16: Sound System Control and Indication
7.2.18.	SANS 7240-19:2008 Fire detection and alarm systems Part 19: Design, installation, commissioning and service of sound systems for emergency purposes
7.2.19.	SANS 10400-O:2011: The application of the National Building Regulations Part O: Lighting and ventilation
7.2.20.	SANS 10400-T:2011: The application of the National Building Regulations Part T: Fire protection
7.2.21.	SANS 10114-1: 2020 Interior Lighting Part 1: Artificial Lighting of Interiors, 4th Ed.


**RESTRICTED**

Document No.	NTP-SPE-4162	Rev No.	1	Page 10 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

ID No.	Description
7.2.22.	SANS 10139:2007 Fire Detection and Alarm Systems for buildings – System design, installation and servicing, Edition 3.1.
7.2.23.	SANS 10142:1 The wiring of Premises - Part 1: Low-voltage installations
7.2.24.	SHEQ-INS-0234: NECSA QMS Requirement for external Design Organisations
7.2.25.	SHEQ-INS-1110: Housekeeping and demarcation
7.2.26.	SHEQ-INS-1120: Lighting (Natural and Artificial)
7.2.27.	SHEQ-INS-7010: Zoning of facilities with hazardous chemical substances
7.2.28.	SHEQ-INS-7030: Surveillance programme for workplaces containing hazardous chemical substances
7.2.29.	SHEQ-INS-7140: Management of hazardous chemical waste
7.2.30.	SHEQ-INS-8030: System for the classification and demarcation of radiological areas
7.2.31.	SHEQ-INS-8050: Radiological surveillance programme for workplaces
7.2.32.	SHEQ-INS-8180: ALARA programme
7.2.33.	SHEQ-INS-8230: Management of Radioactive Discharges to the Atmosphere at the Pelindaba
7.2.34.	SHEQ-INS-8260: Management of Radioactive Effluent and Discharge at the Pelindaba Site
7.2.35.	SHEQ-INS-8310: Requirements in respect of ventilation systems for nuclear facilities
7.2.36.	SHEQ-INS-8360: Necsa Solid Radioactive Waste Management System
7.2.37.	SHEQ-INS-8920: Access Control to Necsa Sites and Its Facilities
7.2.38.	UNSEAL: Department of Health, Requirements for the Safe Use of Unsealed Radioactive Nuclides, Version 2, February 2001
7.2.39.	US Code of Federal Regulations 21 Part 210 – Current Good Manufacturing Practice for Finished Pharmaceuticals
7.2.40.	US FDA office of Regulatory Affairs – Guideline for Facilities and Environmental Conditions
7.2.41.	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.
7.2.42.	WHO Technical Report Series (TRS) No. 957, Annex 3: WHO Good Manufacturing Practices for Pharmaceutical Products Containing Hazardous Substances, 2010.
7.2.43.	WHO Technical Report Series (TRS) No. 1010, Annex 8: WHO Guidelines on Heating, Ventilation and Air-conditioning Systems for Non-Sterile Pharmaceutical Products, 2010.

**7.3. Disclaimer:** Whilst every endeavour has been made to list most requirements, and it is recognized that the URS is not intended as an exclusive approach, the identification of omissions or additional cGMP and other related requirements by prospective suppliers and/or design engineers are mandatory and remain the sole responsibility of the suppliers. NTP has an expectation of a compliant facility from the suppliers. Requirements such as environmental Acts are included in the requirements but may not be exclusive; the onus is on the supplier to comply with the laws of the Republic of South Africa, including municipal by-laws not outlined in this document.

**RESTRICTED**

Document No.	NTP-SPE-4162	Rev No.	1	Page 11 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

**8 RECORDS**

Record	Retention Period	By Whom
None	N/A	N/A

**9 TASK HAZARD ASSESSMENT**

No task hazard assessment is associated with this document.


**10 LIST OF FORMS**

Form Title	Form Number	Exhibit Number
None	N/A	N/A

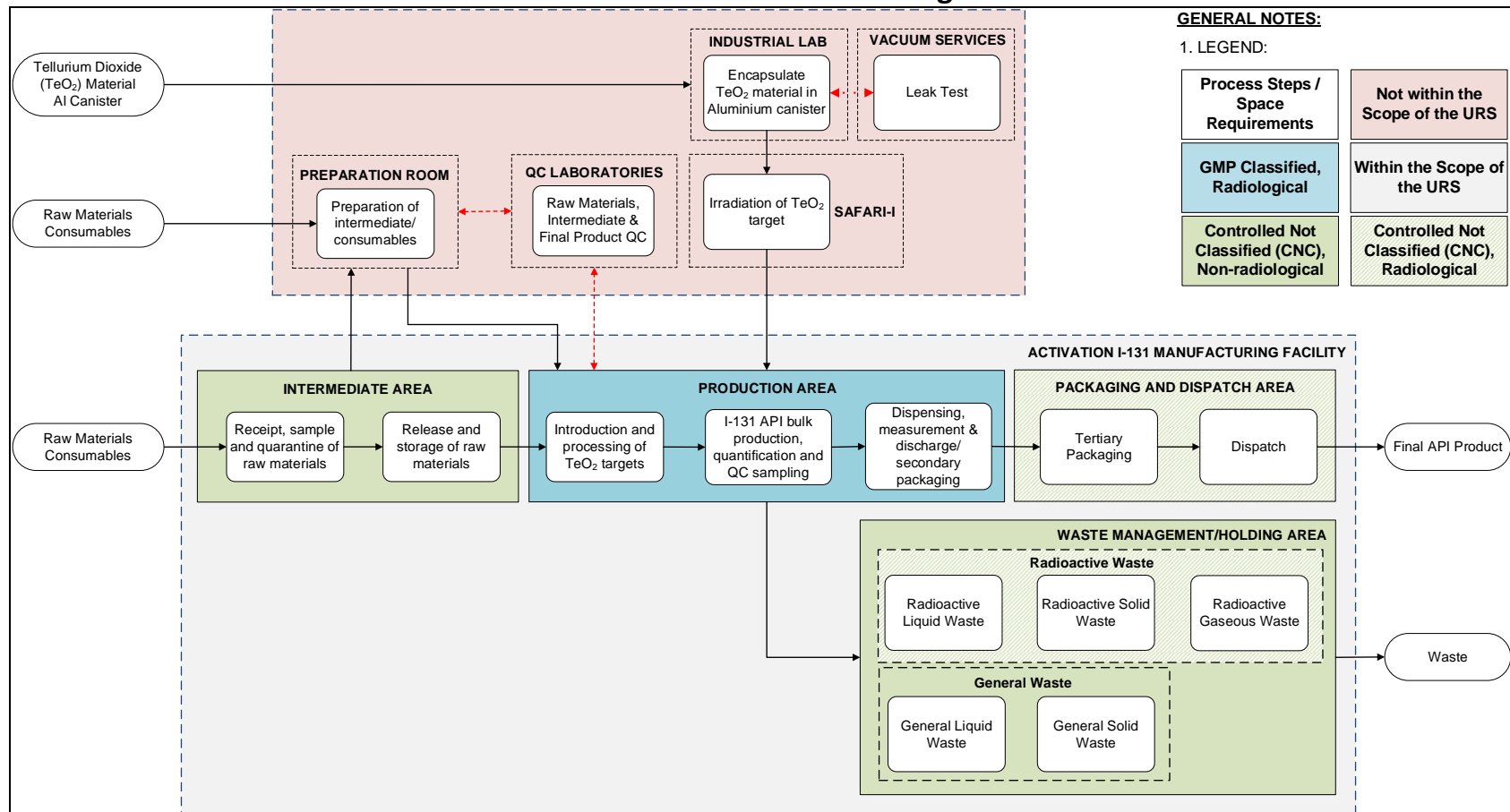
**11 REVISION HISTORY**

Rev.	Date Approved	Nature of Revision	Originated by
1	See title page	First issue	M Mukwevho

RESTRICTED

Document No.	NTP-SPE-xxxx	Rev No.	1	Page 12 of 17	
Title	REQUIREMENT SPECIFICATION FOR THE ACTIVATION I-131 MANUFACTURING FACILITY				
CMS Unique ID	N/A				
Project Number	NTP-PRJ-22/001				

**APPENDIX A:**  
**Overall Process Block Flow Diagram**



NTP-PRG-0300-08 Rev 19

RESTRICTED