1. PURPOSE

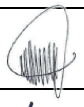
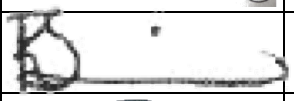
The purpose of this document is to specify the requirements for the design, manufacture, supply, installation and testing of a radiopharmaceutical automated dispensing unit at the P3000 ^{131}I cell. This specification also provides for the following criteria:

a. High system reliability,
b. Low maintenance requirements, and
c. Flexibility in the design of the dispensing unit.

The dispensing unit is to be installed in the existing hot cell (dimension details provided below).

2. SCOPE

The scope of the document covers the requirements for the design, manufacture, supply, installation and testing of a radiopharmaceutical automated dispensing unit at P3000 ^{131}I hot cell. This document does not cover the requirements for routine operations.

ACTION	NAME & CAPACITY	SIGNATURE	DATE
Originated	T Mailula *Team Leader: Hot Production*		2021/10/15
Checked	M Moloisi *Manager: Cold & Hot Production*		2021/10/15
Checked	G Portwig *Hot cell SQEP*		2021/10/15
Checked	K Tsime *Validation Technician*		2021/10/16
QA Approved	L Montjane *Quality Assurance Officer*		2021/10/16
Approved	T Chuene *Responsible Pharmacist*		2021/10/19
Approved	T Moloto *Senior Manager: Radiopharmaceuticals*		2021/10/19
		Implementation Date:	2021/10/22

DISTRIBUTION LIST (1 = Original, 2 and upwards = Electronic Copy)

1 QA Records (P3000)	2 Document Centre	3 Mediodine
4 RPH Pharmacists	5 N Kalume	

Authentication of printed document: This document was printed by:

NAME	SIGNATURE	DATE

3. REFERENCES

This document complies with the requirements of:

EN 61000-3-2:1995	:	Limits for Harmonic current emissions
EN 61000-3-3:1995	:	Limitation of voltage fluctuation and flicker.
EN 61326:1997	:	Electrical equipment for measurement, control and laboratory use
IEC 61010-1	:	Safety requirements for electrical equipment for measurement, control and laboratory use.
ISO-9001:2015	:	Quality Management System Requirements, Fifth Edition 2015
NTP-PRG-0300	:	Control of Documented Information and forms
NTP-PRG-0400	:	Control of Records.
RPH-SOP-7209	:	Standard Operating Procedure for product disposition at NTP Radioisotopes SOC Ltd building P3000.
	:	Guide-to-Good-Manufacturing-Practice for medicines in South Africa, Version 7_July 2019.

The following documents are referenced in this document:
None

4. ABBREVIATIONS AND DEFINITIONS

4.1. The following abbreviations are used in this document:

^{131}I	:	Radioactive Iodine
cGMP	:	current Good Manufacturing Practice
DQ	:	Design Qualification
DTPE	:	Double door transfer system (French: Double Porte pour Transfert Entanche)
FAT	:	Factory Acceptance Test
GAMP 5	:	Good Automated Manufacturing Practice
HMI	:	Human Machine Interface
IQ	:	Installation Qualification
ISO	:	Installation Qualification
OQ	:	Operation Qualification
PLC	:	Programmable Logic Controller
PQ	:	Operation Qualification
QA	:	Quality Assurance
SAHPRA	:	South African Health Products Regulatory Authority
SAT	:	Site Acceptance Test
SC	:	Safety Class
SO	:	System Owner

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

Calibration	:	The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.
Change Control	:	A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.
Validation	:	Documented series of actions that prove that any procedure, process, equipment, material, activity or system performs its intended functions adequately and consistently, and lead to the expected results of uniform batches that meet the required specifications and quality attributes.
Qualification	:	This is the planning, carrying out and recording of tests on facilities, systems and equipment, which form part of the validation process in order to demonstrate that it will perform as intended.
Design Qualification (DQ)	:	The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.
Installation Qualification (IQ)	:	The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.
Operational Qualification (OQ)	:	The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.
Performance Qualification (PQ)	:	The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.
Radiopharmaceutical	:	Radioisotopes tracers are produced under regulatory compliant processes with cGMP compliant raw materials. Regulatory processes include working under Laminar flow, chemical and physical testing (pH, isotonicity, and chemical parameters) to ensure that the final product is sterile, pyrogen-free, safe for human use, and is efficacious. This include both animal and human studies prior to release of the product for sale.

5. GENERAL

Radiopharmaceutical production in the P3000 iodine hot cell is currently synthesised in the Hot Cell using raw iodine before dispensing the solution into gelatine capsule and then loading the closed capsule into a 10ml vial contained in a lead pot before being removed at the back of the cell via the transfer system. The main purpose of a dispensing unit is to label gelatine therapy capsules with ^{131}I solution.

NTP seeks to upgrade the capacity of Hot Cell Iodine dispensing operations by sourcing an upgraded Iodine Dispenser Unit with extended and multiple functionalities in comparison to the existing one. The ^{131}I dispensing unit is to be used to prepare Iodine bulk solution by separating it from raw iodine vials, reconstitute and then divide the bulk solution into high and low activity solution. These solutions are dispensed in minute volumes (µl) into lower part of the hard gelatine capsules as per customer orders. These capsules are capped with the upper part before being measured with a dose calibrator and then taken out of the cell for packaging and dispatch.

6. RESPONSIBILITIES

None associated with this specification.

7. PROCESS

7.1. **The main components of the dispensing unit shall be**:

a. A syringe holder or an equivalent, include the sterile filter holder and the piston to empty and fill the syringe or equivalent. A 1000ul syringe or equivalent is currently used but a bigger size syringe or equivalent will be considered.
b. The compressor or an equivalent for capping of capsules and to hold a size 0 gelatin capsule closure, and
c. The dispenser must be able to produce more than one capsule to a time.

7.2 **Design requirements**

The design of the dispensing unit shall ensure that the unit is suitable for ^{131}I capsule production.

Requirement 1

a. Compact in size to fit into a DPTE (The DPTE space dimensions are as follows Inner Diameter = 260mm, and Length = 400mm) for transfer into the Cell/Added option for entry through the roof (600 x 580 mm (Length and Width).
b. Readily mountable onto the existing cell wall brackets/stand securely on the floor of the cell.
c. Unit operable by PLC/HMI outside the hot cell / use of Tongs once inside the cell.
d. Mechanically lock-in securely a 1ml syringe/tube onto the unit or an equivalent option.
e. The dispenser is subject to regular cleaning (the use of 70% alcohol or equivalent) with possible cleaning automation preferred or cost-effective to replace.

Requirement 2

a. Unit should accommodate an adjustable tray (10ml vial and a capsule holder) for operation intervention.
b. Adjustable to a lower and upper position via the control panel (outside) or use of Tongs.
c. Loading station to hold securely, a 10ml vial (activity refill and rinsing vial) and hold an open lower part powder filled capsules.
d. The station should rotate bi-directional to align the syringe with the capsules.
e. Accommodate minimum of five capsules at a time.

Requirement 3

a. Accurately dispense volumes range of between 1µl-1000µl with +/- 5% deviation.
b. Operate two syringes or equivalent (high and Low) independently for efficient dispensing.
c. Have mechanism to close an open capsule with its cap.
d. Easy to clean off any residues.
e. Must be easy to clean with sterile water/ 70% Alcohol.
f. Must be resistant to decontamination or cleaning agents.

Requirement 4: Connection to power supply

a. Power supply plug is available of 220 Vac and 50 Hz is sufficient to meet the electrical power requirements of the dispensing unit.
b. The equipment needs to have the capability to connect to the facility UPS.

Documentation requirements:

Requirement 5: The following documentations are required as part of hand over of equipment:

a. Technical publications and application notes.
b. Software maintenance and operation documents.
c. Validation and qualification documents of both the unit and the software

Requirement 6: The must be upfront, onsite repairs and on-going technical and IT support Service Level Agreement.

Requirement 7: Agreement on calibration frequency of the equipment. It is preferable that equipment are calibrated at least once every 12 months or as specified by supplier.

Requirement 8: The dispensing unit must be fully compatible with the existing cell box of 755mmx1180mmx855mm (HxLxW). The dispensing unit needs to have enough space so that the production team has access to the cell door. Any modifications required on the existing cell shall be made by Engineering and Projects department.

Requirement 9: The material of construction of all lines and components shall as far as possible be made out of stainless steel 316 L or equivalent in order for the material to be resistant to the radiation levels. Where seals are required Ethylene Propylene Diene Monomer (EPDM)/Shield seal 663 rubber or Viton rubber seals can be used. With the selection of any other type of material the effect of the radiation shall be taken into account. Material certification shall be provided. Equipment cleaning is done with 70% alcohol between batches.

Numbering Requirements:

Requirement 10: Tag numbers and tag plates placed on components of the dispensing unit shall be assigned (numbers) and tags plates supplied by NTP for standardization purposes in terms of the numbering convention and tag specification used for the rest of the facility.

Testing Requirements

The following testing shall be performed on the dispensing unit prior to installation:

Requirement 11: The dispensing unit shall be tested and Factory Acceptance Test (FAT) conducted prior to shipping/delivery to site. During the FAT, the complete dispensing unit functionality, program and recipe management shall be tested. This work shall be conducted by the supplier of the dispensing unit, and witnessed by NTP at the supplier's facility, after which factory acceptance will occur. This is not final acceptance. Timing of the FAT shall be in accordance with the supplier's procurement and delivery plan. Final scheduling shall be finalized 2 weeks minimum in advance of the meetings to ensure sufficient time for travel arrangement.

Requirement 12: The integrated dispensing unit system (dispensing unit, shielded cell and all interfaces) shall be pre-commissioned and Site Acceptance Test (SAT) conducted after final installation in the field prior to hot commissioning. System' testing conducted during the SAT includes all non-operating activities such as adjustments, cold alignment checks, hydrostatic/pneumatic testing, loop checking, motor rotational checks, flushing and blowing-out etc. this work shall be conducted by the supplier of the dispensing unit, and witnessed by NTP, after which hand over or Transfer of Care, Custody will occur. This is not final acceptance.

Quality Requirements

A proper quality control (HPLC and GC analysis) is performed on each batch radiopharmaceutical ^{131}I solution/cap produced using the dispensing unit, in accordance to cGMP and SAHPRA regulations.

Requirement 13: Quality analysis specifications sample:

a. pH : 7 – 10
b. Activity mCi (date of manufacturer): ≥1.0
c. Radiochemical purity : ≥ 90% ≤ 110 %
d. Radionuclide purity : no contaminants
e. Solubility (retrieve from LIMS system) : ≤ 30 minutes

Requirement 14: Validation and Qualification of the unit to be performed by the supply and witnessed by NTP. All documentation (Protocols) to be sent to NTP prior execution for review.

Requirement 15: The supplier and all sub-suppliers shall comply with the requirements of ISO 9001: 2015. Proof of this effect shall be provided to NTP for acceptance.

Requirement 16: The supplier shall issue a certificate of compliance stating that the dispensing unit complies with all the requirements given in this document and is sufficient to ensure production compliance with cGMP requirements.

Requirement17: A complete data pack (including material certificates, material safety datasheets, technical datasheets/specifications, technical drawings/ flow diagrams, maintenance manual, installation manual, operating manual, IQ.OQ, PQ protocols and technical description, which includes the design conditions) shall be provided to NTP for acceptance

Requirement 18: The software used to operate the dispensing unit should comply with the GAMP 5 requirement. The unit should be password controlled, user levels defined and also the audit trail to be accessed.

Requirement 19: The supplier to offer training to maintenance training on troubleshooting and also on the replacement of spare parts. The supplier must offer the operators training on operating and troubleshooting the unit.

8. RECORDS

Record	Retention Period	By Whom
None	None	None

9. TASK HAZARD ASSESSMENT

None

10. LIST OF FORMS

Form Title	Form Number	Exhibit Number
Technical Specification for the Iodine Dispensing Unit Requirement Compliance Checklist	RPH-SPE-3019-01	1

11. REVISION HISTORY

Rev.	Date Approved	Nature of Revision	Originated by
1	2021/06/07	First Issue	T Mailula
2	See title page	New amendments	T Mailula

Form No.	RPH-SPE-3019-01	Rev No.	2	Page **1** of **4**	NTP Actively enhancing life
Title	Technical Specification for the for ^{131}I Dispenser Unit Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to ensure compliance(Test, Inspection, Demonstration or Analysis)	Method description	Does the dispensing unit/system comply with the requirement (Yes/No)	NTP representative who witnessed execution of compliance method (Name, signature)	Supplier representative who executed compliance method (Name, signature)	Comments/Notes
1.	**Requirement 1** a. Compact in size to fit into a DPTE (The DPTE space dimensions are as follows Inner Diameter = 260mm, and Length = 400mm) for transfer into the Cell/Added option for entry through the roof (600 x 580 mm (Length and Width). b. Readily mountable onto the existing cell wall brackets/stand securely on the floor of the cell. c. Unit operable by PLC/HMI outside the hot cell / use of Tongs once inside the cell. d. Mechanically lock-in securely a 1ml syringe/tube onto the unit or an equivalent option. e. The dispenser is subject to regular cleaning (the use of 70% alcohol or equivalent) with possible cleaning automation preferred or cost-effective to replace.	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				
2.	**Requirement 2** a. Unit should accommodate an adjustable tray (10ml vial and a capsule holder) for operation intervention. b. Adjustable to a lower and upper position via the control panel (outside) or use of Tongs. c. Loading station to hold securely, a 10ml vial (activity refill and rinsing vial) and hold an open lower part powder filled capsules. d. The station should rotate bi-directional to align the syringe with the capsules. e. Accommodate minimum of five capsules at a time.	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				
3.	**Requirement 3** a. Accurately dispense volumes range of between 1µl-1000µl with +/- 5% deviation. b. Operate two syringes or equivalent (high and Low) independently for efficient dispensing. c. Have mechanism to close an open capsule with its cap. d. Easy to clean off any residues. e. Must be easy to clean with sterile water/ 70% Alcohol. f. Must be resistant to decontamination or cleaning agents.	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				
4.	**Requirement 4: Connection to power supply** a. Power supply plug is available of 220 Vac and 50 Hz is sufficient to meet the electrical power requirements of the dispensing unit. b. The equipment needs to have the capability to connect to the facility UPS.	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT & SAT				

Form No.	RPH-SPE-3019-01	Rev No.	2	Page **2** of **4**	NTP Actively enhancing life
Title	Technical Specification for the for ^{131}I Dispenser Unit Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to ensure compliance(Test, Inspection, Demonstration or Analysis)	Method description	Does the dispensing unit/system comply with the requirement (Yes/No)	NTP representative who witnessed execution of compliance method (Name, signature)	Supplier representative who executed compliance method (Name, signature)	Comments/Notes
5.	**Documentation requirements.** **Requirement 5:** The following documentations are required as part of hand over of equipment: a. Technical publications and application notes. b. Software maintenance and operation documents. c. Validation and qualification documents of both the unit and the software.	Inspection	Verification design documentation (DQ)				
6.	**Requirement 6:** The must be upfront, onsite repairs and on-going technical and IT support Service Level Agreement.	Inspection	Verification of design documentation (DQ)				
7.	**Requirement 7:** Agreement on calibration frequency of the equipment. It is preferable that equipment are calibrated at least once every 12 months or as specified by supplier.	Inspection	Verification of design documentation (DQ)				
8.	**Requirement 8**: The dispensing unit must be fully compatible with the existing cell box of 755mmx1180mmx855mm (HxLxW). The dispensing unit needs to have enough space so that the production team has access to the cell door. Any modifications required on the existing cell shall be made by Engineering and Projects department.	Inspection	Verification of design documentation (DQ)				
9.	**Requirement 9:** The material of construction of all lines and components shall as far as possible be made out of stainless steel 316 L or equivalent in order for the material to be resistant to the radiation levels. Where seals are required Ethylene Propylene Diene Monomer (EPDM)/Shield seal 663 rubber or Viton rubber seals can be used. With the selection of any other type of material the effect of the radiation shall be taken into account. Material certification shall be provided. Equipment cleaning is done with 70% alcohol between batches.	Inspection	Verification of design documentation (DQ)				
10.	**Numbering Requirements** **Requirement 10**: Tag numbers and tag plates placed on components of the dispensing unit shall be assigned (numbers) and tags plates supplied by NTP for standardization purposes in terms of the numbering convention and tag specification used for the rest of the facility.	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT & SAT				

Form No.	RPH-SPE-3019-01	Rev No.	2	Page **3** of **4**	NTP Actively enhancing life
Title	Technical Specification for the for ^{131}I Dispenser Unit Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to ensure compliance(Test, Inspection, Demonstration or Analysis)	Method description	Does the dispensing unit/system comply with the requirement (Yes/No)	NTP representative who witnessed execution of compliance method (Name, signature)	Supplier representative who executed compliance method (Name, signature)	Comments/Notes
11	**Requirement 11**: The dispensing unit shall be tested and Factory Acceptance Test (FAT) conducted prior to shipping/delivery to site. During the FAT, the complete dispensing unit functionality, program and recipe management shall be tested. This work shall be conducted by the supplier of the dispensing unit, and witnessed by NTP at the supplier's facility, after which factory acceptance will occur. This is not final acceptance. Timing of the FAT shall be in accordance with the supplier's procurement and delivery plan. Final scheduling shall be finalized 2 weeks minimum in advance of the meetings to ensure sufficient time for travel arrangements.	Inspection	Verification of quality documentation				
12	**Requirement 12:** The integrated dispensing unit system (dispensing unit, shielded cell and all interfaces) shall be pre-commissioned and Site Acceptance Test (SAT) conducted after final installation in the field prior to hot commissioning. System' testing conducted during the SAT includes all non-operating activities such as adjustments, cold alignment checks, hydrostatic/pneumatic testing, loop checking, motor rotational checks, flushing and blowing-out etc. this work shall be conducted by the supplier of the dispensing unit, and witnessed by NTP, after which hand over or Transfer of Care, Custody will occur. This is not final acceptance.	Inspection	Verification of quality documentation				
13	**Quality Requirements** A proper quality control (HPLC and GC analysis) is performed on each batch radiopharmaceutical ^{131}I solution/cap produced using the dispensing unit, in accordance to cGMP and SAHPRA regulations. **Requirement 13:** Quality analysis specifications sample: a. pH : 7 – 10 b. Activity mCi (date of manufacturer): 1.0 c. Radiochemical purity: ≥ 90% ≤ 110 % d. Radionuclide purity : no contaminants e. Solubility (retrieve from LIMS system): ≤ 30 minutes	Inspection	Verification of quality documentation				
14	**Requirement 14**: The supplier to perform IQ, OQ and PQ in line with cGMP . The resuslts to be accepted by NTP Validation. Validation guide including all certification to be supplied.	Inspection	Verification of quality documentation				
15	**Requirement 15:** The supplier and all sub-suppliers shall comply with the requirements of ISO 9001: 2015. Proof of this effect shall be provided to NTP for acceptance.	Inspection	Verification of data pack prior to FAT				

Exhibit 1

Form No.	RPH-SPE-3019-01	Rev No.	2	Page **4** of **4**	NTP Actively enhancing life
Title	Technical Specification for the for ^{131}I Dispenser Unit Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to ensure compliance(Test, Inspection, Demonstration or Analysis)	Method description	Does the dispensing unit/system comply with the requirement (Yes/No)	NTP representative who witnessed execution of compliance method (Name, signature)	Supplier representative who executed compliance method (Name, signature)	Comments/Notes
16	**Requirement 16:** the supplier shall issue a certificate of compliance stating that the dispensing unit complies with all the requirements given in this document and is sufficient to ensure production compliance with cGMP requirements.	Inspection	Verification of quality documentation				
17	**Requirement17:** A complete data pack (including material certificates, material safety datasheets, technical datasheets/specifications, technical drawings/ flow diagrams, maintenance manual, installation manual, operating manual, IQ.OQ, PQ protocols and technical description, which includes the design conditions) shall be provided to NTP for acceptance.	Inspection	Verification of data pack				
18	**Requirement 18**: The software used to operate the dispensing unit should comply with the GAMP 5 requirement. The unit should be password controlled, user levels defined and also the audit trail to be accessed.	Inspection	Verification of data pack				
19	**Requirement 19**: The supplier to offer training to maintenance training on troubleshooting and also on the replacement of spare parts. The supplier must offer the operators training on operating and troubleshooting the unit.	Inspection	Verification of data pack				

To ensure compliance with requirement 1:

Action	Answer (Yes/No)	Completed by	Designation	date	Signature
The checklist was complete					
The checklist was signed by all parties					
All the requirements are complied with					