1. PURPOSE

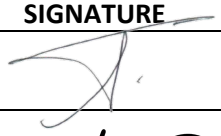
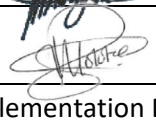
The purpose of this document is to specify the requirements for the design, manufacture, supply, installation, and testing, of a radiopharmaceutical Automated Synthesis unit at the Cyclotron Facility. This specification also provides for the following criteria to be met:

1.1. High system reliability;
1.2. Low maintenance requirements; and
1.3. Flexibility in the design of the Synthesis unit.

The Synthesis unit is to be installed in the existing AGATHA-shielded cell with laminar flow.

2. SCOPE

The scope of the document covers the requirements for the design, manufacture, supply, installation, and testing of a radiopharmaceutical Automated Synthesis unit at the Cyclotron Facility. This document does not cover the requirements for routine operations.

ACTION	NAME & CAPACITY	SIGNATURE	DATE
Originated	T Makate *Manager: Cyclotron Facility*		2021/12/10
Checked	M Modukanele *Process Engineer (E&P)*		2021/12/10
Checked	F Ngwezi *Cyclotron Specialist*		2021/12/10
Checked	E Motsoene *Validation Specialist, Quality Assurance*		2021/12/10
QA Approved	L Montjane *Quality Assurance Officer*		2021/12/10
Approved	T Moloto *Senior Manager: Radiopharmaceuticals*		2021/12/10
		Implementation Date:	2021/12/10

DISTRIBUTION LIST (1 = Original, 2 and upwards = Electronic Copy)		
1 QA Records (P1700)	2 Document Centre	3 Team centre

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3. REFERENCES

3.1 This document complies with the requirements of:

SAHPRA: 4.01_SA-Guide-to-Good-Manufacturing-Practice_Jul19_v 7-1.
European Directive 89/336/EEC concerning electromagnetic compatibility (EMC)
European Directive 73/23/EEC concerning low voltage devices

ISO 9001:2015	:	Quality Management Systems- Requirements, 5th Edition 2015/09/15
NTP-PRG-0300	:	Control of Documented Information and Forms
EN 61326:1997	:	Electrical equipment for measurement, control and laboratory use
EN 61000-3-2:1995	:	Limits for Harmonic current emissions
EN 61000-3-3:1995	:	Limitation of voltage fluctuation and flicker
IEC 61010-1	:	Safety requirements for electrical equipment for measurement, control and laboratory use.
RPH-SOP-7209	:	Standard operating procedure for product disposition at ntp radioisotopes soc ltd building p3000
NTP-PRG-0400	:	Control of Records.

3.2 The following documents are referenced in this document:

ASME B31.3	:	Process Piping, ASME Code for Pressure Piping, B31
ASTM A269	:	Standard Specification for Seamless and Welded Austenitic Stainless Steel Tubing for General Service, A269
ASTM A403	:	Stainless Steel Pipe Fittings refers to the material of forged and rolled austenitic stainless fittings for pressure pipes, A403
NTP-SOP-7077	:	Qualification Procedure of Equipment, Utilities and Facilities.
ISO 87573.1 class1-2-1	:	The purity of compressed air required at a particular point in a compressed air system.
NTP-POL-8520	:	Information security policy
NTP-POL-2911	:	IT computer usage policy
RPH-RTK-7504	:	F-18 FDG Production
GAMP 5	:	A Risk Based Approach to Compliant GxP Computerized Systems.

4. ABBREVIATIONS AND DEFINITIONS

4.1 The following abbreviations are used in this document:

ASME	:	American Society of Mechanical Engineers
ASTM	:	American Society for Testing and Materials
cGMP	:	Current-Good-Manufacturing Practice guidelines
DQ	:	Design Qualification
FAT	:	Factory Acceptance Test

FDG	:	Fluorodeoxyglucose
FDM	:	Fluordeoxymannose
GAMP	:	Good Automated Manufacturing Practice
HPLC	:	High Performance Liquid Chromatography
IQ	:	Installation Qualification
ISO	:	International Organization for Standardization
L&SA	:	Licensing and Safety Analysis
MBq	:	Mega Becquerel
OQ	:	Operation Qualification
PQ	:	Performance Qualification
PLC	:	Programmable Logic Controller
QA	:	Quality Assurance
QRM	:	Quality Risk Management
QCL	:	Quality Class
RIA	:	Radioimmune assay
SAHPRA	:	South African Health Products Regulatory Authority
SAT	:	Site Acceptance Test
SC	:	Safety Class
SLA	:	Service Level Agreement
SME	:	Subject Matter Expect
SOP	:	Standard Operating Procedure
URS	:	User Requirement Specification

4.2 The following definitions are used in 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.
Radiochemistry	:	Radioisotopes tracers used in RIA procedures, chemical and biological research are produced from radiochemical grade raw materials.

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 insure that the final product is sterile, pyrogen-free, safe for human use, and is efficacious. This includes both animal and human studies prior to release of the product for sale.

5. GENERAL

The Synthesis system module is designed as a closed system to minimize radioactivity emission. The vial filling is done with the vial closed, so it is a trans-septum operation. The system consists of:

5.1. The Synthesizer module;
5.2. The control unit;
5.3. Supply lines and
5.4. The operator interface.

Background:

The main purpose of a Synthesis unit is to label specific molecule with Fluorine-18. FDG (2-Fluoro-2-deoxyglucose) and F-18 PSMA (Prostate-Specific Membrane Antigen) Radiopharmaceutical production in the Cyclotron Facility are currently synthesized with the Synthesis unit automatic tracer synthesis module. The Synthesis unit is a computer-controlled, automated system, for the nucleophilic fluorination synthesis, carried out with F-18 received from the Cyclotron target. The program sequence is optimized for high yield and radiochemical purity as well as reliability.

For the synthesis process, only chemicals, a suitable HPLC column and disposable cartridges are needed as per RPH-RTK-7504. Chemical reactions of the radioactive compounds take place inside the reaction vessel of the closed system. The Synthesis unit unit has its own control system and works independently from the cyclotron, second Synthesis unit unit, and dispensing unit or scanner control systems.

The system is housed inside a COMECER shielded cell model AGATHA with laminar flow (class A) which ensures the compliance of production with cGMP regulations. A shielded cell is a structure constructed out of lead and steel separating the Operator and the nuclear material in order to provide shielding for the protection of the operators against radiation. The radiation shielding specified is sufficient for handling activities of a maximum of 10 Ci.

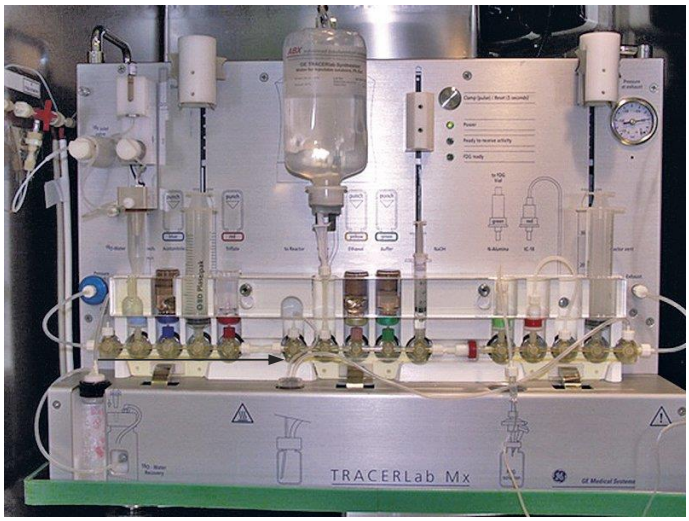

Figure 1: Illustration of the Complete system (Tracerlab in Agatha Hot cell)

The supplier of the current Synthesis unit (GE) has since informed NTP that the Synthesis unit Synthesis unit is to be considered obsolete and out of production. GE will not further guarantee maintenance, spare parts and software updates in the above mentioned machine. For this reason there is a need to install an alternate synthesis unit in order to guarantee production at the cyclotron facility.

6. RESPONSIBILITIES

None associated with this specification.

7. PROCESS

7.1. The main components of the Synthesis unit shall be:

7.1. Connectors for the Fluorine seperation cartridge, the Al_2O_3 purification cartridge, the C-18 seperation cartridge as well as for the sterile filters;
7.2. Several reagent vials, which are necessary to keep the reagent fluids;
7.3. Target water vial with GM-tube for indication of incoming radioactivity;
7.4. $H_2{}^{18}O$ vial for recovering of the used target water;
7.5. The reactor with a pneumatic cylinder for the reactor needle, a magnetic stirrer and a GM-tube for indication of radioactivity during the synthesis;

7.6. HPLC system including:

7.6.1. An eluent pump;
7.6.2. Two eluent reservoirs with degassing;
7.6.3. A fluid detector;
7.6.4. A purification column including pre-column;
7.6.5. A UV-and radioactivity detector for monitoring the seperation;
7.6.6. Eluent collection vessel;
7.6.7. Product collection vessel with GM-tube for indication of radioactivity;
7.6.8. Teflon tubes and solenoid valves for liquid handling.
7.6.9. Waste collection system

7.7. All the following requirements given in this document shall be met:

The checklist (RPH-SPE-7507-01) given in Exhibit 1 shall be completed and signed to ensure that all requirements are complied with as part of the conformance assessment. This document excludes requirements in terms of how commissioning, operation and decommissioning of Synthesis unit must be performed, once delivered, inspected, tested and accepted by NTP.

Design requirements

The design of the synthesis unit shall ensure that the unit is suitable for FDG/PSMA and other tracer's production. F-18 is transferred from the Cyclotron into the synthesis unit, and the final product is transferred to Clio dispening unit.

Requirement 1: The Synthesis unit must be able to perform the following automated functions:

a. Cartridge conditioning;
b. Conditioning of the purification columns;
c. Dissolving of lyophilized precursors;
d. Synthesis phases;
e. Purification;
f. Final formulation;
g. Extensive rinsing at the end of the synthesis.

Requirement 2: The Synthesis interfaces must be able to fit into the following:

a. The utility tie in points (Instrument Air, Nitrogen, helium, power etc.);
b. The existing AGATHA-shielded cell with laminar flow;

Requirement 3: The synthesis unit must be compatible with the Clio volumetric dispenser (39M1T99001.00) for radiopharmaceuticals.

Requirement 4: The synthesis unit must fit into the available dimensions inside the Agatha shielded hot cell.

Dimensional parameters available for Synthesis unit/s is as follows:

a. Length : 670 mm
b. Width : 630 mm
c. Breadth : 520 mm

Requirement 5: Dimensions of the external waste bottle.

The waste bottle is used to collect all waste fluids. Since these fluids are radioactive, the waste bottle has to be shielded to allow back to back syntheses. The waste bottle fits snugly into the discharge system in the existing AGATHA-shielded cell with laminar flow, and must be suitable to discharge the waste bottle safely. Any modifications required (if any) on the existing AGATHA shielded cell shall be made by the supplier. Supplier to provide modifications quote as an option.

Dimensions of the standard 250 ml waste bottle are as follows:

a. Outer diameter : 71 mm
b. Height : 180 mm

Dimensions of tubing currently connecting from the Cyclotron to the Synthesis unit:

c. Inner diameter : Between 2 mm to 4 mm
d. Maximal length : 4000 mm

Requirement 6: Connection to power supply

a. UPS or the equivalent system must be supplied to ensure the unit complete the synthesis process and eventually allow for transfer to the dispensing unit. Uniterrupted power supply source must be quoted with fittings to be done by the supplier to be placed outside of the hot cell and that can be turned off in case of emergency by an easily accessible switch.

b. Power supply of 220 Vac and 50 Hz is sufficient to meet the electrical power requirements of the Synthesis unit.

User interface requirements

Requirement 7: A Laptop is required as an interface, to assist the operator during the preliminary steps before synthesis, to allow visualization of the process, to view and print the reports, to configure the PLC (Programmable Logical Controller) and to perform some tests for maintenance. The user interface computer has a mounting placed close to the hot cell containing Synthesis unit with user instructions in the regional language.

a. The user interface computer must be part of the full package and the software has to be installed on the computer on site. NTP IT department receives and performs initial setup of the interface computer to comply to NTP-POL-8520 and NTP-POL-2911 requirements as per SLA entered into between NTP and supplier.

b. The user interface computer is currently connected to the Synthesis unit through a DB9 connector. The serial communication cable is provided with a 15m extension cable. An opening is available to allow the DB9 connector to pass through with dimension of 35mm or rectangular aperture 20 x 35mm.

c. Remote control box allowing operation of Synthesis unit if unable to use the user interface computer or in case of emergency. Remote control box does not allow performance of self-test of the synthesizer and kit test with no feedback received from the synthesis. This system is supplied ready mounted with its cable and connection plug and opening available with plug dimension 53 x 20mm.

d. Supplier remote login access for software maintenance and upgrades when required.

e. Password protection and user access restriction as defined by level of required access.

f. Open software for layout and process sequence design of any new compound with straightforward execution in production mode. User rights can be easily assigned and the software can operate from anywhere on the LAN.

g. The unit must assure that integrity of data cannot be compromised by external factors and must come with a Risk Assessment of how to handle virus and malware.

h. The software must comply with GAMP 5

Utility requirements

Requirement 8 (Instrument Air): Compressed Nitrogen gas (ISO8573.1 class 1-2-1 air supply by the facility), filtered to remove particles of greater than 5 micrometers, is used to operate all the pneumatic components of the Synthesis unit, i.e., the rotaing actuators, the movement of the elution system down into the reservoir of the cassette, and the clamps holding the cassette in place.

Requirement 9: Instrument air with average humidity of 66% at a pressure ranging between 6.0 bar(g) and 7.0 bar(g) is sufficient to meet the instrument air requirements of the syntheses unit. This is the same spec currenlty used in the Agatha cell for instrumentation. If not sufficient, supplier to communicate minimum requirement so NTP can accommodate.

Requirement 10: Nitrogen

Nitrogen , filtered twice to remove particles greater than 7 micrometer then particles greater than 0.2 micrometers, is supplied to be used during the chemical process. The quality of gas is of high quality as it is a critical factor in the synthesis of FDG – any trace of impurity or moisture in this gas may lead to lower performances.

Nitrogen supply pressure ranging between 2.0 bar(g) and 10.0 bar(g) is sufficient to meet the Nitrogen requirements of the synthesis unit.

Environmental Requirements

Requirement 11: The Synthesis unit will be installed in the existing AGATHA Shielded cell with laminar flow. During synthesis of the FDG/PSMA there is radiation levels in the shielded cell. The maximum radioactivity posted in a cell (handled or produced) is 10 Ci. The Synthesis unit is able to operate at temperatures between 5 and 50 degrees Celcius, with relative humidity of the environment to be below 55%.

Operating Requirements

Requirement 12: The Synthesis unit shall be operated continuously for multiple runs in 24 hours and 7 days a week until maintenance or corrective actions are required, depending on production requirements. The synthesis unit shall has an operating life of up to 15 years in this radiation environment, with support.

Performance Requirements

Requirement 13: Since the Synthesis unit is used for radiopharmaceuticals, in line with cGMP requirements, it is important to have accurate reproducible data all the time.

Requirement 14: Radiation detector for entire process - Highly sensitivity - [18F]FDG and [18F]PSMA – Recommended range: 100µCi - 12Ci, sensitivity 15µCi - Built-in with customizable positioning.

Requirement 15: The unit must have high and reproducible yields independent of starting activity, for FDG uncorrected yield > 75% and high and reproducible yields for F18-PSMA uncorrected yield > 60%.

Requirement 16: Plug and play operation with all reagents needed for the synthesis are provided conditioned in ready-to-use packs.

Requirement 17: F-18 Inlet

The synthesis unit must be able accommodate the irradiated O-18 water which haas the following characteristics:

a. Colorless,
b. Free of any visible contamination and conductivity of no more than 10 microsiemens/centimeter with
c. **Volume between 0.2 to 4ml from a single bombardment, with a possibility of dual beam bombardment with volume of between 6 to 8 ml through a 1/16” x 1/32” polythene or Teflon tube.**
d. The F-18 activity line is connected onto the tube passing through the F-18 inlet pinch valve on the left side of the front panel of the unit.

Any tubings/fitting should be optimised not to lead to losses of starting activity and enriched water.

Requirement 18: F-18 outlet

Final labelled products can be transferred by a vial, but it is connected to the neighboring cell from the outlet of the Synthesis unit cassette with an extended line using commercially available sterile tubing (inner diameter between 1.5 and 2.5mm) with luer connections, through an opening of 15mm (0.6”). During the installation of the cassette onto the Synthesis unit the filter has to be placed at the end of the line, on the needle piercing the stopper of the final vial.

Requirement 19: The accuracy, repeatability and precision of the Synthesis unit volume and specified activity shall be ≤ 5 % of full scale. Supplier to confirm if this has a major cost impact on the design or state achievable accuracy with no major cost impact.

Waste Requirements

Requirement 20: Waste produced by the Synthesis unit shall be minimised as far as practical in order to reduce radioactive waste. This include gaseous emissions, liquid effluent (e.g. from system flushing) and solid waste (e.g. spare parts and consumables).

Requirement 21: Waste bottle with support, shielding and capability of detecting activity sensor in the waste bottle or waste line.

Fitting and Tubing/Piping Requirements

Requirement 22: The standard for stainless steel piping fitting is ASTM A403.

Requirement 23: Any tubing used shall be in accordance with ASTM A269.

Requirement 24: Piping used shall comply in all aspects to ASME B31.3.

Maintenance Requirements

Delivery of Synthesis unit spares shall be scheduled so that the spares are available for use not later than commencement of commissioning.

Requirement 25: Synthesis units should allow the unit to be replaced, have another unit added in a cell or upgraded with the latest configuration setup and versions have to offer after 15 years. The units should be delivered fully wired and ready for future upgrade. The price of any later upgrade consists the difference between the models, shipping of the parts and travel costs.

Requirement 26: Training program to be provided by the supplier in line with NTP training process and supply of training certificates for the participants in the hand-over.

Requirement 27: Full after-sales support on either an ad-hoc basis, or under Maintenance and Service Agreement for up to 15 years. Warranty/Guarantee contract to be in place.

Requirement 28: Ease of access to spare parts with availability of local supplier is an advantage.

Spares shall be recommended for equipment parts that are subject to:

a. Wear, corrosion or erosion during normal operation;
b. Failure that would cause shutdown of the equipment;
c. Damage or breakage during routine maintenance or inspection

Documentation requirements

Requirement 29: The following documentation are required as part of hand over of equipment:

a. Technical publications and application notes.
b. Software maintenance and operation document.

Requirement 30: The must be upfront, onsite repairs and on-going technical and IT support SLA.

Requirement 31: Agreement on Calibration frequency of equipment.

Requirement 32: The synthesis unit is fully compatible with the existing AGATHA-shielded cell with laminar flow (Read in conjuction with requirement 4 above). Any modifications required on the existing cell shall be made by the supplier.

Requirement 33: The material of construction of all lines and components shall as far as possible be made out of stainless steel 316 L / 316 in order for the material to be resistant to the radiation levels. Where seals are required ethylene propylene diene monomer (EPDM) 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 34: Tag numbers and tag plates placed on components of the Synthesis unit shall be assigned (numbers) and tag plates supplied by NTP for standardisation 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 synthesis unit prior to installation:

Requirement 35: The synthesis unit shall be tested and Factory Acceptance Test (FAT) conducted prior to shipping/delivery to site. During the FAT, the complete Synthesis units functionality, programme and receipe management shall be tested. This work shall be conducted by the supplier of the Synthesis 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 finalised 2 weeks minimum in advance of the meetings to ensure sufficient time for travel arrangements.

Requirement 36: The integrated synthesis system (synthesis 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's 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 Synthesis unit, and witnessed NTP, after which hand over or Transfer of Care, Custody and Control will occur. This is not final acceptance.

Quality Requirements

A proper Quality control (HPLC and GC analysis) is performed on each batch radiopharmaceutical FDG solution produced using the Synthesis unit, in accordance to cGMP and SAHPRA regulation.

Requirement 37: Quality Analysis specifications sample 500 microlitre and activity 600 MBq:

a.	pH	:	4.5 – 8.5
b.	Half-life	:	105 – 115 minutes
c.	Radionuclidic Purity at reference date, 08:00	:	F-18 between 90% to 100%
d.	Radiochemical Purity (HPLC)	:	FDM > 95% of the total area of the Radio chromatogram (total activity).
e.	Radiochemical purity (TLC)	:	The sum of the total area under the principal
f.	Chemical Purity	:	Aminopolyether must be less than 2.2mg/MRD
		:	Acetonitrile must be less than 0.04%

	:	Ethanol must be less than 0.5%
		peak > 95% of the total area of the radio-chromatogram (total activity).
g. Identity F-18 (Gamma spectrometry)	:	511 keV gamma line existing Sum peak of 1022 keV may be observed.

Requirement 38: The program must be able to input 10 digit batch numbers (provide a sample image) and use barcode scanner for test/run selection.

Requirement 39: The unit must have capacity to detect the incorrect cassettes being used, detection of faulty setups, unstable test values, faulty environmental conditions when starting and fluctuating environmental conditions while testing. Supplier to indicate compliance in provided documentation.

Requirement 40: Campaigning of batches (From one batch to another) within 10 minutes within the decay period.

Requirement 41: Batch report printable and history retrievable. Automated data collection into a comprehensive batch record.

Requirement 42: Prevention of abusive test attempts and impossibility to erase test results.

Requirement 43: The supplier to demonstrate performance integrity testing and data integrity for the device (same as in QRM). Risk Assessment can be added with the supplied documentation.

Requirement 44: Traceability of original program parameters in case of modification.

Requirement 45: Possibility for the administrator to add comments why parameters were changed, this must be demonstrated or indicated in supplied documentation.

Requirement 46: Launched tests must generate time stamped data and it must be impossible to alter generated data while maintaining audit trail of all changes.

Requirement 47: Assistance with updating the current FDG & PSMA-1007 product dossiers.

Requirement 48: The supplier to perform IQ and OQ, NTP to perform PQ with the supplier in line with cGMP . The resuslts to be accepted by NTP Validation. Validation guide including all certification to be supplied.

Requirement 49: The supplier and all sub-suppliers shall comply with the requirements of ISO 9001:2015 and provide a valid ISO certificate. Proof of this effect shall be provided to NTP for acceptance.

Requirement 50: The supplier shall issue a certificate of compliance stating that the synthesis system complies with all the requirements given in this document and is sufficient to ensure production compliance with cGMP requirements.

Requirement 51: A complete datapack (Including material certificates, material safety datasheets, technical datasheets/specifications, technical drawings / flow diagrams, maintenance manual, installation manual, operating manual, IQ/OQ protocols, technical description which includes the design conditions) shall be provided to NTP for acceptance.

8. RECORDS

None associated with this specification.

9. TASK HAZARD ASSESSMENT

None associated with this specification.

10. LIST OF FORMS

Form Title	Form Number	Exhibit Number
Technical Specification for the automated Synthesis unit at the Cyclotron facility: Requirement Compliance Checklist	RPH-SPE-7507-01	1

11. REVISION HISTORY

Rev.	Date Approved	Nature of Revision	Originated by
1	2021/10/27	First issue	T Makate
2.	See title page	Requirement 1: Added (39M1T99001.00) Requirement 2: Added (a) UPS or equivalent system must be supplied. Requirement 8: Replaced Compressed air with Nitrogen. Requirement 15: Rephrased	T Makate

Rev.	Date Approved	Nature of Revision	Originated by
		Requirement 21: Added detecting activity sensor in the waste bottle or waste line. Requirement 32: Added (Read in conjuction with requirement 4 above) Above Requirement 37: Removed HPLC required quote. Requirement 38: Added (provide a sample image) Requirement 39: Rephrased Requirement 43: Rephrased Requirement 45: Added that this must be documented or indicated in supplied documentation. Requirement 48: Added NTP to perform PQ Requirement 49: Added that the supplier to provide a valid ISO Certificate.	

EXHIBIT 1

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **1** of **10**
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist			

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
1.	**Requirement 1:** The Synthesis unit must be able to perform the following automated functions: a. Cartridge conditioning; b. Conditioning of the purification columns; c. Dissolving of lyophilized precursors; d. Synthesis phases; e. Purification; f. Final formulation; g. Extensive rinsing at the end of the synthesis.	Demonstration	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				
2.	**Requirement 2:** The Synthesis interfaces must be able to fit into the following: The utility tie in points (Instrument Air, Nitrogen, helium, power etc.); The existing AGATHA-shielded cell with laminar flow;	Inspection	Verification of design documentation (DQ)				
3.	**Requirement 3**: The synthesis unit must be compatible with the Clio volumetric dispenser (39M1T99001.00) for radiopharmaceuticals.	Inspection	Verification of design documentation (DQ)				
4.	**Requirement 4:** The synthesis unit must fit into the available dimensions inside the Agatha shielded hot cell. Dimensional parameters available for Synthesis unit/s is as follows: a. Length : 670 mm b. Width : 630 mm c. Breadth : 520 mm	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				
5.	**Requirement 5:** Dimensions of the external waste bottle Dimensions of the standard 250 ml waste bottle are as follows: a. Outer diameter : 71 mm b. Height : 180 mm Dimensions of tubing currently connecting from the Cyclotron to the Synthesis unit: c. Inner diameter : Between 2 mm to 4 mm d. Maximal length : 4000 mm	Inspection	Verification of design documentation (DQ)				
		Test	Perform test during FAT and SAT				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **2** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, check, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
6.	**Requirement 6**: Connection to power supply a. UPS or the equivalent system must be supplied to ensure the unit complete the synthesis process and eventually allow for transfer to the dispensing unit. Uniterrupted power supply source must be quoted with fittings to be done by the supplier to be placed outside of the hot cell and that can be turned off in case of emergency by an easily accessible switch. b. Power supply of 220 Vac and 50 Hz is sufficient to meet the electrical power requirements of the Synthesis unit.	Inspection	Verification of design documentation (DQ)				
7.	**User interface requirements** **Requirement 7:** A Laptop is required as an interface, to assist the operator during the preliminary steps before synthesis, to allow visualization of the process, to view and print the reports, to configure the PLC (Programmable Logical Controller) and to perform some tests for maintenance. The user interface computer has a mounting placed close to the hot cell containing Synthesis unit with user instructions in the regional language. a. The user interface computer must be part of the full package and the software has to be installed on the computer on site. NTP IT department receives and performs initial setup of the interface computer to comply to NTP-POL-8520 and NTP-POL-2911 requirements as per SLA entered into between NTP and supplier. b. The user interface computer is currently connected to the Synthesis unit through a DB9 connector. The serial communication cable is provided with a 15m extension cable. An opening is available to allow the DB9 connector to pass through with dimension of 35mm or rectangular aperture 20 x 35mm. c. Remote control box allowing operation of Synthesis unit if unable to use the user interface computer or in case of emergency. Remote control box does not allow performance of self-test of the synthesizer and kit test with no feedback received from the synthesis. This system is supplied ready mounted with its cable and connection plug and opening available with plug dimension 53 x 20mm. d. Supplier remote login access for software maintenance and upgrades when required.	Inspection	Verification of design documentation (DQ)				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **3** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, check, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
	e. Password protection and user access restriction as defined by level of required access.						
	f. Open software for layout and process sequence design of any new compound with straightforward execution in production mode. User rights can be easily assigned and the software can operate from anywhere on the LAN. g. The unit must assure that integrity of data cannot be compromised by external factors and must come with a Risk Assessment of how to handle virus and malware. h. The software must comply with GAMP 5	Inspection	Verification of design documentation (DQ)				
8.	**Utility requirements** **Requirement 8 (Instrument Air):** Compressed Nitrogen gas (ISO8573.1 class 1-2-1 air supply by the facility), filtered to remove particles of greater than 5 micrometers, is used to operate all the pneumatic components of the Synthesis unit, i.e., the rotaing actuators, the movement of the elution system down into the reservoir of the cassette, and the clamps holding the cassette in place.	Inspection	Verification of design documentation (DQ)				
9.	**Requirement 9:** Instrument air with average humidity of 66% at a pressure ranging between 6.0 bar(g) and 7.0 bar(g) is sufficient to meet the instrument air requirements of the syntheses unit. This is the same spec currenlty used in the Agatha cell for instrumentation. If not sufficient, supplier to communicate minimum requirement so NTP can accommodate.	Inspection	Verification of design documentation (DQ)				
10.	**Requirement 10:** Nitrogen Nitrogen , filtered twice to remove particles greater than 7 micrometer then particles greater than 0.2 micrometers, is supplied to be used during the chemical process. The quality of gas is of high quality as it is a critical factor in the synthesis of FDG – any trace of impurity or moisture in this gas may lead to lower performances. Nitrogen supply pressure ranging between 2.0 bar(g) and 10.0 bar(g) is sufficient to meet the Nitrogen requirements of the synthesis unit.	Inspection	Verification of design documentation (DQ)				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **4** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, check, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
11.	**Environmental Requirements** **Requirement 11**: The Synthesis unit will be installed in the existing AGATHA Shielded cell with laminar flow. During synthesis of the	Inspection	Verification of design documentation (DQ)				
	FDG/PSMA there is radiation levels in the shielded cell. The maximum radioactivity posted in a cell (handled or produced) is 10 Ci. The Synthesis unit is able to operate at temperatures between 5 and 50 degrees Celcius, with relative humidity of the environment to be below 55%.						
12.	**Operating Requirements** **Requirement 12:** The Synthesis unit shall be operated continuously for multiple runs in 24 hours and 7 days a week until maintenance or corrective actions are required, depending on production requirements. The synthesis unit shall has an operating life of up to 15 years in this radiation environment, with support.	Inspection	Verification of design documentation (DQ)				
13.	**Performance Requirements** **Requirement 13:** Since the Synthesis unit is used for radiopharmaceuticals, in line with cGMP requirements, it is important to have accurate reproducible data all the time.	Check	Verification of design documentation (DQ)				
14.	**Requirement 14:** Radiation detector for entire process - Highly sensitivity - [18F]FDG and [18F]PSMA – Recommended range: 100µCi - 12Ci, sensitivity 15µCi - Built-in with customizable positioning.	Demonstration	Perform test during FAT and SAT				
15*.	**Requirement 15:** The unit must have high and reproducible yields independent of starting activity, for FDG uncorrected yield > 75% and high and reproducible yields for F18-PSMA uncorrected yield > 60%.	Inspection	Perform test during FAT and SAT				
	High and reproducible yields independent of starting activity, F18-PSMA uncorrected yield > 60%.	Inspection	Perform test during FAT and SAT				
16.	**Requirement 16:** Plug and play operation with all reagents needed for the synthesis are provided conditioned in ready-to-use packs.	Inspection	Verification of design documentation (DQ)				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **5** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
17.	**Requirement 17:** F-18 Inlet The synthesis unit must be able accommodate the irradiated O-18 water which haas the following characteristics: a. Colorless, b. Free of any visible contamination and conductivity of no more than 10 microsiemens/centimeter with c. **Volume between 0.2 to 4ml from a single bombardment, with a possibility of dual beam bombardment with volume of between 6 to 8 ml through a 1/16" x 1/32" polythene or Teflon tube.** d. The F-18 activity line is connected onto the tube passing through the F-18 inlet pinch valve on the left side of the front panel of the unit. Any tubings/fitting should be optimised not to lead to losses of starting activity and enriched water.	Inspection	Verification of design documentation (DQ)				
18.	**Requirement 18:** F-18 outlet Final labelled products can be transferred by a vial, but it is connected to the neighboring cell from the outlet of the Synthesis unit cassette with an extended line using commercially available sterile tubing (inner diameter between 1.5 and 2.5mm) with luer connections, through an opening of 15mm (0.6"). During the installation of the cassette onto the Synthesis unit the filter has to be placed at the end of the line, on the needle piercing the stopper of the final vial.	Inspection	Verification of design documentation (DQ)				
19.	**Requirement 19:** The accuracy, repeatability and precision of the Synthesis unit volume and specified activity shall be ≤ 5 % of full scale. Supplier to confirm if this has a major cost impact on the design or state achievable accuracy with no major cost impact.	Test	Verification of design documentation (DQ)				
20.	**Waste Requirements** **Requirement 20:** Waste produced by the Synthesis unit shall be minimised as far as practical in order to reduce radioactive waste. This include gaseous emissions, liquid effluent (e.g. from system flushing) and solid waste (e.g. spare parts and consumables).	Inspection	Verification of design documentation (DQ)				
21.	**Requirement 21:** Waste bottle with support, shielding and capability of detecting activity sensor in the waste bottle or waste line.	Inspection	Verification of design documentation (DQ)				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **6** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
22.	**Fitting and Tubing/Piping Requirements** **Requirement 22:** The standard for stainless steel piping fitting is ASTM A 403.	Check	Verification of quality documentation				
23.	**Requirement 23:** Any tubing used shall be in accordance with ASTM A269.	Check	Verification of quality documentation				
24.	**Requirement 24:** Piping used shall comply in all aspects to ASME B31.3.	Check	Verification of quality documentation				
25.	**Maintenance Requirements** Delivery of Synthesis unit spares shall be scheduled so that the spares are available for use not later than commencement of commissioning. **Requirement 25:** Synthesis units should allow the unit to be replaced, have another unit added in a cell or upgraded with the latest configuration setup and versions have to offer after 15 years. The units should be delivered fully wired and ready for future upgrade. The price of any later upgrade consists the difference between the models, shipping of the parts and travel costs.	Inspection	Verification of quality documentation				
26.	**Requirement 26:** Training program to be provided by the supplier in line with NTP training process and supply of training certificates for the participants in the hand-over.	Check	Verification of design documentation (DQ)				
27.	**Requirement 27:** Full after-sales support on either an ad-hoc basis, or under Maintenance and Service Agreement for up to 15 years. Warranty/Guarantee contract to be in place.	Inspection	Verification of design documentation (DQ)				
28.	**Requirement 28:** Ease of access to spare parts with availability of local supplier is an advantage. Spares shall be recommended for equipment parts that are subject to: a. Wear, corrosion or erosion during normal operation; b. Failure that would cause shutdown of the equipment; c. Damage or breakage during routine maintenance or inspection.	Inspection	Verification of quality documentation				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **7** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
29.	**Documentation requirements** **Requirement 29:** The following documentation are required as part of hand over of equipment: a. Technical publications and application notes. Software maintenance and operation document.	Inspection	Verification of quality documentation				
30.	**Requirement 30:** The must be upfront, onsite repairs and on-going technical and IT support SLA.	Inspection	Verification of quality documentation				
31.	**Requirement 31**: Agreement on Calibration frequency of equipment.	Inspection	Verification of quality documentation				
32.	**Requirement 32:** The synthesis unit is fully compatible with the existing AGATHA-shielded cell with laminar flow (Read in conjuction	Inspection	Verification of quality documentation				
	with requirement 4 above). Any modifications required on the existing cell shall be made by the supplier.						
33.	**Requirement 33:** The material of construction of all lines and components shall as far as possible be made out of stainless steel 316 L / 316 in order for the material to be resistant to the radiation levels. Where seals are required ethylene propylene diene monomer (EPDM) 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)				
34.	**Numbering Requirements** **Requirement 34:** Tag numbers and tag plates placed on components of the Synthesis unit shall be assigned (numbers) and tag plates supplied by NTP for standardisation purposes in terms of the numbering convention and tag specification used for the rest of the Facility.	Inspection	Verification of design documentation (DQ)				
35.	**Testing Requirements** The following testing shall be performed on the synthesis unit prior to installation: **Requirement 35:** The synthesis unit shall be tested and Factory Acceptance Test (FAT) conducted prior to shipping/delivery to site. During the FAT, the complete Synthesis units functionality, programme and receipe management shall be tested. This work shall	Inspection	Verification of design documentation (DQ)				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **8** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
	be conducted by the supplier of the Synthesis 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 finalised 2 weeks minimum in advance of the meetings to ensure sufficient time for travel arrangements.						
36.	**Requirement 36:** The integrated synthesis system (synthesis 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's 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 Synthesis unit, and witnessed	Inspection	Verification of design documentation (DQ)				
	NTP, after which hand over or Transfer of Care, Custody and Control will occur. This is not final acceptance.						
37.	**Quality Requirements** A proper Quality control (HPLC and GC analysis) is performed on each batch radiopharmaceutical FDG solution produced using the Synthesis unit, in accordance to cGMP and SAHPRA regulation. **Requirement 37:** Quality Analysis specifications sample 500 microlitre and activity 600 MBq: a. pH : 4.5 – 8.5 b. Half-life : 105 – 115 minutes c. Radionuclidic Purity at reference date, 08:00:F-18 between 90% to 100% d. Radiochemical Purity (HPLC):FDM > 95% of the total area of theRadio chromatogram (total activity). e. Radiochemical purity (TLC) : The sum of the total area under the principal f. Chemical Purity: Aminopolyether must be less than2.2mg/MRD : Acetonitrile must be less than 0.04% : Ethanol must be less than 0.5% peak > 95% of the total	Analysis	Verification of quality documentation				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **9** of **10**	
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
	area of the radio-chromatogram (total activity). g. Identity F-18 (Gamma spectrometry): 511 keV gamma line existing Sum peak of 1022 keV may be observed.						
38.	**Requirement 38:** The program must be able to input 10 digit batch numbers (provide a sample image) and use barcode scanner for test/run selection.	Demonstration	Verification of quality documentation				
39.	**Requirement 39:** The unit must have capacity to detect the incorrect cassettes being used, detection of faulty setups, unstable test values, faulty environmental conditions when starting and fluctuating environmental conditions while testing. Supplier to indicate compliance in provided documentation.	Demonstration	Verification of quality documentation				
40.	**Requirement 40:** Campaigning of batches (From one batch to another) within 10 minutes within the decay period.	Demonstration	Verification of quality documentation				
41.	**Requirement 41:** Batch report printable and history retrievable. Automated data collection into a comprehensive batch record.	Inspection	Verification of quality documentation				
42.	**Requirement 42:** Prevention of abusive test attempts and impossibility to erase test results.	Demonstration	Verification of quality documentation				
43.	**Requirement 43:** The supplier to demonstrate performance integrity testing and data integrity for the device (same as in QRM). Risk Assessment can be added with the supplied documentation.	Inspection	Verification of quality documentation				
44.	**Requirement 44:** Traceability of original program parameters in case of modification.	Inspection	Verification of quality documentation				
45.	**Requirement 45:** Possibility for the administrator to add comments why parameters were changed, this must be demonstrated or indicated in supplied documentation.	Demonstration	Verification of quality documentation				
46.	**Requirement 46:** Launched tests must generate time stamped data and it must be impossible to alter generated data while maintaining audit trail of all changes.	Demonstration	Verification of quality documentation				
47.	**Requirement 47:** Assistance with updating the current FDG & PSMA-1007 product dossiers.	Inspection/Demonstration	Verification of quality documentation				

Form No.	RPH-SPE-7507-01	Rev No.	2	Page **10** of **10**	NTP Actively enhancing life
Title	Technical Specification for the Synthesis Unit/System: Requirement Compliance Checklist				

Requirement No.	Requirement	Method used to Ensure Compliance (Test, Inspection, Demonstration or Analysis)	Method Description	Does the Synthesis unit/System Comply with the Requirement (Yes/No) Kindly provide details:	NTP Representative Who Witnessed Execution of Compliance Method (Name, Signature)	Supplier Representative Who Executed Compliance Method (Name, Signature)	Comments/Notes
48.	**Requirement 48:** The supplier to perform IQ and OQ, NTP to perform PQ with the supplier in line with cGMP . The resuslts to be accepted by NTP Validation. Validation guide including all certification to be supplied.	Inspection/Demonstration	Verification of quality documentation				
49.	**Requirement 49:** The supplier and all sub-suppliers shall comply with the requirements of ISO 9001:2015 and provide a valid ISO certificate. Proof of this effect shall be provided to NTP for acceptance.	Check	Verification of quality documentation				
50.	**Requirement 50:** The supplier shall issue a certificate of compliance stating that the synthesis system complies with all the requirements given in this document and is sufficient to ensure production compliance with cGMP requirements.	Inspection/Demonstration	Verification of quality documentation				
51.	**Requirement 51:** A complete datapack (Including material certificates, material safety datasheets, technical datasheets/specifications, technical drawings / flow diagrams, maintenance manual, installation manual, operating manual, IQ/OQ protocols, technical description which includes the design conditions) shall be provided to NTP for acceptance.	Inspection/Demonstration	Verification of quality documentation				

To Ensure Compliance with Requirement 1:

Action	Answer (Yes/No)	Completed By	Designation	Date	Signature	Corrective Actions Required	Comments
The checklist was completed.							
The checklist was signed by all parties.							
All the requirements are complied with.							

* The inspection and test are applicable to Requirements 15