QUALITY ASSURANCE OF RADIOPHARMACEUTICALS

with addition of

Critical Impact Assessment

JOINT WORKING PARTY:
UK RADIOPHARMACY GROUP
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INTRODUCTION

The purpose of this document is to advise all NHS and academic units that manufacture radiopharmaceuticals, and their auditors, on recommended minimum standards for Quality Assurance, rather than best practice, as was the case with the previous version [1]. Should a decision be made not to adhere to these minimum standards, the rationale for that decision must be documented and approved. The minimum standards are not restricted to ^{99m}Tc and there will be additional product testing requirements for therapy and other SPECT and PET radiopharmaceuticals.

A radioactive medicinal product or radiopharmaceutical is defined in The Medicines (Administration of Radioactive Substances) (MARS) Regulations 1978 [2] as a medicinal product which contains or which generates a radioactive substance and which is, contains or generates that substance in order, when administered to a human being, to utilise the radiation emitted therefrom.

The preparation of radiopharmaceuticals in a hospital is an activity which must comply with the principles of Good Manufacturing Practice (GMP), as specified in European Directive 2003/94/EC and incorporated in the UK into the Medicines Act 1968 [3]. In Radiopharmacies operating under a 'Section 10 exemption' from the Medicines Act where operation under the supervision of a pharmacist is required, compliance with the principles of GMP is audited according to EL (97)52 [4] by an approved Pharmacy Quality Assurance (QA) Specialist. Radiopharmacies with a Manufacturer's 'Specials' Licence (MS) are inspected by the Medicines and Healthcare Products Regulatory Agency (MHRA). One of the principles of GMP covers Quality Assurance, and this is therefore an integral part of the practice of Radiopharmacy.

Quality Assurance as it applies to Radiopharmacy differs from other applications for the following reasons:

a. The batch size may only be one and products are often used within 12 hours of preparation. This makes it impossible to complete all pharmacopoeial tests prior to release.

b. Sterility cannot be assured by sterility testing alone. Other test methodology such as end of session broth fills should be considered. (See section 7)

c. Manufacture may involve the production of a new chemical entity from licensed starting materials. This has implications for radiochemical purity testing. (See section 6.2.)

In order not to reproduce text unnecessarily, this document should be read in conjunction with the current Rules and Guidance for Pharmaceutical Manufacturers and Distributors [5], the Eudralex website [6], The Quality Assurance of Aseptic Preparation Services [7], Aseptic Dispensing for NHS Patients [8], Isolators for Pharmaceutical Applications [9]. These source documents form the basis of this latest edition and the guidance issued here, applies to all Radiopharmacies. It must be emphasized that this document only aims to give guidance for compliance with the pharmaceutical aspects of radiopharmaceutical manufacture. Other legislation, whilst mentioned, is not exhaustively covered.

This document has been subject to extensive consultation. A second review is planned in the future, and any comments should be sent to the Chair of the UK Radiopharmacy Group.

CONTENTS

1. RADIOPHARMACEUTICALS AND THE MEDICINES ACT 1968

The preparation of radiopharmaceuticals in a hospital is an activity regulated under the terms of the Medicines Act 1968 [3]. The activity may be either licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) as 'Specials' manufacture, or performed under the supervision of a pharmacist by virtue of the exemption in Section 10 of the Act. For Clinical Trials, where the product has been defined as an Investigational Medicinal Product (IMP), manufacture is regulated by the Clinical Trials Directive 2001/20/EC which is incorporated in the UK as The Medicines for Human Use (Clinical Trials) Regulations 2004 [10] and must take place in a unit with a Manufacturing Authorisation Investigational Medicinal Product Licence, MA (IMP).

The standard of Quality Assurance as outlined in this document applies to Specials and Section 10 manufacture. There may be additional requirements for IMPs as defined in Annex 13 of the EU Guide. [6, 11].

1.1 Definitions and responsibilities

1.1.1 Responsibilities of the Chief Pharmacist

The Chief Pharmacist is responsible for ensuring the safe and secure handling of medicines on behalf of the Trust. With regard to radiopharmaceuticals this responsibility will vary depending on the type of facility supplying the radiopharmaceuticals to the Trust. These responsibilities are summarised below.

a. When manufacture takes place in a specials licensed non-pharmacy run department with no pharmacy input, Chief Pharmacists would be carrying out their responsibilities by 'out-sourcing' to a suitable licence holder [5]. They must ensure that there is a formal contract defining standards and responsibilities and be responsible for monitoring these standards to reassure themselves that there are no major GMP issues.

b. In a unit with a supervising pharmacist operating under section 10 exemption, the Chief Pharmacist is ultimately responsible and as such should performance manage the supervising pharmacist to ensure compliance with guideline documents. They should also be in receipt of the EL(97)52 audit reports and summaries and sign off any action plans in response to these audits.

c. Where Nuclear Medicine Departments receive multi-dose vials from a supplier external to the Trust, the ultimate responsibility of the Chief Pharmacist cannot be devolved. They must ensure that there is a written agreement drawn up with Nuclear Medicine and the Trust Board devolving the management of the function and ensuring compliance with both the MARS Regulations 1978 and IR(ME)R Regulations 2000 [12]. They must also be satisfied that the Nuclear Medicine Department is carrying out the various processes of these agreed functions to an appropriate standard, ensuring the use of vials is in accordance with it's licence.

Additionally Chief Pharmacists have responsibility under NPSA Safety Alert No 20 [13] to ensure that ARSAC licence holders have in place Trust approved protocols for staff training and administration of non-radioactive medicines administered by healthcare professionals as an adjunct to a nuclear medicine study.

1.1.2 Licensed units

In radiopharmacy units which operate by virtue of a Manufacturer's 'Specials' Licence issued by the MHRA, staff members other than pharmacists may be designated on the licence as persons responsible for Production or Quality Control but will be determined for eligibility and suitability to be on the MS licence by the MHRA. These persons (and their nominated deputies) have clearly defined duties outlined in chapter 2 of the Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007 [5].

Responsibilities of the person responsible for Quality Control

Whether based in the Pharmacy department, Nuclear Medicine department or external Quality Control Laboratory, there must be a nominated Quality Controller. Their responsibilities are to:

a. Provide advice on procedures and techniques (in conjunction with radiopharmacists, where appropriate).

b. Provide advice on master documentation such as the procedure manual, specifications, method sheets and record sheets, and approve these where appropriate.

c. Make regular visits to the unit for general quality assurance purposes.

d. Ensure the provision of an agreed environmental monitoring and microbial testing service, monitor the results obtained, and discuss any problems that occur with the staff of the Radiopharmacy Unit, and with the Regional Quality Assurance Specialist if appropriate, with a view to their resolution.

e. Ensure the provision of an analytical testing service for raw materials and finished products.

f. Assist in self-inspection if required.

g. Ensure there are service level agreements and technical agreements with other departments (e.g. Estates) and any external agencies (e.g. testing laboratory).

In licensed units, the Quality Controller is responsible for release of products, although they may nominate a suitably trained individual to carry out the function. The responsibility cannot be delegated.

Responsibilities of the Production Manager

The Production Manager has the responsibility to:

a. Ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality.

b. Approve instructions relating to production operations and to ensure their strict implementation.

c. Ensure that the production records are evaluated and signed by an authorised person before they are sent to the Quality Control Department.

d. Check the maintenance of their department, premises and equipment.

e. Ensure the appropriate validations are done.

f. Ensure that the required initial and continuing training of their department.

Shared responsibilities of the Quality Control and Production Manager

In addition to the above, the Heads of Quality Control and Production generally have some shared, or jointly exercised, responsibilities relating to quality. These may include,

a. Authorisation of written procedures and other documents including amendments
b. Monitoring and control of the manufacturing environment
c. Plant hygiene
d. Process validation
e. Training
f. Approval and monitoring of suppliers and materials
g. Approval and monitoring of contract manufacturers
h. Design and monitoring of storage conditions for materials and products
i. Retention of records
j. Monitoring of compliance with the requirements of Good Manufacturing Practice
k. Inspection, investigation and taking of samples, in order to monitor factors which may affect the quality of the product

1.1.3 Non-licensed units

Supervision

The pharmacist responsible for supervision should be in the department and be in a position to intervene at any part of the radiopharmaceutical preparation process. He/she should be aware of what is going on and able to ensure that the process is carried out in the prescribed manner.

In practice this requires the pharmacist to:

a. Be fully conversant with all approved systems of work and documentation associated with the radiopharmaceutical preparation process.
b. Verify that all prescriptions or protocols have been adhered to before preparation commences.
c. Release products prepared for issue [7].

Authorised Pharmacist

The person designated by the Accountable Pharmacist to supervise the aseptic process and release the product for use.

Accountable Pharmacist (previously Responsible Pharmacist)

The pharmacist responsible for all aspects of the services within a Radiopharmacy unit. The duties include the approval of all systems of work and documentation used in the unit. This person is also an Authorised Pharmacist.

2. PURCHASE AND TESTING OF STARTING MATERIALS

All goods received should be checked against the order for correctness of delivery. Records of radioactivities [14], batch numbers and quantities received should be kept. In addition a visual inspection should be carried out prior to acceptance. This applies equally to chemical and radionuclide precursors, generators, kits and ready-to-use finished products.

Products or kits with a European Marketing Authorisation or bearing a UK Product Licence, should be used wherever possible. Unlicensed starting materials should not be used where there is a licensed equivalent available [15, 16]. However, considerations other than equivalent active ingredient – such as a special clinical need – may legitimately influence the choice of agent. Where an unlicensed starting material must be used, preference should be given to a material that has a Marketing Authorisation in the European Union (EU) or one with a Mutual Recognition Agreement.[1]

When unlicensed kits, radiopharmaceuticals, radiochemicals or non-radioactive products are used, the prescriber must be made aware of their responsibilities, although the purchaser assumes the responsibility for their quality.

Quality requirements for non-radioactive precursors may be stated in the respective monographs of the European Pharmacopoeia (17). If no monograph is available, the general monograph on Substances for Pharmaceutical Use applies, and a programme of testing should be implemented. It is to be noted that certain provisions of this monograph are not applicable to radiopharmaceuticals and are covered by the general monograph for radiopharmaceutical preparations. Suppliers should be requested to supply a "Certificate of Analysis" (CofA) meeting the requirements of the UK Guidance on Certificates of Analysis [5] for each batch supplied. If this is not possible, a certificate of conformance to documented specifications may be accepted. There is no requirement to hold CofAs for starting materials licensed in the EU. For non-licensed starting materials there is a need to formally assess the CofA and approve them for use. Radionuclidic purity should also be determined according to local protocols.

There should be a procedure in place to verify the compliance of starting materials with Transmissible Spongiform Encephalopathy (TSE) Regulations and The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [S.I. 2003/1680] & EMA/410/01 rev.3 [18,19], unless manufactured or imported by the holder of a UK MS Licence who is responsible for ensuring compliance. Independent checks for TSE are not required for unlicensed products used as starting materials supplied by the holder of an MS licence and EU licensed starting materials.

All non-radioactive starting materials used in the preparation of radiopharmaceuticals should be submitted to normal Quality Control procedures and be formally released by the Quality Controller before use. For licensed starting materials, receipt checks should also include verification that the product Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) have not changed since the previous receipt. Where changes are noted, there should be an impact assessment conducted and if the change requires a modification of the manufacturing instructions, change management should be invoked.

[1] Countries which currently have Mutual Recognition Agreements for medicines with the EU are Canada, Australia, New Zealand, Switzerland and Japan (limited scope: does not include sterile products, blood products, active pharmaceutical ingredients and clinical trial materials).

3. FACILITIES AND EQUIPMENT

A system of planned preventative maintenance (PPM) must be operated to ensure that all facilities and equipment used in the preparation of radiopharmaceuticals are regularly maintained and calibrated where appropriate. Records and logs must be kept for all equipment irrespective of whether maintenance and calibration is performed in house or by external contractors.

Change control must be used when introducing new equipment to the unit. Validation will be required and this can be incorporated into any Installation, Operational and Performance Qualification.

PPM must be carried out on the air handling unit on a regular basis. This usually includes cleaning external grilles, changing filters, checking pulleys and belts and electrical checks on components, for example the frost battery. Even where internal estates workers carry out the PPM, it is important that a permit to work system or equivalent is used, and the unit is officially accepted as fit for use afterwards. Any reports must be reviewed and signed off to confirm all required work has been carried out. A service level agreement and technical agreement should formalise this.

Constant care must be taken to ensure that all facilities and equipment remain fit for purpose in the interim period and that any necessary maintenance is carried out.

There should be a system to ensure that users are made aware of any alarm condition in the required timeframe.

3.1 Radionuclide calibrator

Performance parameters are to be measured at the frequencies shown in Table 1.

Table 1. Frequencies of radionuclide calibrator tests

Parameter	Acceptance	Daily	Annually
High voltage			
Display			
Zero adjust			
Background			
Check source (Relative response)			
Accuracy			
Repeatability			
Subsidiary calibrations			
Linearity			

Acceptance criteria are normally controlled as part of Operational Qualification (OQ) and /or Performance Qualification (PQ) for new calibrators or after major repairs. All spreadsheets and other software solutions used for calculations should be validated, controlled and secure.

Comprehensive details of how the various measurements may be made are described in Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and their Quality Control [20].

3.2 Other equipment

Other equipment such as centrifuges, refrigerators, particle counters (where installed), manometers, radiation monitors and doserate meters must also be subject to PPM monitoring and re-calibration as appropriate.

4. DOCUMENTATION

4.1 Controlled documents

Good documentation constitutes an essential part of the Quality Assurance system. A system of control should be in place such that changes to documents are made only by personnel approved to do so, and the location and number of authorised copies of a document should be specified, so that only current documents are in use.

A Standard Operating Procedure (SOP) should be written and independently approved for each procedure or activity associated with the operation of the unit. These should be reviewed at specified intervals of typically not longer than two years unless otherwise justified. A system of change control should be in place.

A system of documentation should be in operation such that the history of each preparation can be adequately traced as outlined in the current Rules and Guidance for Pharmaceutical Manufacturers and Distributors [5]. For departments operating under Section 10 exemption, the audit trail should extend from prescription verification to the administration of individual patient doses.

A staff training manual for all grades of staff should be written and independently approved.

A specification should be prepared for finished radiopharmaceuticals. For IMPs, written specification of starting materials are also required, as part of the Product Specification File.

4.2 Record Keeping

Records of the following should be kept:

a. Purchase of radioactive products and ingredients

b. Generator elution, yield, [^{99}Mo] Molybdenum breakthrough and aluminium ion breakthrough if required

c. Product preparation, QC and release

d. Environmental and microbiological control including aseptic operator validation and trend analysis

e. Aseptic process validation

f. Laboratory cleaning and maintenance

g. Equipment and plant calibration and maintenance

h. Staff training and continuing professional development

i. Transport of radioactive materials [21]

j. Radioactive contamination monitoring and radioactive waste disposal

k. Product defects and SOP non-conformance i.e. when a procedure is performed in a manner other than that described in the relevant SOP

l. Inspections and audits

5. PHARMACEUTICAL ENVIRONMENTAL MONITORING

Environmental monitoring of the cleanroom facility and associated workstations (Laminar Air Flow Cabinets (LAFCs) and isolators) within the Radiopharmacy should be performed regularly to demonstrate that radiopharmaceuticals are being prepared in an environment that meets national standards. Tests may be considered as 'Physical Testing' where a parameter of a piece of equipment is measured or as 'Microbiological Testing' where samples are taken to give an indication of the microbiological cleanliness of the facility. Standards and guidelines are available for many of the physical and microbiological tests which must be carried out (Rules and Guidance for Pharmaceutical Manufacturers Annex 1 [5, 6], ISO 14644 [22], Pharmaceutical Isolators [9], Parenteral Society Technical Monograph No 2 [23], ISO 12469[24]). A suitable programme of monitoring is given in Tables 2 and 3 with frequencies in line with the QA of Aseptic Preparation Services standards [7]. These should be considered as a minimum requirement, which may be increased as local conditions demand.

5.1 Physical Testing

The parameters to be tested with the recommended minimum frequency of testing are shown in Table 2.

Table 2. Environmental monitoring physical tests

Test	**Minumum Frequency**
Glove integrity test and/or visual inspection of isolator glove and sleeve assembly	Sessional
Isolator pressure differential and airflow rate	Recorded Daily - measured continously *
Pressure differential across room and workstation HEPA filters	Recorded Daily - measured continuously*
Pressure differential between rooms in aseptic suite and adjacent areas	Recorded Daily - measured continuously *
Isolator pressure decay test (leak test)	Weekly
Isolator alarm test	Weekly
Air velocities of workstation and uniformity of LAFC & laminar flow isolators	3-Monthly
Air change rates of the clean rooms	3-Monthly

Airborne particles in classified rooms	3-Monthly
Workstation & room HEPA filter efficiency & integrity of seals and joints	Yearly
KI discus protection test (LAFCs only)	Yearly

* Air Handling Unit should be alarmed. If fitted, the alarm should be tested regularly.

5.2 Microbiological monitoring

Microbiological monitoring of the environment should be carried out using a combination of settle plates, surface sampling and active air sampling at appropriate intervals, as agreed locally or as specified in the Quality Assurance of Aseptic Services [7] and Isolators for Pharmaceutical Applications [9]. Recommended minimum frequencies are outlined in Table 3. A raised monitoring frequency is specified for the critical zones of the workstations where aseptic manipulations are performed.

Table 3. Environmental monitoring microbiological tests

Test	**Frequency**
Settle plates in critical zones (LAFC/Isolators) in operational state	Sessional
Glove prints / finger dabs in critical zones (LAFC & Isolator) in operational state	Sessional
Settle plates in background environment, room and isolator transfer devices & change facilities in operational state	Weekly
Microbiological surface samples in LAFC/Isolator & Isolator Transfer Device and background environment in operational state	Weekly
Airborne viable organisms in LAFC/isolator, transfer device and background environment	3-Monthly

5.3 Action / alert levels

An alert level is defined by the user as giving early warning of a potential drift from normal conditions, which, when exceeded require investigation to ensure the process and environment are under control. An action level is the microbiological or physical level set by the user which, when exceeded, requires immediate follow-up as well as investigation with subsequent corrective action [7].

5.3.1 Physical tests

If test results are found to exceed recommended parameters, then tests must be repeated and a satisfactory repeat test confirmed in duplicate. Otherwise further action must be taken to identify and rectify the problem in line with local procedure. All corrective actions taken and

subsequent results must be fully documented.

5.3.2 Microbiological tests

Alert and action limits should be established as part of the validation of a new facility or retrospectively for established sites if this was not conducted at the time. This should include identification of typical organisms. This information can be used subsequently as part of environmental monitoring investigations.

If the results of microbiological testing exceed action levels, then corrective action will depend on the type, extent and duration of the observed contamination.

Excursions from action levels may only require an additional clean and close monitoring of subsequent test results or a repeat test with examination of the control systems. Repeated excursions must be further investigated according to local protocol. If contaminants are found in the critical zone Grade A, then the causative organism must be identified to the genus level as a minimum and the likely source determined.

If levels of contamination continue to be above the acceptable limits then further investigation must be employed so as to trace the potential source. Gross contamination in any test requires immediate action which may include additional microbiological monitoring, identification of the organism(s), a complete clean down of the aseptic facility, re-training of staff, repeat testing for an extended period until the contamination has been eliminated. Such circumstances should also include a documented consideration of the justification for continued supply. Similarly all corrective actions taken and subsequent results must be fully documented. Procedures must be established to deal with repeated patterns of contamination involving the same individual.

6. FINISHED PRODUCT TESTING AND QUALITY ASSURANCE

This section lists those parameters by which the quality of radiopharmaceutical raw materials and final products are regularly checked. In some instances, due mainly to considerations of patient safety, certain simple checks are performed on every purchased radiopharmaceutical before administration. It is accepted that full testing of ^{99m}Tc kit preparations to British Pharmacopoeia [25] or EP standards is impractical and unnecessary.

6.1 Radionuclidic purity

For unlicensed finished products radionuclidic purity should be established according to local protocols.

For generator produced radionuclides this entails testing for the presence of the parent radionuclide in an eluate. For ^{99m}Tc generators this is to be performed at a minimum on the first eluate from each new generator [26] or if there is a concern that the column could have been disturbed – for example the generator has been moved. The EP limit is 0.1% (1 kBq ^{99}Mo per MBq ^{99m}Tc). Other generator systems may require testing on a different frequency.

6.2 Radiochemical purity (RCP)

RCP testing of products made using non-licensed starting materials is required for every batch / reconstituted kit, unless a validated, GMP-compliant system for manufacture and release is in place. Routine RCP testing of radiopharmaceuticals made using licensed starting materials is more controversial. Proponents of regular routine testing would argue that as a new chemical

entity is formed, this should be tested to ensure it is compliant with specifications. Others would argue that poor RCP values have negligible effect on scan quality and the test is therefore unnecessary.

As a minimum standard, RCP testing is required for off-label manufacture, i.e. if a product is not made either exactly according to the manufacturer's instructions or in accordance with in-house validations (which would themselves need to be supported by RCP testing). An example of this is when too high an activity is inadvertently added to a kit. In times of ^{99}Mo molybdenum shortage, discarding what could be a kit with perfectly satisfactory radiolabelling could result in cancellations of appointments and delays in diagnosis and treatment. An RCP test before release could support the use of the product and makes the decision to release it an objective rather than a subjective one. The decision to release must also be supported by a procedure giving specified activity limits within which to operate, e.g. ±10%. Releasing a kit with an activity greater than the limit is not acceptable on the basis of a single RCP test result.

In addition, RCP testing will play a key role in assessing the following:

a. Assessing the impact of change and investigation of problems: RCP testing can form part of the assessment and validation of planned changes. Routine regular testing can identify adverse effects on product quality as a result of unanticipated impact of change – for example a requirement for different cleaning materials to combat microbiological growths in the cabinet breaking down radiolabelled complexes. It can also be used to investigate the impact of problems, such as breakdown of a refrigerator.

b. Patient Safety: RCP testing can identify defective products, which can result in patient harm. For example, the use of ^{99m}Tc HMPAO for confirmation of brain death. The biodistribution seen where brain death has occurred is identical to that seen with a pertechnetate brain scan. An RCP test is required in this event to demonstrate the injected product complies with specifications for free pertechnetate levels [27].

Where altered biodistributions are reported [28], these have to be investigated to ascertain whether they are caused by poor radiolabelling or by other factors, such as patient medication.

The frequency of RCP testing should be determined locally, taking into account the following risks:

a. Any change, planned or unplanned e.g. new type of kit, change of saline, change in disinfectants, generator manufacturer

b. Off-label manufacture e.g. dilution, adding additional activity

c. Unlicensed Products

d. Cold chain transport of both finished products and cold kits

e. Therapeutic products

f. Kit characteristics e.g. tin content

g. Time since last elution may have an influence for some kit

Only performing RCP testing in the event of a problem, when it is important that the test is carried out effectively is not recommended, as the staff's skills will not have been maintained. It is recommended that any staff carrying out RCP testing must perform the tests at sufficient frequencies to maintain their competence. If this is not possible, there should be a formal agreement with another nearby Radiopharmacy for the testing to be performed if required.

RCP testing methods

These may be specified in the BP [25], EP [17] or the manufacturer's SPC. RCP testing is commonly performed by thin layer chromatography or using solid phase extraction cartridges. These techniques have limitations [29] but are sufficiently sensitive to provide an estimation of expected radiochemical impurities rather than a true measure of radiochemical purity as defined by the European Pharmacopoeia. They are practical even in small radiopharmacies, and provide a means of detecting defective products. It should be noted that the results may be operator dependent but frequent testing supports maintenance of operator competence.

Action to be taken in the event of a failure

The first action should be to confirm the test result is valid, following the local out of specification procedure. If the failure is confirmed, the users must be contacted so that the ARSAC certificate holder and prescribing physician, if not the same person, can make a decision on whether to use the product. The next product made from that batch must then be tested before it is used in a patient. If the product continues to fail, the kit manufacturer should be informed, and routine RCP testing must form part of the ongoing investigation into the failures. Further guidance on the appropriate action to be taken may be found on the MHRA website (www.mhra.gov.uk).

Investigational Medicinal Products (IMP)

Products manufactured under an MA (IMP) [10] may require RCP testing in accordance with the Clinical Trial Application (CTA).

6.3 Chemical Purity (aluminium breakthrough)

For ^{99m}Tc generator eluates this entails testing for breakthrough of aluminium ion from the column, usually with a spot test. Aluminium testing should be performed if using the following products:

a. Products where the manufacturer specifies a limit for eluate aluminium content e.g. Myoview for which the eluate should contain no more that 5ppm, the European Pharmacopoeia limit [17].

b. Products where drug interactions have been reported e.g. colloidal preparations [30].

Consideration should also be given to products to be used in children, where high aluminium levels could in theory cause harm [31, 32].

If required, common practice is to test the first elution of each new generator, rather than test every eluate used to manufacture products falling into any of the above categories.

6.4 Total radioactivity or radioactive concentration

To be measured on every product prior to release. Radioactive concentration may be assumed by inference from the volumes dispensed and verified by a visual check or calculated directly from the weight of solution within the vial.

6.5 Appearance and freedom from gross particulate contamination

To be performed on every manufactured vial prior to release. Individual doses are not checked in order to reduce radiation dose to the eyes. An important visual check is that the correct kit is in

the vial shield. This may be done when the kit is cold (ie non-radioactive), provided that there is security thereafter in the process for labelling the vial shield etc. However, there may be a potential that the label on the shield is for the wrong kit. Confirmation of this can be done quickly post-compounding.

6.6 Particle size of particulate radiopharmaceuticals

A visual check to confirm appearance and freedom from gross particulates and visible aggregates to be performed on every product prior to release. It is recognised that testing to BP standards by microscopy is impractical in most radiopharmacies.

6.7 Non-filterable activity

The test is relevant to particulate radiopharmaceuticals including unlicensed nanosized colloids. It is used to determine the percentage of activity associated with particles of a particular size by measuring the activity retained on a filter with an appropriate pore diameter.

6.8 pH

To be measured on unlicensed, in-house, or research products where control of pH is critical, e.g. ^{68}Ga Gallium generator eluate.

6.9 Defect reporting and Pharmacovigilance

Any confirmed minor defects [33] must be reported to the manufacturer of the material involved. Major defects must also be reported to the Defective Medicines Report Centre (DMRC) of the MHRA.

The MHRA also requires those manufacturing medicines for administration to patients to report any adverse events [34].

It is also recommended that drug defects and adverse events be reported via The British Nuclear Medicine Society (BNMS) reporting system.

7. STERILITY ASSURANCE

Sterility assurance may be considered as a collective of a number of testing and monitoring parameters, which might include, but not be restricted to, the following elements: sterility testing, environmental monitoring, validation of the operator's aseptic technique, process validation, end of session broth fills and, where appropriate, pyrogen / endotoxin testing.

7.1 Sterility testing

For ^{99m}Tc-radiopharmaceuticals the issue of whether or not individual products would support microbial growth has made sterility testing an uncertain area, and in view of this, with the exception of the technetium generator, process and operator validation through broth simulations is considered to supplement sterility testing as a means of assuring sterility.

The aim of a sterility assurance programme is not to demonstrate the sterility of each generator or kit, but to demonstrate that the preparation process in the Radiopharmacy results in an acceptable level of sterility assurance.

Products for injection that are made from non-sterile starting materials, such as PET radiopharmaceuticals and some radiolabelled antibodies and peptides, and anything made using open procedures (with the exception of blood labelling), must be subject to sterility testing on

every batch. A sample from the final product should be taken for testing.

Protocols for sterility testing are shown in Table 4. Frequencies of testing are shown in Table 5.

Testing the first eluate of a new generator is no longer a minimum requirement because it is a licensed product for which the supply chain has been fully validated. However, should the test carried out on the final unmanipulated eluate fail, having a result for the first eluate does provide valuable data. If being performed, the first test must not be on the remnants of a used eluate. If all the eluate from the first elution is required, one method could be to re-elute the new generator immediately, and in effect, test this second elution.

Should growth be detected in any sample, a documented action plan should be put into effect to investigate the cause and implement Corrective and Preventative Action (CAPA).

Table 4. Suitable protocols for sterility testing

METHOD	DETAILS	ADVANTAGES	DISADVANTAGES
1. Direct inoculation in the Radiopharmacy	Use two media as described the British Pharmacopoeia (BP) [25] *	Sample placed in growth-promoting medium immediately	Additional radiation handling Incubation needs to be controlled and validated, and will be more complex than in option 2 below
2. Inoculation outside of the Radiopharmacy	Allow to decay before submitting for sterility testing Must not have been manipulated outside grade A zone	Minimal radiation handling	Some organisms may not survive the decay period
3. Elution of generator directly into broth (last eluate only)	Dispense 10ml double strength broth into elution vials and elute in 10ml	Mimic elution process Sample placed in growth-promoting immediately	Generator cannot be used after testing has occurred

*Inoculation of up to 10ml eluate into a 100ml vial of single strength broth would be suitable. Consideration to leaving some eluate as a retained sample should be considered in case a positive result occurs and a re-test is required – but note some organisms may not survive the period before retest.

Table 5. Frequency of Testing

ITEM TO BE TESTED	FREQUENCY	ADVANTAGES	DISADVANTAGES
Final unmanipulated eluate	Once	Gives assurance of sterility of generator throughout its period of use.	
Kit residue	Weekly	Builds up bank of data to support sterility assurance of manufactured products	Effect of some kits components may result in false negatives May have to leave to decay if incubating in uncontrolled radiation area. This may affect the integrity of the test [35]
'End of session' broth fill	Weekly per operational workstation	It is a test of the product, process and operator	

7.2 Pyrogen / Endotoxin Testing

Radiopharmaceuticals made from licensed kits are not required to be pyrogen tested. Like sterility testing however, products such as PET radiopharmaceuticals and some radiolabelled antibodies and peptides that are made from non-sterile starting materials, should be subject to a pyrogen test (as per requirements of the European Pharmacopeia – see individual monographs) [17]. It may be more appropriate to perform a test for bacterial endotoxins using the limulus amoebocyte lysate (LAL) test which may be conveniently performed prior to administration using for example the Endosafe-PTS Kinetic Assay. This hand-held reader plus disposable test cartridge gives quantitative results in 15 minutes and can detect endotoxin levels from 0.01 EU/mL to 10 EU/mL. The European Pharmacopoeia sets a limit of (175/V) EU (Endotoxin Units)/mL where V is the maximum recommended dose in millilitres.

8. VALIDATION

Validation is the demonstration that a procedure reproducibly achieves its desired outcome. For a new build or refurbishment a Validation Master Plan (VMP) is a GMP requirement. Advice can be found in the national Pharmaceutical QA Committee advisory document, Validation Master Plans [36].

It is particularly important in radiopharmacy as routine practice involves the release of products for administration to patients without the results of testing being available. Reasons for this practice include: no sample to test when the batch size is one container; a test sample that may not be representative of the whole batch; and sterility tests that are retrospective due to the short

shelf-life of the products. Validation of the procedures used in the radiopharmacy is therefore the means of providing assurance that products will be of the required quality.

Validation should be undertaken in the following areas:

a. Microbiological validation of processes, facilities and the aseptic technique of operators
b. Transfer of materials into and out of the controlled work zone
c. Cleaning processes
d. Training
e. Computer systems and software
f. Analytical techniques, such as RCP testing
g. Equipment such as TLC scanners, HPLC systems and calibrators
h. Process equipment LAFCs, isolators etc
i. Changing procedures

Practical details of many of the processes involved in validation are given in Appendix 2 of the QA of Aseptic Preparation Services [7]. Further guidance on two crucial aspects is given below.

8.1 Operator Validation

Operator validation is performed to demonstrate an individual has satisfactory aseptic technique. Each operator who prepares radiopharmaceuticals should perform the validation test at least every six months. The basis of the test is the aseptic transfer of aliquots from a container of sterile fluid microbiological growth medium to sterile vials using techniques that are employed during the routine preparation of radiopharmaceuticals. A satisfactory result is the absence of microbiological contamination upon incubation of all the vials produced.

The number of transfers will vary according to local circumstances, although it is recommended that it should reflect the maximum workload during a typical dispensing session. An operator who is new to the radiopharmacy should not be authorised to prepare products until a satisfactory result has been achieved. This is normally a minimum of three consecutive tests. Operators who work infrequently in a unit, for example those who provide backup at times of staff shortages, should also carry out a test at regular intervals as for permanent staff. Should growth occur in the test media, operators are required to undergo reassessment. If they fail they will need to be retrained and reassessed by passing three further tests before they can work in the facility again.

If it adequately reflects the procedures used in the radiopharmacy, the universal operator validation test described in Appendix 2 of the QA of Aseptic Preparation Services [7] may be used to assess aseptic technique. The use of this test will potentially allow members of staff to change employment without the need for full re-validation, and may allow comparison of staff performance between units.

8.2 Process Validation

Process validation must mimic the entire process with substitution of nutrient media in place of starting materials. It is performed to demonstrate that the procedures used to prepare a radiopharmaceutical result in a sterile product. The methodology should be of sufficient complexity to challenge the processes employed during radiopharmaceutical preparation. There may be a need to perform more than one type of test to validate processes that employ different

techniques. For example, validation of the process used to prepare a standard ^{99m}Tc radiopharmaceutical requires a different test from the process used to prepare ^{99m}Tc leucocytes. The transfer of materials into the controlled work zone forms part of the validation test and if the process involves interactions between two or more operators, this should be reflected in the design of the test.

The number of containers filled during a process test should be at least equivalent to the largest sessional workload prepared. The frequency of testing should be at least 6 monthly unless the process changes.

9. TRAINING

A written training programme to provide the above should be available and completion of the training should be documented. A system for the evaluation of training should be implemented, focusing in particular on practical skills. The employer is also charged with ensuring that staff undertake continuing education and training after qualification.

The person managing or supervising the unit should review the competencies of staff to perform adequately formally once a year. Additional training should be put in place to rectify deficiencies. A GMP update should be carried out for all staff at least every 2 years.

9.1 Radiopharmacy Training

Initial training should be provided for all staff working in Radiopharmacy departments in the aspects of Quality Assurance and Radiation Safety with which they are involved. This includes staff undertaking:

a. Preparation

b. Release

c. Quality Control and analytical techniques

d. Cleaning

e. Transport [21]

f. Appropriate level of understanding of relevant legislation

The training should be appropriate to the tasks performed and a description of the training and records of completion should be maintained.

9.2 Quality Assurance training

Elements of training should include:

a. An appropriate knowledge of GMP

b. Calibration and monitoring of equipment

c. Working practices in the Radiopharmacy including general Health and Safety and manual handling

d. Competence in the necessary aseptic skills

e. A knowledge of pharmaceutical microbiology

f. Preparation of individual doses

g. Documentation

h. Decay correction calculations

9.3 Radiation Safety training

Regulation 4.4 of the Ionising Radiation (Medical Exposure) Regulations 2000 [12] mandates the employer to ensure that all operators involved in radiopharmaceutical preparation are appropriately trained, certificated and records kept.

Elements of radiation safety training should include:

a. Working practices in the Radiopharmacy, including radiation Health and Safety and Local Rules

b. Radiation monitoring and protection

c. Dealing with spillages

d. Preparation of individual doses

e. Documentation

10. RELEASE OF PRODUCTS

A formal, recorded decision of approval must be taken by an authorised person before a product is released for use. In the case of an unlicensed unit this must be an Authorised or Accountable Pharmacist. In a unit holding a Manufacturer's 'Specials' Licence (MS), this is the Quality Controller or a suitably trained deputy. The act can be delegated but not the responsibility. In this case, release for use does not have to be carried out by someone with the equivalent level of knowledge to a Qualified Person (QP), since they are carrying out a function delegated to them by the Quality Controller. Release and certification of products manufactured under a full Manufacturing Licence e.g. an IMP licence or a Product licence cannot be delegated to anyone other than a QP named on the licence. See footnote[2] for further information

The authorised person is not normally the person who prepared the product, although there may be no alternative under emergency situations. Routine expectation is that the person performing delegated release for use function is operationally independent from the production of the product they are releasing on the day of manufacture. In cases where manufacture and release are performed by the same person, this should be considered the exception rather than the rule and only where the patient risks of not receiving the dose are outweighed by the risks of receiving a product which has not been subject to independent check. All the components used in the preparation and the final vial must be retained for a retrospective review by an authorised person.

There should be a document detailing the individuals who can perform release for administration / shipment and the provisions in place to ensure independence from manufacturing. The retrospective review conducted by QA/QC should include a review of the continued effectiveness of the release process together with results from sterility, media fills, environmental monitoring, investigations and other indicators of continued compliance such as maintenance and physical monitoring.

The authorised person (as defined in 9.1) should be suitably trained and have documented evidence of competence.

There should be a written release procedure. This should state that the person releasing products for use should have an awareness of the current validation status of the unit and any deviations or errors during the process.[2]

Release can only be effected if the product:

a. Complies with the release specification.

b. Has been prepared according to Good Manufacturing Practice.

There should be a written procedure for dealing with products failing to meet the required standard. Such events are documented and investigated.

There should be a written procedure for the recall of defective products. The recall procedure should be tested annually.

A log of errors/near misses should be maintained and these should be reported via a national scheme eg the CIVAS error report scheme [37].

11. INSPECTION AND AUDIT

There is a requirement for a system of recorded self-inspection [5, 6]. The purpose of this is to monitor the implementation and compliance with GMP principles and current standards, and to propose necessary corrective measures. It is necessary that self-inspections should be conducted in an independent way. Whilst the manager of a radiopharmacy unit and the associated quality controller may operate a local system of self-inspection, a regular (every 12-18 months) audit of a unit not covered by a manufacturer's licence must be carried out by Regional Quality Assurance Specialists [4]. A unit with a manufacturer's licence undergoes regular inspection by the MHRA on a risk-based frequency but should also undergo an annual audit by an independent person possessing the appropriate pharmaceutical expertise. Further advice on quality audits and their application has been published by the NHS Pharmaceutical Quality Control Committee [38].

In addition to the regulatory aspects of audit as outlined above, the British Nuclear Medicine Society (BNMS) can undertake invited organisational audits of nuclear medicine departments. This process includes the radiopharmacy, and looks at all aspects of the practice of radiopharmacy both within the unit itself and its relationship and interaction with the wider department [39]. The BNMS Radiopharmacy audit tool examines radiation safety, as well as GMP, as it applies to Radiopharmacy.

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[2] The concept of 'retrospective release' is not a legal term and should not be used, although it has developed in Radiopharmacy because of the difficulties of carrying out release without all the data which is usually available

This must not be confused with retrospective review which should be performed to ensure that the manufacturing operation is continuing to operate in a GMP-compliant state and products supply is in line with the specifications and the requirements of the prescribers. This may include review of sterility test data

A further review of documentation may be performed by the Quality Controller at a later date to give a retrospective QA review, rather than a so-called 'retrospective release'. This would not be considered product release, as the product will have already been administered to the patient.

Parametric release refers solely to the release of products bearing marketing authorisation which are released without full end product testing, and relies upon in-process tests and controls, as described in Annex 17 of the Rules and Guidance for Pharmaceutical Manufacturers and Distributors [5].

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Appendix to Quality Assurance of Radiopharmaceuticals: A Critical Impact Assessment

Introduction

The Quality Assurance of Radiopharmaceuticals document identifies a number of minimum standards for the preparation and testing of radiopharmaceuticals. These minimum standards have been arrived at through reference to relevant documents (EU GMP[1], QA of Aseptic Preparation Services[2,] Annex 3 to PE010 PIC/S Guide to Good Practices for the Preparation of Radiopharmaceuticals in Healthcare Establishments[3]) and by consultation with the NHS Pharmaceutical Quality Assurance Committee and the Medicines and Healthcare products Regulatory Agency (MHRA)[4].

This briefing paper is designed to complement the Quality Assurance of Radiopharmaceuticals[5] document (QAR), and is intended to provide additional assistance to service providers and auditors of the impact of failure to comply with the specifications or minimum standards, as well as providing some advice on cause and recommended actions. This briefing does not address every point raised in the QAR[5] document.

Where equipment or processes fail, a deviation report is expected. The report must include root cause, impact and corrective and preventative actions. Any changes made as a result must be impact assessed and implemented if they are appropriate via a change control process. Note: Changes may not always be considered appropriate after impact assessment has been carried out. Where appropriate an effectiveness check should also be carried out and the auditor should confirm this.

Section 3: Facilities and Equipment

3.1. Failure of Dose Calibrator Tests

Rationale for performing the test: The dose calibrator is a key piece of equipment, which directly impacts on the radiation dose the patient receives. In order to achieve GMP[1] and comply with the Ionising Radiation (Medical Exposure) Regulations (IRMER[6]), it is important to regularly assess whether the dose calibrator is measuring radioactivity accurately. The required checks are described by the National Physical Laboratory (NPL) protocol for establishing and maintaining the calibration of medical radionuclide calibrators and their quality control[7] (QC). The required QC includes daily checks using a long-lived check source to assess the relative responses for the various radionuclides being measured that day (consistency check). Other daily checks include assessment of high voltage, display, zero adjust and background. On a less frequent basis (minimum annually) accuracy, repeatability, linearity and subsidiary calibrations are performed. These are usually performed by the medical physicist expert and the data should be reviewed for integrity.

Possible causes of failure: Electrical/electronic failure, leakage of pressurised ionisation chamber

Suggested Actions:

- Failure of the voltage check could mean the battery needs changing in older calibrators. If not battery-powered, the calibrator cannot be used, and will have to be removed for repair.
- A high background could mean the dipper is contaminated, or there is a radioactive source or contamination nearby. Decontamination or identification of the source of the high background is required. If resolved, and a repeat background test shows acceptable levels, then the calibrator can continue to be used.
- If the accuracy check fails, the calibrator must be taken out of operation for repair, and must not be used. This is also true for failure of any consistency checks. However, in this case it may still be safe to use the calibrator for those radionuclides where the consistency check has passed. In this situation the Medical Physics Expert (MPE) should be contacted before use.
- If the linearity check fails then it may still be possible to use the calibrator for measuring doses only within a limited activity range. However, in this situation the MPE should be contacted before use and this should be recorded as a temporary change control.

Impact of failure: If the dose calibrator is not measuring the radioactivity accurately, an incorrect dose could be drawn up for the patient. There is also the risk that kits could be made up outside of the manufacturer's specifications if the activity cannot be accurately measured.

3.2. Failure of Other Equipment

Fridges / Freezers: All medicines or their precursors must be appropriately stored to maintain their efficacy for their shelf-life. If fridges/freezers fail, an assessment of whether the stock can still be used must be undertaken. Any stock which can still be used must be moved to a fridge or freezer which is functioning properly and has temperatures within the limits specified. The contents of a failed fridge or freezer should be listed. The decision whether to continue to use the item or discard should be provided for each item. If continued use is to occur, the rationale and conditions for continued use should be specified. Any stock which cannot be used must be disposed of appropriately. A deviation report must be completed, and this must include root cause, impact and corrective and preventative actions.

All other equipment referred to in the document must be removed for repair / re-calibration in the event of failure.

Section 5: Pharmaceutical Environmental Monitoring

5.1: Physical Testing

- **Glove/sleeve/gauntlet integrity test / Isolator pressure decay test**

Rationale for performing the test: The working zone of the isolator should be maintained at EU[1] Grade A. These checks assess whether the isolator has any leaks in it that will compromise this environment. This is especially important with negative pressure isolators. The sessional glove integrity test is a way of assessing whether any of the gloves or glove ports have any holes in before use. It is not as sensitive as the isolator pressure decay test, and should be accompanied by a visual inspection. The isolator pressure decay test should be done

on at least a weekly basis, and more frequently if a leak is suspected.

Note: The manner in which the inspection is carried out is important and personnel should be requested to demonstrate this. For example, they may not inspect the weak points such as where the glove/sleeve/gauntlet is attached to the isolator and between the fingers. Rough parts poor finishing in the isolator may also cause damage.

Possible causes of failure: Leaks around seals, eg doors, screen or door not fastened correctly, holes in gloves/sleeves/gauntlets.

Suggested actions: The source of the leak must be identified. If appropriate the seal or glove must be changed before the isolator can be used again. If the isolator continues to fail the leak test, it is possible that the front screen or a door is not fastened correctly. If this does not solve the problem gaskets should be carefully examined for damage and replaced if necessary. The final test is to carcass test the isolator using DOP smoke to ensure the leak does not compromise the Grade A environment. If the Grade A zone is compromised a temporary fix should be made. Otherwise it should be monitored for further deterioration and fully investigated at the next service.

Impact of failure: The Grade A environment is likely to be compromised, which poses a risk to product quality. The isolator must be taken out of use until the leak has been repaired or a temporary fix made (see above). The impact assessment which forms part of the deviation report should take into account the likelihood of products being contaminated and any subsequent risk to patient safety. For closed procedures, the risk is small but not removed.

- **Isolator pressure differential**

Rationale for performing the test: Pressure differentials are needed to ensure the critical area is not compromised when doors are opened. The dispensing chamber is the most critical and air from the elution chamber or transfer hatch should not enter when a connecting door is opened.

Possible causes of failure: imbalance in inflow and extract for each compartment

Suggested actions: reset the inflow / extract balance

Impact of failure: Potential influx of lower grade air could compromise quality of critical zone and potentially lead to contamination of the products prepared there.

- **Isolator airflow rate and HEPA filter pressure differential**

Rationale for performing the tests: Airflow rate is needed to ensure the critical area is not compromised by low air change rate and is especially important for turbulent flow isolators. HEPA filter pressure differential is needed to ensure a hole in a HEPA filter does not allow the ingress of low grade air.

Possible causes of failure: Fans not performing well, damper closed too much or supply filter blocking or holed.

Suggested actions: The two should be read in comparison with each other. If both readings

fall, open the supply dampers. If the flow rate decreases and the HEPA filter pressure increases, the HEPA filter may be blocked and requires changing. If the flow rate increases and the HEPA filter pressure decreases, the HEPA filter may be holed and requires DOP testing. If adjusting dampers does not correct the problem, examine the fans.

Impact of failure: Low flow rate could reduce the rate of removal of particles generated in the isolator when undertaking manual tasks and could potentially lead to contamination of the products prepared there.

- **Air change rates of the clean rooms and pressure differential between rooms in aseptic suite and other areas**

Rationale for performing the tests: Air change rates are designed to sweep rooms clear of particles generated during use. A positive pressure is required between different grades of clean rooms and between the aseptic suite and adjacent unclassified areas. It is important to monitor this overpressure continually – preferably with continuous recording via a Building Management System (BMS) as is often the case in newer units – and to record readings on a daily basis. This gives confirmation that the required minimum pressure differential has been achieved and the air handling is operating satisfactorily. It is particularly important that there is an alarm on the room pressure differential. It is also important to confirm that the alarms will work if activated. Room pressure differentials should be read in comparison with terminal HEPA filter results.

Possible causes of failure: A reduction in air change rate is often associated with a fall in room pressure differentials. If room and HEPA filter results both fall or increase there could be a problem with the AHU; If the room pressures change but the HEPA filter is unchanged; air flow balancing could be required; pressure relief flaps may be blocked or sticking.

Suggested actions: If the required minimum pressure differential is not achieved, production/preparation must cease immediately, and the cause of the failure investigated. It cannot resume until the cause of the failure has been rectified, and the correct pressure differential achieved. Consider trends of results for the unit, eg has there been a sudden change or is the change gradual?

A gradual drop in room pressures and air change rates is often normal for designs of clean room suites and indicates when filters should be changed. A sudden change should be addressed by checking for defects or blockages in supply or extracts. For example, boxes placed against an extract grille.

A catastrophic failure of the air supply should be indicated by an alarm system which does not reset itself. A deviation report is required and a full investigation carried out. It may require additional cleaning before the room can be brought back into use after the fault is corrected.

The reading should be verified and it must be checked that it isn't caused simply by a pressure relief flap sticking, for example. Consideration should be given to whether the unit requires cleaning – the response should be proportionate. A full clean may not be required if there is a slight fall, but will be required if all areas are out of specification, or if there is no pressure differential. The advice of Quality Assurance personnel must be sought if possible to inform the decision. Depending on the extent of the excursion, the activity in the suite and the length of time, the unit may require extra cleaning. Microbiological monitoring will be required if

there has been an absence of pressure differential.

Impact of failure: If the room pressure differentials are not achieved, the quality of the room air could be compromised. This in turn could compromise the quality of the air in the critical zone, and poses a risk to product quality and patient safety as a result.

- **Room HEPA filter efficiency, integrity of seals and joints, and pressure differential across room HEPA filters**

Rationale for performing the tests: HEPA filters are in place to capture particles over a certain size and prevent them from entering the clean room. As a result, they gradually accumulate particles and therefore have a limited lifespan. This accumulation causes the pressure across the filter to rise. Monitoring the pressure differential on a regular basis is therefore important as it indicates when the filters need to be changed to maintain the appropriate EU[1] classification, air change rate and room pressure differentials. It is important to monitor Air Handling Unit (AHU) pressures continually – preferably with continuous recording via a BMS as is often the case in newer units – and to record HEPA filter readings on a daily basis. This gives confirmation that the required supply has been achieved and the air handling is operating satisfactorily.

Possible causes of failure: The pressure will rise as the filter is used, as described above, so an increase will indicate that it needs changing. The usual accepted limits are double the initial clean pressure drop – in most cases, this will be 500 Pascals. The frequency at which the filters need to be changed will vary, and this can depend on a number of factors. The usual causes of an increased filter change frequency are environmental. If building work is being carried out nearby, it is likely that there will be more particles in the air which will accumulate on the filters. However, it is also worth reviewing the whole air handling system to ensure the pre-filters which have been installed are suitable, and the housing around them is sealed, as this can also cause more particles to reach the point of the terminal HEPA filters.

Conversely, there could be a hole in the HEPA filter, which would cause the pressure across the filter to drop. Potentially an increase in the room pressure differentials could also be seen in this case.

Suggested actions: Rise in terminal HEPA filter pressures near or beyond the limit for pressure differential: change the filters; review AHU particularly if HEPA filters require changing more frequently than 10 years. The limits for changing the filters should be sufficient to allow time to order and replace the filters before they get to the point where the unit has to cease operation due to inadequate air flow.

Pressure drop – confirm readings are valid then perform DOP test. If a leak is detected perform a temporary repair or cease operation and replace filters as soon as possible.

Impact of failure: As HEPA filters accumulate particles, they become blocked and it is likely that the air change rate will be compromised unless a constant supply system has been fitted into the supply. As a result, the pressure in the duct could increase and leaks that will not reseal themselves could form. Conditioned air will be lost from the system and could compromise the design specification.

If the pressure drops – particularly if it is sudden – this could mean there is a leak and if the

leak is in the terminal HEPA filter box, the room would be receiving inadequately filtered air. Product quality may be compromised if immediate action is not taken.

- **Air velocities of workstation and uniformity of laminar flow cabinets and isolators**

Rationale for performing the test: Uniformity is the test carried out to check for laminar flow. If the velocity is high, the laminar flow can break up. If the velocity is too low particles will not be swept away.

It is important therefore to assess whether the laminar flow is uniform in order to ensure operator and product protection are not compromised. This is true for both LAFs and laminar flow isolators. Some microbiological safety cabinets are fitted with two fans. However, they do not all alarm when one of the fans fail for example.

Possible causes of failure: Fan failure or filter blockage.

Suggested actions: If the velocity is low, cease manufacture and have workstation checked by contractor. Replace fan(s) if necessary. If the uniformity fails replace filter(s) at the earliest opportunity.

Impact of failure: If laminar flow or minimum air velocities are not achieved, the quality of the air in the critical zone could be compromised, as could operator protection. This could affect both products and operator safety.

- **Particle Counts**

Rationale for performing the test: There are limits set under the principles of Good Manufacturing Practice for particle numbers in clean rooms. It is important to demonstrate on a regular basis that the facility complies with those limits, in use and at rest.

Possible causes of at rest failure: Hole in a HEPA filter; insufficient cleaning; room pressure differential low.

Suggested actions: Check the condition of the HEPA filter and replace if necessary. Check the room pressure are maintained above limits 24/7, Perform an additional clean, incorporating the use of a HEPA filtered vacuum cleaner if dust is suspected, and repeat the test. If the failure is genuine and cannot be rectified, the facility cannot be used until the problem has been addressed.

Impact of failure: High levels of particles could compromise product quality. Although the risk is minimised by where products are made using closed procedures, it is not removed. As well as the direct risk to product quality, there is a risk to the continuation of the clean facility if it cannot meet the limits and therefore cannot be validated.

Possible causes of in use failure: Low air change per hour; inappropriate gowning or movement in the clean room; inadequate transfer processes. Spraying with disinfectant.

Suggested actions: Check the room input velocities and air change rate. Check the staff are appropriately gowned and act appropriately. Ensure that low linting items are used in the clean room. Spraying with a disinfectant is accepted and the particle count should reduce once the

disinfectant has vaporised. If particles are generated in a grade A environment, there should be sufficient time for their removal before critical manipulations or operations are carried out. Note: turbulent flow isolators take longer to clear than a laminar flow design.

Impact of failure: High levels of particles could compromise product quality. Although the risk is minimised by where products are made using closed procedures, it is not removed. As well as the direct risk to product quality, there is a risk to the continuation of the clean facility if it cannot meet the limits and therefore cannot be validated.

- **KI discus operator and product protection test (Class 2 safety cabinets only)**

Rationale for performing the test: The Potassium Iodide (KI) operator protection test demonstrates that the laminar flow is preventing air from inside the cabinet leaving via the front aperture, and hence, not potentially contaminating the operator. The product protection test demonstrates that the inflow air is not compromising the critical area with room air. The product protection is not generally performed by contractors because the KI is not easy to clean up after the test.

Possible causes of failure: Fan failure; imbalance in room pressure differentials; inappropriate location of items inside or outside the cabinet; room airflow pattern is poor around the front of the cabinet.

Note: The Class 2 safety cabinet should not be moved away from its commissioned location and the room should not be altered without re-commissioning the cabinet.
A KI discus failure can usually be corrected by adjusting the inflow and/or down flow fan speeds. If speed adjustment is not possible to rectify the problem, new HEPA filters may be required. Note fan replacement is usually indicated by a velocity or uniformity failure.

Suggested actions: Replace fan. Rebalance the room pressures; re-position items inside or outside the cabinet; adjust the airflow in the room with deflectors or baffles.

Impact of failure: Radioactive aerosol may escape from the cabinet or room air may contaminate the work area and compromise a product.

5.2 Routine Microbiological Monitoring

- **Sessional Settle plate failure**

Rationale for performing the test: Performing sessional settle plates is a GMP requirement and allows the quality of the environment used for the preparation of products to be monitored.

Possible causes of a failure:

Failure of the transfer sanitisation process (consider all materials, particularly the technetium generator), inappropriate siting of items such as burn bins fan failure, leaks, holes in filter, failure of the cleaning process, Isolator leak

Suggested actions: Identification of the contamination if possible to species level, assess the number of organisms to determine the severity of the failure, obtain the trend failure rate to

determine the appropriate action. Perform an additional clean and identify possible causes based on the identification report if the trend is low and take corrective action. If the count is excessively high or there is a significant trend developing, carry out full root cause analysis and investigation of all possible failure points if the failure is persistent or widespread. Review monitoring data environmental monitoring data for the facility (including review of operator trends); review isolator test results such as leak test, pressures etc, review impact on batches such as sterility test results; look at validation of processes; review validation processes, for example, for wipe and spray validation; review cleaning; review procedure for installation of technetium generator; continue to monitor trends; review operator technique, review equipment. If the trend analysis indicates the failure is not an isolated event and a corrective action has not been identified, the operation could be going out of control and additional testing will be required. A report justifying continued use of the facility should be produced.

Impact of Failure: The impact of a single out-of-specification result, which is shown to be eradicated after cleaning may be difficult to assess unless the sterility test or other test results identify a problem. However, a single sessional settle plate failure cannot be ignored as it could be the first indication that the process is going out of control. Widespread or repeated out-of-specification results may pose a potential patient safety risk. If investigation indicated the growths represent a problem for patient safety, the batches prepared may have to be recalled. If products are deemed to be affected, a recall would be needed, along with notification to the MHRA.

- **Finger Dab Failure**

Rationale for performing the test: Performing sessional finger dabs is a GMP requirement and allows the assessment of the microbiological quality of the parts of the operator in direct contact with the product being manipulated and close contact to critical aseptic manipulations..

Possible causes of a failure:
Transfer of microbiological contamination to gloves from dispenser or transfer from materials in Grade A area: This could arise from a failure of transfer sanitisation process, failure of cleaning process/breach of isolator,failure to sanitise gloves/breach of gloves Ineffective transfer sanitisation of materials. already in the facility, i.e. environmental

Suggested Actions: Identification of the contamination if possible to species level; root cause analysis and investigation of all possible failure points if the failure is persistent or widespread. However, the response needs to be proportionate: a single out-of-specification result needs to be noted, and repeated after cleaning, but will not require the full root cause analysis Review dab data for all operators and environmental monitoring data for the facility; look at the microorganism identity; review impact on batches; look at validation of processes; introduce dabs for wipe and spray operators either as an investigation or permanently to give extra data; review cleaning; looking at frequency with which operator is spraying gloves during process; review operator technique; continue to monitor trends. The use of triple wrapped, sterile packs of consumables should be considered to reduce the need for transfer disinfection. The use of sporicidal wipes for outer packaging should be considered if spores are identified on finger dabs. (The routine use of sporicidal agents is not current advocated, as it can have a negative impact on product performance.)

Impact of failure: The impact of a single out-of-specification result, which is shown to be eradicated after cleaning may be difficult unless the sterility test or other test results identify a

problem.. However, widespread or repeated out-of-specification results may pose a potential patient safety risk. If investigation indicated the growths represent a problem for patient safety (e.g. an objectionable organism[4]), the batches prepared may have to be recalled. If product has been used, a recall would still be needed, along with notification to the MHRA and a report justifying continued use of the facility produced.

- **Room Settle plate failure**

Rationale for performing the test: Performing room settle plates is a GMP requirement and allows the quality of the background environment used for the preparation of products to be monitored.

Possible causes of a failure: Failure of change process or incorrect gowning, operator infection / illness environmental issues, for example, building work, poor clean room technique, equipment – fan failure, leaks, holes in filter, Already in the facility i.e. reversal of air flow into a room creating an environmental problem, failure of the cleaning process, excess cardboard or paper present

Suggested actions: The suggested actions should follow a similar approach as indicated for sessional settle plates. As well as looking at operator technique, the clean room pressure cascade should be reviewed; review cleaning; review procedure for installation of technetium generator; continue to monitor trends; review operator technique, review equipment.

Impact of Failure: The impact of a single out-of-specification result, which is shown to be eradicated after cleaning may be difficult to assess unless the sterility test or other test results identify a problem. However, widespread or repeated out-of-specification results may pose a potential patient safety risk. If investigation indicated the growths represent a problem for patient safety (e.g. an objectionable organism[4]), the batches prepared may have to be recalled. If products are deemed to be affected, a recall would be needed, along with notification to the MHRA and a report justifying continued use of the facility produced.

- **Contact plate failure**

Rationale for performing the test: Performing contact plates is a GMP requirement and allows the efficiency of the cleaning and disinfection process to be assessed.

Possible causes of a failure: Failures on benches, trolleys and workareas could be due to components; failure of transfer sanitisation process (consider all materials, particularly the technetium generator). Failures on clean room floors are likely to be caused by operators; shedder, inappropriate gowning or footwear, inappropriate activity. General failures can be caused by inappropriate cleaning fluids and equipment, air handling failure, filter leak or already in the facility, i.e. environmental

Suggested actions: The suggested actions should follow a similar approach as indicated for session settle plates. As well as looking at operator technique, the clean room pressure cascade should be reviewed; review the frequency of cleaning; review procedure for installation of technetium generator; continue to monitor trends; review operator technique, review disinfectant used. Review the impact on batches; look at validation of cleaning; review validation processes, for example, for disinfectant and technique; review usage; review activities especially the number of staff and frequency of use, review equipment.

Impact of failure: Potential patient safety risk; contamination could get into a critical zone compromising the production process. The impact of a single out-of-specification result, which is shown to be eradicated after cleaning is difficult to assess unless the sterility test or other test results identify a problem.. However, widespread or repeated out-of-specification results may pose a potential patient safety risk. Consideration should be given to settle plate and finger dab results as well. If investigation indicated the growths represent a problem for patient safety, the batches prepared may have to be recalled along with notification to the MHRA and a report justifying continued use of the facility produced.

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- **Airborne micro test failure**

Rationale for performing the test: Performing in use room airborne micro tests is a GMP requirement and allows the quality of the environment used for the preparation of products to be monitored. It is usually carried out quarterly at the same time as operator or process validation. It is useful to understand the at rest airborne micro levels when qualifying a clean room or clean air device.

Possible causes of a failure: Failure of change process or incorrect gowning, operator infection / illness environmental issues, for example, building work, poor clean room technique, equipment – fan failure, leaks, holes in filter, Already in the facility i.e. reversal of air flow into a room creating an environmental problem, failure of the cleaning process, excess cardboard or paper present

Suggested actions: Identification of the contamination, assess the number of organisms to determine the severity of the failure. As well as looking at operator technique and session plate results, the clean room pressure cascade should be reviewed. review cleaning; review procedure for installation of technetium generator; review daily and weekly monitoring for trends, review aseptic technique and manufacturing procedures.

Impact of Failure: The impact of a single out-of-specification result, may be difficult unless the broth kit test or other test results identify a problem. However, widespread or repeated out-of-specification results may pose a potential patient safety risk. If investigation indicated aseptic technique represent a problem for patient safety, the batches prepared may have to be recalled. If products are deemed to be affected, a recall would be needed, along with notification to the MHRA and a report justifying continued use of the facility produced.

6. Finished Product Testing and Quality Assurance

6.2. Radiochemical Purity (RCP) Analysis Failure

Rationale for performing the test: Manufacture of radiopharmaceuticals involves the creation of a new chemical entity, and radiochemical purity testing also gives assurance that the manufacturing operation is capable of consistently producing products which are suitably radio-labelled. This is not required for every batch prepared (although some units may do so); it should be carried out for each batch of radiopharmaceuticals prepared using unlicensed starting materials, in the event of manufacturing a radiopharmaceutical outside of the specifications of the manufacturer and in order to investigate any unusual biodistributions.

Possible causes of a failure: Genuine fail of binding of technetium to diagnostic imaging agent (ie failure of radiolabelling procedure); operator error (in performing RCP test); using unvalidated or incorrect method; using incorrect materials; using inappropriate equipment.

Suggested actions: Follow the Out of Specification (OOS) procedure. This is likely to include repeating the test – but be careful you aren't 'testing to pass'; if future tests pass, assurance that the result is correct can be gained by reviewing scans to determine whether the biodistribution is unusual; review test results for other kits from same batch; review method in manufacturer's SmPC; review materials – including expiry; review equipment, eg are proper tanks used?; review operator technique, e.g. are they touching the strips?; refresh operator training; review how chromatography strips are assayed. If the test result is a release criterion, an OOS procedure must be in place which must be followed in this instance. (Refer to MHRA OOS procedure[8])

Impact of failure: Low radiochemical purity could result in a poor quality image, and in the worst case scenario, in inaccurate diagnostic information or repeat radiation exposure. If the failure is confirmed, the Nuclear Medicine staff / Nuclear Medicine Clinician or Radiologist should be informed. An investigation in line with the local Out of Specification results procedure should be carried out, with root cause analysis an appropriate corrective and preventative actions being put in place. Local practice for RCP testing may vary: some centres carry this out as a part of a Quality Assurance process, in which case the dose may already have been used. Others may perform RCP testing as part of the release process. Assessment of patient impact must be conducted and, if the dose has not already been used, the decision may be made not to use the product if the result is confirmed.

7.1 Sterility Testing

- **Failure of Sterility Test**

Rationale for performing the test: Providing sterility assurance is a GMP requirement to assure the microbiological quality of the product. This could be provided through sterility testing or end of session broth fills, or a combination of both. There is some indication that certain radiopharmaceuticals inhibit bacterial growth, but a good way of providing additional assurance of sterility would be a weekly end of session broth fill in addition to retrospective sterility testing on manufactured kits and on the last elution of the technetium generator.

Possible causes of a failure:

- Contamination of sample resulting in a genuine test failure
    - Contaminated Starting materials
    - Contaminated consumables used in process
    - Poor decontamination of items into the clean room and clean air device
    - Aseptic processing failure such as decontaminating gloves regularly
    - Poor aseptic technique
    - Contaminated generator/eluate
    - Microbial contamination introduced during administration
    - Microbial contamination introduced post administration
    - Cracked vial
    - Poor container integrity
    - Failure of the clean air device and/or air handling unit
    - HEPA filter failure

- Failure to follow procedures

- Contamination introduced by the test laboratory resulting in a false positive
  - Contaminated media
  - Contaminated consumables used in process
  - Aseptic processing failure such as decontaminating gloves regularly
  - Poor disinfection of items into the critical zone
  - Cracked media bottle
  - Failure of the clean air device and/or air handling unit
  - HEPA filter failure
  - Failure to follow procedures

Suggested Actions: **O**btain a copy of the out of specification report from the laboratory to determine whether an assignable cause has been identified. Investigation of all possible failure points to establish root cause; review of other sterility test and end of session broth fill data; settle plate, finger dabs, sessional session plate and contact plate results, and identify organisms to species level and strain if possible and compare with a list of organisms routinely found in the unit; repeat the test if possible; consider impact on other batches; review eluate sterility data; review sterility testing arrangements; review operator technique. Check the records for all patients receiving doses on the day of the failure. Inform the clinician.

Impact of failure: Potential patient safety risk; may have to notify the DMRC or MHRA and a report justifying continued use of the facility produced. If investigation indicates unequivocally that the failure is not due to the manufacturing process, the report can be closed. If the product has not been used, the procedure for Recall and Corrections should be used, although it is unlikely the actual batch could be recalled unless the half-life is long. In the event of notification to DMRC at the MHRA, the Consultant would need to be informed.

- **Failure of End of Session Broth Test**

Rationale for performing the test: End of session broth tests can be carried out in lieu of sterility tests provided the test is sensitive to all the processes involved in preparing a product. In radiopharmacy it usually involves adding remnants of hot finished product to tryptone soy broth. It should be noted that this media will not encourage the growth of anerobic organisms such as *clostridium difficile*, a full sterility test is required to detect such organisms. It does remove the possibility of a failure being due to a laboratory test.

Possible causes of a failure:

- Contamination of sample resulting in a genuine test failure
  - Contaminated Starting materials
  - Contaminated consumables used in process
  - Poor decontamination of items into the clean room and clean air device
  - Aseptic processing failure such as decontaminating gloves regularly
  - Poor aseptic technique
  - Contaminated generator/eluate
  - Cracked media vial
  - Poor media container integrity
  - Failure of the clean air device and/or air handling unit
  - HEPA filter failure
  - Failure to follow procedures

Suggested Actions: Investigation of all possible failure points to establish root cause; review of other sterility test and end of session broth fill data; settle plate, finger dabs, session plate and contact plate results, and identify organisms to species level if possible and compare with a list of organisms routinely found in the unit; repeat the test if possible; consider impact on other batches; review eluate sterility data; review sterility testing arrangements; review operator technique. Check the records for all patients receiving doses on the day of the failure. Inform the clinician.

Impact of failure: Potential patient safety risk; may have to notify the DMRC or MHRA and a report justifying continued use of the facility produced. If investigation indicates unequivocally that the failure is not due to the manufacturing process, the report can be closed. If the product has not been used, the procedure for Recall and Corrections should be used, although it is unlikely the actual batch could be recalled unless the half-life is long. In the event of notification to DMRC at the MHRA, the Consultant would need to be informed.

8. Validation

8.1 Failure of Operator Broth Transfer Validation

Rationale for performing the test: Operators should be validated to give assurance that they have the appropriate level of expertise to safely carry out aseptic manipulations and maintain the sterility of starting materials, components and the product. They could demonstrate aseptic technique through performing a process validation test.

Possible causes of failure: Growth in broth or on associated plates could be as a result of contamination in the environment, poor disinfection technique or could come from the operator.

Suggested actions: Identify organisms to species level if possible and compare with a list of organisms routinely found in the unit; Root cause analysis and investigation of all possible failure points is required to establish an assignable cause. The same operator should carry out a repeat validation immediately or at the first opportunity. If no assignable cause or an assignable cause attributed to the operator has been made, the operator should be suspended from performing aseptic work until retraining and revalidation has been successfully undertaken.

If the broth is clear but a failure is as a result of growth on finger dab, follow the guidance in section 5.2.

Impact of confirmed failure: The operator cannot be considered validated for aseptic manipulations and cannot undertake any aseptic work until they have passed their broth test. They will need to repeat the test unsupervised, and if they pass, can recommence aseptic processing. If they continue to fail, an investigation into their technique should be carried out by observation and discussion and an assessment of any work they have been doing may be required.

Failure of Process Validation

Rationale for performing the test: Processes should be validated to give assurance that they

have the appropriate level of control to produce aseptic products. It is important to assess aseptic manipulations and maintain the sterility of starting materials, components and the product. The validation should represent the worst case from an aseptic point of view i.e. the maximum number of finished products made in a session and incorporate all elements of the procedure..

Possible causes of failure: A failure could be associated with the manufacturing procedure or the operator undertaking the work. Growth in broth or on associated plates could be as a result of contamination in the environment, poor disinfection technique, a poorly designed protocol or could come from the operator.

Suggested actions: Identify organisms to species level if possible and compare with a list of organisms routinely found in the unit; Root cause analysis and investigation of all possible failure points is required to establish an assignable cause. The same operator should carry out a repeat validation immediately or at the first opportunity. If an assignable cause attributed to the operator has been made, the operator should be suspended from performing aseptic work until retraining and revalidation has been successfully undertaken. If no assignable cause or an assignable cause attributed to the process has been made, the process should be suspended until the process has been amended and revalidation has been successfully undertaken.

If the broth is clear but a failure is as a result of growth on finger dab, follow the guidance in section 5.2.

Impact of confirmed failure: The process cannot be considered validated for use unless it has passed the broth test. If attributed to the operator the failure should be treated in a similar way to an operator validation. If attributed to the process it requires amendment and the test repeated using several operators. If it passes, the unit can recommence aseptic processing. If it continues to fail, a full investigation into the facilities and process should be carried out by observation and discussion and an assessment of all test data. The Medicines Inspector should be notified and a report justifying continued use of the facility produced.

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