The Responsibilities of Chief Pharmacists for Radiopharmaceuticals

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Introduction

Chief Pharmacist responsibilities with respect to radiopharmaceuticals have come more to the fore recently as a result of changes to the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) in 2017[1]. The Chief Pharmacist is now required to play an active role in the process of applying for Employer licences under IR(ME)R, which are required in order to legally administer radiopharmaceuticals to patients.

Under the new arrangements, the application for the Employer Licence includes information on the facility, equipment, staff training and capacity for radiopharmaceutical provision. An individual doctor's clinical suitability is assessed and approved under the Practitioner Licencing process.

The Employer Licence under IR(ME)R and the Chief Pharmacist

Employer licences confirm approval of the arrangements made by the employer to provide a safe Nuclear Medicine service. Licences are usually valid for 5 years and require amendment when there are local changes to a service. The employer must give details of the facility and equipment provided, along with the arrangements for manufacture or procurement of radiopharmaceuticals and information about the scans to be performed. The Administration of Radioactive Substances Advisory Committee (ARSAC) will assess whether there are suitable arrangements in place for the type of service being offered.

The Employer licence application has to be signed by a number of key individuals:

i. The Medical Physics Expert

ii. The Medical Director or Chief Executive Officer

iii. The person responsible for sealed sources (if used)

iv. The Chief Pharmacist, or person taking responsibility for the safe use of any **procured** radioactive substances if there is no onsite Radiopharmacy (In the NHS this will always be the Chief Pharmacist. For non-NHS organisations this should be an individual with the equivalent responsibility)

v. The staff member responsible for Radiopharmacy if there is an onsite facility.

This represents a change as previously the Chief Pharmacist did not need to sign ARSAC applications. There is also a requirement for the person responsible for Quality Assurance on any locally held MS and / or MIA (IMP) licence to be named on the application.

Responsibilities

EEC Directive 2001/83[2] defines a medicine as 'any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or animals'. Applying this definition, radiopharmaceuticals are medicines.

Within NHS organisations, the safe use of medicines falls under the remit of the Chief Pharmacist (or similar title e.g. Director of Pharmacy) as the person corporately accountable for the delivery of pharmaceutical services.

The Chief Pharmacist's signature on the Employer Licence application confirms they have satisfied themselves that sufficient and appropriate arrangements for safe use of radiopharmaceuticals are in place - one way of doing so would be through independent audit. The arrangements for safe use encompass procurement, manufacture / preparation (if appropriate), receipt, storage, handling, administration, supply and disposal, each of which are described in this document.

A summary of the Chief Pharmacist's responsibilities can be found in Table 1.

However, the Chief Pharmacist will not themselves be responsible for putting all the required measures in place – for example, the IRMER protocols – and for many there is a shared responsibility, since as well as being medicines, and therefore being subject to medicine law, radiopharmaceuticals are radioactive and are therefore subject to other legislation. Various stakeholders will be involved on a day-to-day basis, and their duties may vary in different departments. In addition to the Chief Pharmacist and the Radiopharmacy or Nuclear Medicine Lead, stakeholders are likely to include the IR(ME)R Practitioner Licence holder(s), the Radiation Protection Adviser (RPA), The Medical Physics Expert (MPE) and the Radioactive Waste Adviser (RWA). Many of these responsibilities are defined and documented under the relevant legislation. For example, the Ionising Radiation Regulations describe the responsibilities of the RPA. The Environmental Permitting Regulations require organisations to have an RWA, and IR(ME)R requires an MPE to be appointed. Table 2 gives some examples of how these responsibilities can be shared, with suggestions for supporting documentation.

The Chief Pharmacist should ensure that appropriate governance arrangements and roles and responsibilities are clear and documented. This could be though a Quality Agreement. A template is provided in Appendix 1, which should be tailored to meet individual needs.

Table 1: Summary of Chief Pharmacist Responsibilities

Responsibility	Meaning in practice
Governance	If manufactured in house, appropriate governance arrangements are in place; to include sight of external audit reports and action plans, capacity planning sign off and ongoing monitoring of this and other KPIs. For out-sourced services, due diligence must be in place for the supplier(s).
Procurement	Appropriate suppliers are being used; Where purchasing Specials from a Radiopharmacy, Technical agreements are in place and are robust (note SLAs not required when purchasing finished products with a Marketing Authorisation); licensed materials used where possible; arrangements for procurement of unlicensed drugs should comply with unlicensed drugs policy. Note: Whilst sign-off of a certificate of analysis would be required if a Radiopharmacy / Pharmacy were receiving Specials, this is not required for Nuclear Medicine department. See Procurement section for more information.
Receipt and storage	Appropriate arrangements for security during delivery and receipt, and for subsequent storage are in place. If out of hours, appropriate diligence has been discharged with respect to checks on individuals carrying this out. Storage conditions comply with those recommended by the manufacturer;
Manufacture	Principles of GMP are being upheld; Appropriate environmental monitoring is being performed and is satisfactory; Governance arrangements and KPIs satisfactory **Note: Microbial environmental monitoring is not required in Nuclear Medicine drawing up facilities, as there are no standards with which to compare growths. Although the drawing up area should be supplied with Grade A air, it is not a Grade A area.**
Administration	The ARSAC Practitioner is responsible for IR(ME)R protocols; the Chief Pharmacist should assure themselves that these are in place and contain the required details with respect to the administration of all medicines (radiopharmaceuticals and adjuvant medicines); For example, the medicine name, form, strength and route of administration.
Supply	Where non-radioactive adjuvant drugs are used, any supply (as opposed to being given as part of the administration process) has suitable arrangements in place.
Capacity	If in-house manufacture occurs, a Capacity Plan is in place and has been approved by Chief Pharmacist; ongoing monitoring of capacity is in place with suitable governance arrangements for reporting. Ensure that appropriate staffing resilience arrangements are in place to meet governance and operational requirements.
Disposal	Radioactive materials must be disposed of according to the relevant legislation; the Chief Pharmacist must assure themselves that these arrangements are also suitable for disposal of medicines. Non-radioactive adjuvant drugs must be disposed of appropriately as medicines

The Chief Pharmacist needs to be assured that all arrangements for supply, disposal and administration in non-NHS organisations, including Universities and Clinical trials Units, are in line with the expectations outlined in this document. This includes administration of radiopharmaceuticals to healthy volunteers as well as to patients..

Service Governance Arrangements

There are a variety of different arrangements in place across the country, depending on whether radiopharmaceuticals are manufactured / prepared on site or are bought in, whether the Radiopharmacy is part of the Pharmacy department or not, and whether or not they have a Manufacturers' Specials Licence from the Medicines & Healthcare products Regulatory Agency (MHRA). The arrangements will dictate how much direct involvement the Chief Pharmacist has. However, **in all scenarios the Chief Pharmacist has overall responsibility for the safe use of radiopharmaceuticals in the organisation**. Some of the more common scenarios are described below:

1. Manufacture takes place in a Specials' licensed Radiopharmacy department. The named Licence holder may be a Pharmacist , or a Non Pharmacist Healthcare professional. Where the licence holder is a Pharmacist, they are professionally accountable to the Chief Pharmacist.

When the licence holder is a Non Pharmacist Healthcare Professional, it is important the Chief Pharmacist has oversight of the unit. They should attend the MHRA inspection opening and close-out meetings and should receive a copy of the MHRA report acknowledging any deviations reported along with the action plan. An arrangement whereby progress with the action plan, KPIs and capacity information is fed back to the Chief Pharmacist should be in place.

2. Preparation takes place in a Section 10 exemption Radiopharmacy. All aseptic preparation should be carried out by, or under the supervision of, a pharmacist authorised by the Accountable Pharmacist. This unit may be located within, or be a part of the Pharmacy Department, the Nuclear Medicine department or the Medical Physics department. Pharmacists working within Section 10 are professionally accountable to the Chief Pharmacist and may be managerially accountable to the Chief Pharmacist. It is recommended that the Chief Pharmacist and the Accountable Pharmacist agree a suitable management structure within the aseptic unit to ensure that the requirements of the Aseptic Services Product Approval framework are met at all times the unit is operational.[11] It is envisaged that the Chief Pharmacist would performance manage – either directly or indirectly – the Accountable pharmacist and would be responsible for compliance with standards in documents such as the QA of Aseptic Preparation Services[(3)] (QAAPS 5), Quality Assurance of Radiopharmaceuticals[(4)], Guidance Note14[(5)] and Yellow cover guide – Guidance on the Definition of supervision as applied to section 10 Aseptic Units 2nd Edition 2018[(6)].

The Chief Pharmacist should receive the EL(97)52[(7)], audit reports and summaries, and should sign off the action plan produced in response to any external audit.

3. Nuclear Medicine departments order and receive single / multi-dose vials from external radiopharmacies, or commercial companies (for finished radiopharmaceutical products) and draw up the patient doses themselves (as per the requirements in the UKRG safe drawing up guidance document). Procurement may be carried out entirely by the Nuclear Medicine department, or some elements could be procured by Pharmacy. An SLA must be in place with the external Radiopharmacy, with appropriate KPIs, which should include quality as well as operational / delivery elements. Compliance with GMP standards should be confirmed.

In this scenario, the ultimate responsibility of the Chief Pharmacist cannot be devolved; however, the management of the procurement process can be. A written Quality Agreement should be drawn up with Nuclear Medicine and approved by the organisation's board (or committee with suitably senior responsibility within the organisation).

In addition, the Chief Pharmacist should be satisfied that the Nuclear Medicine Department is carrying out the various processes of these agreed functions to the appropriate standard; ensuring the use of radiopharmaceuticals is in accordance with its Marketing Authorisation – for example that no 'dispensing' occurs in advance and that patient doses are drawn up immediately prior to administration (the drawing up of the patient dose is then considered part of the administration process rather than a pharmaceutical activity).

Where doses are drawn up in the Nuclear Medicine department, the recommendations in the 'Safe Drawing up of Radiopharmaceuticals' document[(8)] should be followed. Some existing facilities provide basic dose preparation areas – such as shielding, a tray and an area segregated from high traffic/patients. However, if a new department or upgrade of facilities is planned, a dedicated small bench-top workstation for withdrawal of patient doses in a separate dose preparation area should be included as part of the risk reduction strategy for inadvertent microbial contamination of IV products from multidose vials. (This does not apply to unit dose syringes or vials.)

Procurement

Usual practice for procurement of medicines would be for the Pharmacy Department to carry out the purchase, receipt and subsequent storage of medicinal products until prescribed or requested by a ward or department. However, radiopharmaceuticals are often purchased, received and stored outside of the Pharmacy remit as:

1. The medicines in this case are radioactive and need to be stored in controlled radiation areas.
2. The products are often purchased for use the same day and are regularly used for manufacture or dispatched before the Pharmacy department is open.
3. The ordering requires specialist knowledge of decay profiles of each radionuclide.
4. Disposal of radioactive medicines must follow a specific process in line with the relevant Environment Agency.

Purchase arrangements will vary. It may be carried out by the Radiopharmacy, which may or may not be part of the Pharmacy Department, or by the Nuclear Medicine department itself should there not be a Radiopharmacy on site.

It is important to remember that even when the ordering and receipt functions are carried out elsewhere, the Chief Pharmacist is ultimately responsible for ensuring that effective governance arrangements are in place across the organisation for procurement of all medicines, whether prepared in clinical areas, in Pharmacy or outsourced. (QAAPS 5.1.10)

This may result in the Chief Pharmacist being responsible for activities outside his or her area of direct managerial control.

It is therefore accepted that the day-to-day management for safe and secure handling of radiopharmaceuticals may be devolved.

It is important to define and document the responsibilities for procurement of radiopharmaceuticals from external radiopharmacies or from commercial companies (for finished radiopharmaceutical products). Specifications for purchased products are important and should be current and formally documented. Up-to-date knowledge of the planned patient doses and amount of radioactivity required is necessary.

The Chief Pharmacist must approve any procurement of unlicensed medicines (unlicensed finished products and radiopharmaceuticals made using unlicensed starting materials) and be assured that appropriate pharmaceutical quality assessments have been undertaken. See below.

It is suggested that these responsibilities be documented through a closely monitored technical (quality) agreement, an example of which is provided in Appendix A for information.

Presentation and Licence Status

Radiopharmaceuticals may be presented as:

1. Single dose units (in syringes or vials) prepared from licensed starting materials
2. Multiple dose presentations
    - Licensed radiopharmaceutical reconstituted in accordance with its SPC and supplied in its original container. Licensed for multiple dosing.
    - Licensed radiopharmaceutical reconstituted according to its SPC and then subsequently repacked aseptically into a glass vial. The original kit may have been split into two or more aliquots. Unlicensed for multiple dosing but may be necessary because of limited starting material availability or to keep staff radiation exposures to a minimum.
3. Unlicensed radiopharmaceutical in a single or multi-dose presentation.

Reference to the presentation and arrangements around supply of radiopharmaceuticals made using unlicensed starting materials should be made in the Quality Agreement

The governance arrangements for the supply and purchase of unlicensed medicines should comply with MHRA Guidance Note 14. Roles and responsibilities of both parties should be detailed in a technical agreement (see below). Further guidance can be found in the RPS Professional Guidance for the Procurement and Supply of Specials (December 2015) https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/toolkit/specials-professional-guidance.pdf

The receiving Nuclear Medicine department must ensure that Chief Pharmacists are informed in the event of any supply issues which result in use of unlicensed alternatives.

Note: the responsibility for assuring the quality of unlicensed starting materials, including approval of its Certificate of Analysis, lies with the supplying Radiopharmacy

Governance arrangements for New Studies

A mechanism should be in place for the introduction of new Nuclear Medicine investigations or treatments. This should describe the arrangements which need to be in place to comply with all regulations, as well as addressing the internal processes required such as ensuring approval by the Drug and Therapeutics / Medicines Management Committees as relevant. **This will ensure the Chief Pharmacist, as one of the individuals required to sign the ARSAC Employer Licence application, is kept appraised of any new developments in Nuclear Medicine.**

Receipt and Storage

Wherever receipt takes place, there should be suitable arrangements for holding radioactive material and for cold storage, as appropriate. In particular, the organisations should be able to evidence knowledgeable receipt of radioactive materials by an authorised individual. Preferably the delivery should be signed for by someone employed by the organisation. Many organisations now have all their deliveries in working hours so that a member of Radiopharmacy, Pharmacy or Nuclear Medicine staff can take receipt. However, in some cases this is not possible – for example, if a generator is delivered in the early hours of the morning for use that day. In this case, signed receipt may be carried out by other staff – for example, a member of the security team, who may or may not be employed by the organisation. In this scenario, the Trust should identify a person responsible and accountable for ensuring appropriate security arrangements are in place. This should include vetting any organisations employed by the Trust to carry out security activities including receipt of radiopharmaceuticals. The vetting process must be documented and must demonstrate that the security company employed by the Trust has the appropriate experience and knowledge to carry out work it has been engaged to undertake and its employees have the required character based again on suitable checks.

There should be a procedure in place and security staff should be trained appropriately to ensure safe and secure handover to the responsible department, as well as having some basic radiation awareness training, which can be given as written instructions as part of their induction training.

The Chief Pharmacist should be aware of the arrangements as they have a responsibility to ensure appropriate storage conditions are in place for all medicines. The Radiation

Protection Adviser should be satisfied that the arrangements for receipt of radioactive material are appropriate.

Supply

The Chief Pharmacist should assure themselves that the principles of GMP are being upheld. Where an organisation has an on-site Radiopharmacy, the Chief Pharmacist should be provided with the MHRA inspection report or EL(97)52[6] audit report, along with the associated action plans as a minimum. There should also be regular reports of progress against the action plans. Where supply is being outsourced, the inspection or audit report should be made available on request. The Chief Pharmacist should have sight of any SLAs or contracts for supply.

Prescriptions for radiopharmaceuticals

All practitioner licence holders under IR(ME)R are currently medical doctors, and authorisation of the referral for each individual patient acts as the prescription. **Diagnostic Radiopharmaceuticals and adjuvant medicines are Prescription Only Medicines but they do not therefore require a separate prescription or Patient Group Direction if the medicine being given at the hospital as part of the administration process:** Licenced Practitioners are responsible for the local IR(ME)R protocols, and these should include details of Prescription Only Medicines (POMs) to be administered as part of the examination. These details must be specific for the medicine in question – i.e. they should include all the usual details found in a prescription, such as full name, strength, form and route of administration.

However, supply – for example, where the patient needs to take medication away to take at home – does require a separate prescription, or for the referrer to indicate that they authorise supply. One way of doing this could be to include in an electronic referrals system a check box that the referrer must tick to authorise supply of, for example, thyroid blocking medication as detailed in the Nuclear Medicine Thyroid Blocking Protocol, with a hyperlink in the relevant IR(ME)R protocol. Essentially the referring doctor has signed an electronic Prescription for Thyroid Blockade which is then documented by the Radiopharmacy team, along with confirmation the patient's medication and allergy history have been checked.

Therapeutic radiopharmaceuticals, are not administered against an IRMER protocol, as therapy doses are dependent on the individual patient needs. A prescription is therefore always required.

Regulatory Arrangements for Administration

Provision for administration by non-medical staff is made in the Human Medicines Regulations (Regulation 214 and 240) and these have been updated as a consequential amendment within the IR(ME)R 2018 Amendment Regulations.

Regulation 240 of HMR allows operators to *administer* POMs that are included in the protocols required by IR(ME)R provided that certain conditions (A-E as follows) are met:

A. The prescription only medicine is administered by an operator acting in accordance with the local IR(ME)R procedures and protocols (IR(ME)R regulation 6(1) and 4)

B. The medical exposure has been authorised by—

- an IR(ME)R practitioner; or
- where it is not practical for an IR(ME)R practitioner to authorise the exposure, by an operator acting in accordance with written guidelines issued by an IR(ME)R practitioner.

C. The IR(ME)R practitioner is the holder of a licence issued under the relevant Ionising Radiation (Medical Exposure) Regulations (depending on whether England, Scotland and Wales, or Northern Ireland)

D. The prescription only medicine is not a controlled drug.

E. In the case of a prescription only medicine that is not a radioactive substance, it is specified in protocols.

Training for Drawing Up and Administration

In all of the above scenarios, Chief Pharmacists should assure themselves that the employer has in place approved procedures for staff training in relation to drawing up of and administration radiopharmaceuticals and of non-radioactive medicines administered by healthcare professionals other than medically qualified doctors as an adjunct to a Nuclear Medicine study. Arrangement for drawing up of radiopharmaceuticals should follow UKRG guidance.

Training should include:

- Provision of appropriate training materials
- A training plan, which identifies how training is to be delivered and competency to be assessed.
- Records of training which should provide assurance of competency.
- Referral to approved procedures for drawing up and for administration of the medicines involved.

Sufficient technical information (e.g. Summary of Product Characteristics SmPCs) should be available at the point of use to allow every medicine to be prepared and administered safely to the patient and to enable instant referral in the case of an adverse reaction or untoward event.

Capacity

All Radiopharmacies should have a capacity plan. Where organisations have an on-site Radiopharmacy, Chief Pharmacists should have oversight of this plan, and should have assurance

that performance against it is being monitored and any concerns or deviations are reported.

The Chief Pharmacist is responsible for ensuring that the capacity plan is approved by senior hospital management external to the Radiopharmacy, for example at board level, to enable it to be effective at managing workload in the wider organisational context. As Radiopharmacy Services are generally staffed by small teams with varying skill mix, the Chief Pharmacist should also ensure that appropriate staff resilience and succession planning arrangements are in place to meet all regulatory and operational requirements

Where supply is out-sourced, the responsibility for ensuring capacity is not exceeded lies with the organisation providing that service.

Confirmation that the Radiopharmacy has sufficient capacity to provide the service must be documented in the IR(ME)R Employer Licence application.

Disposal

Arrangements for disposal should comply both with regulations for disposal of radioactive material and with those for disposal of medicines. Both the Chief Pharmacist and the Radiative Waste Adviser should have oversight of the arrangements. However, compliance with the requirements for disposal of radioactive materials is the primary concern.

Technical (Quality) Agreements

The Technical (Quality) Agreement should have a clear scope and should define and document the responsibilities of all parties. The type of agreement may depend on the local arrangements for Radiopharmacy supply. For example, if the Chief Pharmacist is the line manager of the Radiopharmacy lead, a formal agreement is not considered necessary, but if the entire Radiopharmacy service is outsourced, a Technical (Quality) Agreement (TA) is essential. The template TA provided in Appendix A, includes a table of responsibilities between contract giver and contract acceptor which may form the basis of such a Technical (Quality) Agreement. This is not exhaustive, and it may be necessary to add in specific additional responsibilities – for example, approving clinical requests or making transport arrangements.

Note: If outsourcing supply of radiopharmaceuticals, a suitable Technical Quality Agreement should be in place between the Chief Pharmacist and the supplying Radiopharmacy, and there should be a separate technical agreement between the Chief Pharmacist and the Nuclear Medicine Department.

Table 2: Some examples of how responsibilities for radiopharmaceuticals can be shared, with supporting documentation requirements

Responsibility	Chief Pharmacist	MPE/ RWA	IR(ME)R practitioner licence holder	Radiopharmacy Lead	Comments	Examples of Documentation required
Clinical request for administration \ application of radio-pharmaceutical			X		IR(ME)R practitioner licence holder to justify medical exposure to radiation.	IR(ME)R written protocols for radiopharmaceuticals, including details of all adjunctive medicinal products required for each individual procedure Clinical guidance oversight by IR(ME)R practitioner: SOP for treatment pathway. Signed referral documentation for individual patients
Establish protocols (including administered radiation doses and process) for each procedure/investigation/treatment	X	X	X	X	Multidisciplinary agreement to set up protocols and procedures for each procedure/investigation/treatment	Diagnostic Reference Levels (DRLs), standard radioactivity administered, IR(ME)R written procedures, SOPs for treatment pathways, details of adjuvant drugs, Contingency plans, Risk assessments, Local Rules
Quality Assessment of unlicensed medicine / supplier	X		X	X	Supplier approval is required prior to the purchase of an unlicensed medicine. This includes authenticating licence details and ensuring compliance with GMP.	Radiopharmaceutical Quality Agreement / SOP for purchase of unlicensed radiopharmaceuticals
Disposal	X	X		X	Radioactive materials must comply with requirements for disposal of radioactive materials; non-active may be medicines and therefore must comply with disposal of medicines requirements. Monitoring required for all waste leaving the department	Disposal records for radioactive waste
Ordering Non-Technetium products	X			X	Order generated by trained staff, checked by second member of staff against holding permits limits before sending to company Radioactive supplies received into dedicated delivery area. Signed for by trained staff after checking existing stock level and holding permit limits	SOP for ordering and receipt of non-technetium products
Procurement of starting materials for manufacture of Radiopharmaceuticals				X	Supplier approval not required for licensed products on approved list	SOP for ordering licensed starting materials

References

1. The Ionising Radiation (Medical Exposure) Regulations 2017 http://www.legislation.gov.uk/uksi/2017/1322/contents/made (accessed 1 June 2020)

2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to the manufacture of medicinal products. https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF (accessed 1 June 2020)

3. Beaney AM ed. (2016) on behalf of NHS Pharmaceutical Quality Assurance Committee and the Royal Pharmaceutical Society. Quality Assurance of Aseptic Preparation Services. 5th edn. London: Royal Pharmaceutical Society.

4. UK Radiopharmacy Group (UKRG) and NHS Pharmaceutical Quality Assurance Committee (PQAC) (2016). Quality Assurance of Radiopharmaceuticals. Edition 4A.https://cdn.ymaws.com/www.bnms.org.uk/resource/resmgr/guidelines/qa_of_radiopharmaceuticals_e.pdf (accessed 1 June 2020).

5. Medicines and Healthcare products Regulatory Agency (MHRA) (2014). The supply of unlicensed medicinal products ("specials"). MHRA Guidance Note 14. London: Medicines and Healthcare products Regulatory Agency. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials (accessed 1 June 2020).

6. Guidance on the Definition of supervision as applied to section 10 Aseptic Units 2nd Edition 2018, published by the NHS Pharmaceutical Quality Assurance Committee 2018

7. NHS Executive (1997). Executive Letter (97) 52: Aseptic Dispensing in NHS Hospitals. London: Department of Health.

8. UK Radiopharmacy Group (UKRG) (2012) Safe drawing up of radiopharmaceuticals in nuclear medicine departments https://cdn.ymaws.com/www.bnms.org.uk/resource/resmgr/guidelines/ukrg_drawing_up_feb-12.pdf (accessed 1 June 2020).

APPENDIX A: Sample

Template for Technical Quality Agreement

Note: This will need to be tailored to individual arrangements

TECHNICAL QUALITY AGREEMENT

For Radiopharmacy Services

Between

Chief Pharmacist

[Organisation]

And

Radiopharmacy Department

[Organisation]

Validity: This agreement is valid for 24 months after the date of the final signature or earlier if requested by either party

Version:

Quality Agreement

For Radiopharmacy Services

This Quality Agreement is between:

Chief Pharmacist (CG)

Name:

Organisation:

And

Radiopharmacy Department (CA):

Name:

Designation:

Department and organisation:

This agreement is effective as of the date of the final signature and shall be reviewed every 2 years or earlier if deemed necessary by either party.

This agreement is executed in duplicate, all of which shall be deemed originals, and all of which shall constitute one and the same agreement binding upon both parties.

Scope

This agreement defines the roles and responsibilities between CG and CA relating to the purchase, receipt, supply, storage and end disposal of finished radiopharmaceuticals products and of starting materials which are to be used to prepare (the following) radiopharmaceuticals:

• Insert list if required

(Note: Unless only a small number of products are procured, it is not advisable to insert a list, which could quickly become out of date)

Accountability and Responsibilities

The following key stakeholders have duties and responsibilities for the purchase, receipt and storage, disposal and administration of radiopharmaceuticals

IR(ME)R Practitioner Licence holder

IR(ME)R legislation requires the administration of radioactive materials to patients to be justified by a licensed Practitioner. Under this legislation, these individuals fulfil the IR(ME)R Practitioner role.

The organisation's IR(ME)R written procedures outline the roles and responsibilities of the IR(ME)R Referrer, Practitioner and Operator.

These practitioner licence holders are clinically responsible for the administration of radioactive medicinal products.

The IR(ME)R Practitioner's licence is used in conjunction with an IR(ME)R Employer's licence. Both need to be in place for a particular Practitioner to justify an examination involving a radioactive administration at a particular site. Other healthcare professionals can perform certain roles provided they have been appropriately trained and entitled according to the employer's written procedures.

The Chief Pharmacist should be satisfied that suitable protocols are in place for the use of radiopharmaceuticals, which are in keeping with the terms of the Product Licence and Manufacturers' specifications. If using unlicensed products, or licensed products outside of the terms of the Product Licence, the IR(ME)R practitioner licence holder should have the approval of the Chief Pharmacist and, if necessary, the Trust Drug and Therapeutics Committee.

Chief Pharmacist / Director of Pharmacy

The Chief Pharmacist has overall accountability for the safe use of medicines within the organisation.

Head of Nuclear Medicine Physics (MPE)

The Head of Nuclear Medicine Physics has responsibilities for delivering the following

- Medical Physics Expert advice (MPE) (as defined in IR(ME)R, MDGN)

The MPE is a key signatory on the I(RM)ER employer licence process.

Radioactive Waste Adviser (RWA)

The Radioactive Waste Adviser has responsibilities for delivering the following

- Radiation Waste advice (RWA, as defined in EPR2010)

Radiation Protection Adviser (RPA)

The RPA has a responsibility to ensure that a suitable Radiation Protection Supervisor (RPS) is appointed for the Radiopharmacy. The RPA's main role is to ensure that the organisation is complaint with IRR17. The RPA shall liaise with the other key stakeholders.

Subject of the Agreement

The Chief Pharmacist has overall accountability for the safe use of medicines within the organisation. Due to the nature of the starting materials, medicinal products used in the manufacture/preparation of radiopharmaceuticals, the tasks of purchase, receipt and storage will be performed by the Radiopharmaceutical Purchasing Department instead of within Pharmacy.

The Chief Pharmacist (CG) hereby acknowledges that they are relying on the experience and skill of Radiopharmaceutical Purchasing Department staff, coupled with compliance with this agreement, to ensure purchase, receipt and storage of starting materials for the preparation of radiopharmaceuticals is carried out in an appropriate manner and in line with current standards and guidelines.

Purchase

The CA is responsible for the purchase of all finished radiopharmaceutical products and starting materials used in the preparation of radiopharmaceuticals. Materials (medicinal products), which possess a UK marketing authorisation shall always be purchased where available. Where such a licensed product is not available, an unlicensed product may be purchased following a successful quality assessment. The following steps should be performed:

1. Inform the Chief Pharmacist and IR(ME)R practitioner licence holder that an unlicensed medicine requires to be purchased. This notification should be done in writing and a disclaimer should be signed by the IR(ME)R practitioner licence holder. The IR(ME)R practitioner licence holder is clinically responsibility for the use of the product in their patients.

2. Medicines used to prepare radiopharmaceuticals should be purchased according to a supplier approval procedure which ensures the product associated with the lowest pharmaceutical quality risk is purchased and that the supplier has the appropriate regulatory status to supply the material e.g. a wholesale dealers authorisation (WDA(H)) or Manufacturer's Specials licence.

   The quality assessment / supplier approval should be performed prior to the purchase of an unlicensed medicine. This may include obtaining certificates of analysis, authenticating licence details and ensuring compliance with GMP. A risk-based approach should be adopted when making the decision to use an unlicensed medicine, and requests for clinical use should be processed according to the organisation's unlicensed medicines policy.

   The import of a medicine which is licensed within the EU is often the preferred alternative when a UK licensed product is not available. Risk mitigation to ensure the medicine is safe to use may need to be undertaken e.g. products that are not available in English language should be overlabelled and have technical information provided in English.

3. The supplier should have been audited, either by the purchasing party or on behalf of the NHS by the UK Radiopharmacy Group or by the NHS Pharmaceutical Quality Assurance Committee.
   a. Documented assurance of compliance with GMP by the manufacturer should be in place.

4. There should be a system for accessing patient identifiers, if required

Receipt

Batch numbers of all products should be recorded upon receipt

Appropriate checks should be performed to ensure that the correct product has been received, the integrity of the product has been maintained and that there is no reason to believe the medicine has been falsified or tampered with. Any concerns should be escalated.

SmPC's should be reviewed for version changes with each new batch received.

Storage and Dispatch

All products / starting materials should be stored and transported in compliance with the manufacturer's recommendations and Good Distribution Practice (GDP) where appropriate. Controlled radiation storage should be used where recommended.

The area in which these medicines are stored should be dedicated for medicinal products only and bioburden shall be kept to a minimum.

Products which do not have a UK marketing authorisation shall be quarantined upon receipt until an appropriate assessment can be made.

All fridges, freezers and ambient storage areas should be monitored, appropriately validated and maintained as necessary. All fridges, freezers and storage areas should be locked and secured. Storage should be in appropriate areas e.g. not adjacent to sinks and not in the same room as sluices.

Staff should be provided with appropriate personal protective equipment (PPE) to undertake their role and be appropriately trained to handle these types of medicines.

Supply and Disposal

All radiopharmaceutical products should be supplied in accordance with the Human Medicines Regulations 2012.

The Chief Pharmacist must approve unlicensed supplies.

Disposal should comply with the requirements of the Environmental Permitting (England and Wales) Regulations SI 2010, the Environmental Authorisations (Scotland) Regulations 2018 or the Radioactive Substances Act 1993 (Northern Ireland)

Quality Assurance

Minimum standards for Quality Assurance and Control identified in the QA of Radiopharmaceuticals [3] should be followed.

A suitable pharmaceutical quality system shall be maintained. The Chief Pharmacist shall be notified of all deviations through reporting of trends. This should include complaints, incidents and environmental monitoring failures. The Chief Pharmacist should also be assured that self-inspections are carried out and findings acted on as appropriate.

All planned changes shall be assessed using a change control procedure. Outsourcing of any activities should be agreed with the Chief Pharmacist prior to implementation.

Any incident which results in closure of the unit or the allocation of a red or amber risk rating should be reported to the Chief Pharmacist, along with subsequent investigation outcomes.

All products which do not have a UK marketing authorisation should be subject to an assessment for suitability of use and subsequent approval for use if the assessment is deemed satisfactory.

All documents shall be retained according to current regulatory guidance.

Records should be maintained to allow all components of a specific product to be traced to the recipient.

The CA is responsible for identifying any products which are associated with a recall through national reporting channels. They are responsible for recalling any affected stock and for appropriate segregation of any recalled stock.

The CA shall liaise with other healthcare professionals as deemed appropriate by the level of the recall / risk to patients who may have received a recalled product.

A system to record any complaints and pharmacovigilance events should be maintained. Any complaint or adverse reaction deemed significant should be reported to the Chief Pharmacist in a timely manner (normally within 24 hours).

Internal Audit

Internal audit shall be undertaken according to a pre-defined schedule and any major or critical deficiencies shall be notified to the Chief Pharmacist, with an action plan proposing corrective and preventative actions, in a timely manner (normally within 48 hours?)..

External Audit

CA shall feedback the outcome of any external audit, including the relevant action plan to address any deficiencies cited, to CG in a timely manner.

Staffing and Training

All staff involved with assessment, purchase, receipt, storage and handling of radiopharmaceuticals should be trained and confirmed as competent.

All Radiopharmaceutical Purchasing Department staff should be trained and confirmed as competent in all relevant aspects of the ordering receipt and storage procedures.

All Radiopharmaceutical Purchasing Department staff should be trained in the principles of Good Manufacturing Practice (Current EU GMP and GCP where an MIA (IMP) is held)

References

Appendices

Appendix 1 Responsibilities

Appendix 2 Quality Agreement Approval

Appendix 3 Key Contact Persons

Appendix 1

Responsibilities

	CG	CA	Comments
1. Regulatory Processes			
Comply with any and all EU and other local current applicable laws, regulations and guidelines relating to GDP.		✓	
Ensure pharmacovigilance systems are in place to collect, evaluate and collate information concerning all suspected adverse events / reactions.	✓	✓	
Report pharmacovigilance events to CG.		✓	
Ensure competent authorities are notified of all complaints concerning suspected adverse events / reactions / lack of effect according to existing regulations and requirements.	✓	✓	
Report any minor defects to the manufacture and regulatory body as appropriate		✓	

	CG	CA	Comments
2. Purchase			
Purchase sterile materials from bona fide suppliers.		✓	
Assess the quality of starting materials for use		✓	
Ensure all starting materials are TSE/BSE free		✓	
Maintain a supplier qualification programme		✓	
Check that the condition of all containers, closures, seals and labelling of delivered starting materials are satisfactory for use		✓	
Approve materials for use		✓	
Notify CG and the IR(ME)R practitioner licence holder in writing that an unlicensed medicine is to be purchased, as necessary		✓	
Source a signed disclaimer enabling the purchase of an unlicensed medicine from the IR(ME)R practitioner licence holder as necessary		✓	
Mitigate any risks associated with an unlicensed product e.g. by overlabelling those not labelled in English language		✓	

	CG	CA	Comments
3. Storage /Receipt			
Qualification / Validation of storage sites for materials, as appropriate.		✓	
Store all materials under appropriate conditions as defined by the manufacture		✓	

and in compliance with GDP requirements.			
Record the batch numbers of all externally sourced products and starting materials received to maintain an audit trail of all products received to patient level		✓	
Provide staff with appropriate PPE to handle the products		✓	
Quarantine all unlicensed medicines on receipt until an assessment has been performed by a competent person		✓	

	CG	CA	Comments
4. Changes			
Maintain a suitable change control system and provide a summary report of all significant changes to CG every 12 months.		✓	
Maintain a suitable unplanned deviation system and provide a summary report of all significant changes to CG every 12 months.		✓	
Provide results of any investigation relating to a major or critical unplanned deviation in written format to CG and in a timely manner.		✓	This investigation should include proposed corrective and preventative actions.
No work should be sub-contracted without the prior written agreement of CG.		✓	

	CG	CA	Comments
5. Documentation			
Ensure that all records of manufacture and distribution are clear, readily available and retained for the period required by current legislation. Records shall ensure the traceability of the origin and destination of Products.		✓	
Ensure written procedures are available to describe all operations that may affect the quality of products.		✓	
Maintain complete and accurate records relating to the ordering, receipt and storage of purchased products.		✓	
Store all documents and records so that they are easily retrievable and stored protected from loss and damage.		✓	
Archive documents according to current regulatory guidance.		✓	
Maintain a record of batch numbers of all starting materials received and supplied, or returned in the event of a recall.		✓	

	CG	CA	Comments
6. Complaints			
Acknowledge any complaints from CG or recipients of starting materials purchased within 24 working hours.		✓	
Inform CG of all quality complaints raised in a timely manner		✓	

Investigate and document any complaint relating to the quality of materials. All corrective and preventative actions should be documented, as appropriate.		✓	
Report back to CG the outcome of any complaints in written format within 20 working days.		✓	

	CG	CA	Comments
7. Recalls			
In the event of a material being recalled, arrange for the collection, re-stocking and segregation of products affected. This also includes products which were manufactured using a recalled starting material.		✓	Should comply with timelines as specified in regulations
Maintain a product recall procedure for use, when necessary, to recall a defective product, and test the procedure at least annually.		✓	This also includes products which were manufactured using a recalled starting material or component.
Advise CG if they have received products which are / contain starting materials which are subject to a MHRA Drug Alert or Recall.		✓	Should comply with timelines as specified in regulations

	CG	CA	Comments
8. Audit			
Provide reasonable access, at agreed pre-determined times, to permit audits of the relevant facilities and documents by CG or the regulatory authorities.		✓	
Undertake the necessary quality audits of CA if deemed necessary	✓		
Undertake the necessary quality audits of subcontractors, as required for assurance of this agreement.		✓	
Conduct internal audit in order to monitor the implementation of and compliance with GDP and GMP (as appropriate).		✓	
Propose necessary corrective measures following internal audit.		✓	
Make available evidence of adherence to internal audit schedules.		✓	
Make available evidence of closure of audits and / or inspections, and the anticipated date of the next audit / inspection.		✓	
Conduct inspections of all subcontractors in order to monitor the implementation of and compliance with GMP and /or GDP.		✓	

	CG	CA	Comments
9. Waste			
Arrange for the safe disposal radiopharmaceutical waste at agreed intervals in accordance with relevant legislation. This will include recalled and returned stock		✓	

	CG	CA	Comments
10. Training			
Adequately train staff involved in roles defined within this agreement as appropriate to their role.	✓	✓	
Ensure staff comply with relevant legislation and NHS requirements concerning both patient and commercial confidentiality e.g. General Data Protection Regulation.	✓	✓	

Appendix 2

Quality Agreement Approval

Agreed on behalf of CG

Name:	Name:
Title: Chief Pharmacist	Title: (Deputy)
Signature: _____	Signature: _____
Date: _____	Date: _____

Agreed on behalf of CA

Name:	Name:
Title: QA/Radiopharmacy (Radiopharmacy Representative)	Title: (Deputy)
Signature: _____	Signature: _____
Date: _____	Date: _____

Appendix 3

Key Contact Persons

CG

Name	Designation	Contact Details	E-mail
	Chief Pharmacist		
	Deputy		

CA

Name	Designation	Contact Details	E-mail
	QA/Radiopharmacy Representative		
	Deputy		