

Safe drawing up of radiopharmaceuticals in nuclear medicine departments

UK Radiopharmacy Group on behalf of BNMS

Correspondence to ukrg@bnms.org.uk

Summary

Many Nuclear Medicine departments in the UK draw up and administer individual patient doses from stock vials of the chosen radiopharmaceutical in designated clinical injection areas. Although this has been the practice for many years, it does not conform to the quality standards required for pharmaceutical preparation under European Community Good Manufacturing Practice (EU GMP) [1].

This document is intended to provide guidance to Nuclear Medicine Departments on the provision and design of clinical facilities, procedures, documentation, training and audit in order to

minimise the risks that arise from drawing up patient doses of radiopharmaceuticals in areas other than controlled pharmaceutical environments.

Radiopharmaceuticals are medicinal products, and the responsibility for their safe and effective use usually rests ultimately with the Chief Pharmacist for the Trust. The term which is used to describe the processes of ensuring safe use of medicines is 'Medicines Management'. It is intended that following these guidelines will support compliance with this.

1. Introduction

Whilst some Nuclear Medicine departments are supplied with individual patient doses contained within a syringe, many receive either single or multidose vials which require further manipulation in clinics.

Compounded radiopharmaceuticals for parenteral use, including those made from kits, must be manufactured aseptically in a clean room in compliance with Annex III of EU GMP [1]. Where they are presented to Nuclear Medicine staff as multidose vials, procedures must be in place to ensure that the doses are drawn up and used safely, and that the integrity of the product is maintained. Drawing up patient doses immediately prior to administration however does not require a full clean room facility.

The maximum shelf life for sterile products for human use after first opening or following reconstitution was addressed in 1999 by the European Agency for the Evaluation of Medicinal Products (EMA) [2]. Radiopharmaceuticals are specifically excluded from this advice because, as part of their marketing authorisation, the kits used in the preparation of Tc99m products are intended to provide doses for more than one patient, and are marketed as multidose vials.

2. The issues

2.1 Potential microbial contamination

2.1.1 Drawing up from a multidose vial

When more than one injection is withdrawn from a multidose vial in an uncontrolled, non-pharmaceutical area over an extended period, the risk of microbial

contamination is increased [3,4]. To minimise this risk, it is now generally accepted that multiple withdrawals are best performed centrally within the pharmacy or radiopharmacy department where appropriate aseptic dispensing facilities are available. This was one of the principal recommendations of the Breckenridge report [5] (and subsequently reinforced for all parenteral medicines by the NPSA in Patient Safety Alert 20 [4]).

Drawing up the dose and labelling it in advance means it becomes a separate pharmaceutical 'dispensing' activity which must be undertaken in a controlled pharmaceutical environment and can only be undertaken under the direct supervision of a pharmacist or in a unit with an MHRA 'Specials' Licence.

Published data have shown that when injections are drawn up in wards or clinics and not administered immediately, there is an increased risk of microbial contamination that can lead to infection [6-8]. To eliminate this risk, nursing policies and procedures specify that injections are drawn up and administered immediately. This normally entails a single dose vial being reconstituted with a suitable diluent, followed by immediate withdrawal of the required volume and administration. The vial is used for one patient and any residual solution is disposed of immediately.

When a dose is drawn up from a vial immediately before administration, the drawing up is considered to be part of the administration process and can be undertaken in the Nuclear Medicine Department. However, when the withdrawal is from a multidose

vial, the environment in which the procedure is undertaken should be controlled.

2.1.2 The environment for drawing up

Marketing Authorisations have been granted to the manufacturers of kits by the Medicines and Healthcare products Regulatory Agency (MHRA) on the basis that once reconstituted with a suitable activity and volume of sodium Tc-99m pertechnetate solution, the product may be used in a clinical area, using 'non-touch' technique, over the period of their working shelf life, which may be up to 12 hours. This clinic-based activity that involves the extended use of a preservative-free sterile injection for a period of several hours is unique in the UK in the context of the clinical setting for IV injectables.

Although inadvertent microbial contamination of a patient from a radiopharmaceutical administration as a result of drawing up the dose in a clinic has not been reported, the theoretical risk must be managed. The first choice for managing this risk is to eliminate it by drawing up all doses within the radiopharmacy. However, this is not always possible and could also affect the ability of the department to be flexible should patient appointments be delayed (resulting in radioactive decay to below the administered dose range) or when additional doses are urgently required.

When multidose containers are supplied, it is recommended that the risk of microbial contamination be managed as follows:

- The patient dose is drawn up in an area of the clinic supplied with Grade A air (see Facilities section).
- The area is subject to a regular cleaning regime using sterile disinfectant and wipes. The area is cleaned immediately before use and all materials entering the area are sprayed with sterile 70% alcohol and wiped with a sterile wipe.
- 'Non-touch' aseptic technique is employed for withdrawing a patient dose from a vial.
- The dose is administered immediately.
- A risk assessment is in place which takes account of the facility, equipment, processes, training, documentation and consequences if the patient were to be denied the dose.

One of the aims of this document is to support the completion of that risk assessment.

2.2 Misadministration of a radiopharmaceutical

Whilst the process of administration of radiopharmaceuticals is to be addressed separately in a future BNMS document, it is appropriate to mention here the sequence that should be undertaken in the event of misadministration of a radiopharmaceutical. Administration of a dose to the wrong patient or

administration of incorrect activity are the most likely adverse events that may happen due to poor design of facilities for drawing up, procedures, documentation, training and lack of audit. Any incident of misadministration involving the wrong patient will necessarily be reportable internally via the hospital error/near miss system (clinical incident form) and externally to the Care and Quality Commission (CQC), in accordance with the Ionising Radiation (Medical Exposure) Regulations (IRMER) [9]. The Service Manager will also report unintended radiation doses to CQC for all cases where the wrong patient receives a radiation dose. Should the right patient receive a dose much greater than that intended due to a procedural failure then the need to report to the IRMER coordinator via the CQC website is determined by reference to Regulation 4(5) of the IRMER [9]. Should the right patient receive a dose much greater than that intended due to equipment malfunction then the need to report to the HSE is determined by reference to Regulation 32(6) of the Ionising Radiations Regulations 1999 [10]. Further advice can be found at the Department of Health website [11] or on the BNMS website (www.bnms.org.uk). Reporting arrangements differ in the devolved administrations although the radiation dose levels are the same.

This reported data can be requested by any interested third party under the Freedom of Information Act [12] and thus can be freely published.

It is recommended that the risk of misadministration be managed as follows:

- There is an independent check of the dose by a second person at the time of drawing up.
- The syringe (in its shielded container) is transported to the patient and injected immediately.

3. NPSA Risk Assessment of drawing up from multidose vials in clinical areas

One of the recommendations of the NPSA Patient Safety Alert 20 'Promoting safer use of injectable medicines' is the completion of a risk assessment of injectable medicines procedures and products in all clinical areas to identify high risks and develop an action plan to minimise them.

The NPSA developed a risk assessment tool which identified eight risk factors associated with individual injectable medicines, their preparation and administration [4]. Products are categorised as red, amber or green, dependent on the number of risk factors met, where red indicates the highest risk and green indicates the lowest risk, thus facilitating a method of risk stratification.

When radiopharmaceuticals are drawn up in nuclear medicine departments from multidose vials supplied

by a radiopharmacy, two scenarios exist within current practice:

1. A ready-to-use multidose vial is supplied and the patient dose is prepared by calculating the volume required and withdrawing the dose in one aseptic manipulation. Using the NPSA risk assessment tool, the scoring of this scenario is shown in table 1.
2. A multidose vial that requires further dilution prior to injection into the patient i.e. the process involves a more complex calculation and several aseptic manipulations. The scoring of this scenario is shown in table 2.

The main conclusion that can be drawn from the NPSA work is that where radiopharmaceuticals are being

drawn up in the nuclear medicine department, the risk is lower when the multidose vial is supplied in a ready to use form. This is therefore the preferred method. Where this is not possible, written procedures must be in place to support the process and reduce risk associated with further dilution of vial contents.

4. Responsibilities and practical arrangements in hospitals

In the hospital setting, managing the problems elaborated above will mean that for a Nuclear Medicine Department receiving multidose vials from a radiopharmacy, the Trust Chief Pharmacist has

Table 1. NPSA risk assessment tool score for ready to use multidose vial

Risk Factor	Description	Met
1 Therapeutic risk	Where there is a significant risk* of patient harm if the injectable medicine is not used as intended	Yes
6 Use of a part vial or ampoule.	Example: 0.5ml required from a 10ml vial	Yes
Total number of risk factors		2
Risk category		Green
NPSA recommendation		Risk reduction strategies should be considered

*Patient management altered by incorrect interpretation of image

Table 2. NPSA risk assessment tool score for multidose vial that requires further manipulation

Risk Factor	Description	Met
1 Therapeutic risk	Where there is a significant risk* of patient harm if the injectable medicine is not used as intended	Yes
2 Use of a concentrate	Where further dilution is required before use, i.e., initially calculated volume is too small	Yes
3 Complex calculation	Any calculation with more than one step required for preparation and/or administration, e.g., decay to correct time and volume	Yes
4 Complex method	More than five non-touch manipulations involved or others including syringe-to second vial transfer, preparation of a burette, use of a filter	Yes
6 Use of a part vial or ampoule, or use of more than one vial or ampoule	Examples: 5ml required from a 10ml vial or two x 5ml ampoules required for a single dose	Yes
Total number of risk factors		5
Risk category		Amber
NPSA recommendation		Risk reduction strategies are recommended

*Patient management altered by incorrect interpretation of image

responsibility for the quality of the radiopharmaceutical, and this cannot be devolved. However, the ultimate clinical responsibility remains with the Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holder [13]. Thus a written agreement should be in place between Pharmacy and Nuclear Medicine and approved by the Trust Board. This agreement should devolve the management of the function and ensure compliance with the necessary requirements of guidance and regulations relating to both the pharmaceutical and radiological nature of the radiopharmaceutical. In addition, the Chief Pharmacist must 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 a product is in accordance with its Summary of Product Characteristics (SPC). For example, that doses are drawn up immediately prior to administration, not in advance. Thus the drawing up of the doses can be considered part of the administration process.

5. Facilities

This section outlines the facilities required for drawing up radiopharmaceutical doses from multidose vials in clinical areas. To avoid unnecessary repetition, further information and greater detail may be found in the Medical and Dental Guidance Notes 2002 [14].

A dedicated room should be designated for this purpose. It may be in or in close proximity to the clinical administration area. It must be sited away from patient and staff thoroughfares, and potentially contaminated areas such as toilets and sluices. The following design characteristics should be incorporated:

- Protection of products: Environment in which doses are drawn up to be supplied with Grade A air [15]. This may be achieved by use of a laminar flow cabinet, benchtop isolator/laminar flow or vertical fan filter modules. The latter can be retro-fitted to existing walls and occupy an area over the bench surface of approximately 650mm x 650mm. They cost in the region of £2500, not including fitting. In each case, an air velocity of 0.36 – 0.54m/s must be achieved at the working position [16]. It is recommended that this be incorporated into all refurbishment projects and new builds. Ideally it should be incorporated into existing facilities even if refurbishment is not planned. If this is not possible, a detailed risk assessment must in place, and must be approved by the Chief Pharmacist.
- An indicator to show that the air flow is operating correctly and the cabinet or work station should remain switched on throughout the working day.

- Although the supply of Grade A air for drawing up radiopharmaceuticals for immediate administration does not require a full EU GMP facility and associated environmental microbial monitoring programme (as required for the preparation of radiopharmaceuticals), any equipment used to supply the Grade A air must be subject to a regular maintenance programme.
- Radiation protection by using an L-shaped barrier shield. The barrier must not interrupt the supply or passage of Grade A air over the working zone. It should offer eye protection.
- Ease of cleaning of area supplied with Grade A air, and surrounding room.
- Security of radioactive materials (see also section 8. Storage and security) [17].
- Construction of benching that is capable of supporting lead shielding and allowing decontamination and disinfection regimens. Corion and Trespa are suitable materials for benching.
- Location of sharps bins, secure lead safe and calibrators such that they do not compromise air flow patterns.
- Hand washing facilities/alcohol gel dispensers/gloving station. Sinks should not be sited near the grade A environment.
- Storage for components to be used for drawing up and subsequent administration e.g. syringes and needles.
- Storage for protective garments and decontamination equipment.
- Computer or workstation to access patient information systems.
- Lockable refrigerator.

6. Drawing up

There may be several different radiopharmaceutical multidose vials stored within the vicinity of the area in which drawing up is performed. To minimise the possibility of microbial contamination, errors during drawing up and potential misadministration, the following practices are recommended:

- A process is in place to ensure verification of the correct radiopharmaceutical to be drawn up. This means that either the patients referral card or list of patient names and the studies they are due to undergo must not only be available but must actively be checked against when drawing up the dose. If the list of patient names and procedures has been transcribed by hand from elsewhere, it

must have been checked, and that check must be documented, for example, by initialling the list.

- All items introduced into the work area are subject to an appropriate disinfection regime – for example ‘Spray and Wipe’.
- Only the correct product is present in the work area during the drawing up of an individual patient dose.
- The area is clean, uncluttered and as free from interruption and distraction as possible (see Facilities).
- The volume that will have the required activity is calculated for the patient dose.
- Where possible, ready-to-use vials are supplied such that they do not require further dilution. If further dilution is required, appropriate procedures are in place (see Documentation).
- A protective garment is worn.
- The vial septum is disinfected with a sterile swab and allowed to dry for at least 30 seconds prior to puncture [4].
- A fresh needle/syringe assembly is used for each patient dose.
- A ‘non-touch’ aseptic technique is used to withdraw the dose i.e. surfaces from which microbial contamination may be introduced are not touched.
- A check is performed to demonstrate that the dose calibrator is reading correctly on the setting to be used [18].
- A documented independent check of activity is performed on each dose prior to injection.
- Individual doses prepared in a clinical area are drawn up immediately prior to injection to minimise the risk of microbial contamination see section 13.1.2 in ref [3].
- On withdrawing a dose from a radiopharmaceutical vial (particularly a technetium-99m product), air is not deliberately introduced into the vial to equalise the pressure as this can create impurities through oxidation of the product and may result in reduced image quality.
- Appropriate secure storage is available for multidose vials (see also section 9. Storage and security [17]).

7. Documentation

7.1 Written procedures

The acts of drawing up and administering radiopharmaceutical patient doses from a stock vial

must be fully covered by written procedures regardless of whether single or multidose vials are being used.

As part of the documentation for these processes, there must be a written IRMER procedure for assessment of administered activity [9]. This procedure would normally include the following:

- Steps to verify and double check that the correct product is being used.
- Details of how to calculate the volume of radiopharmaceutical that needs to be drawn up from the stock vial in order to achieve the desired administered activity.
- Measurement of the syringe patient dose in a radionuclide calibrator prior to injection.
- Checking of the calibrator setting.
- A statement on how accurately the measured activity should match the desired activity (e.g. within $\pm 10\%$).
- If a label is applied to the syringe after drawing up, matching of the syringe label details to the details on the request card and finally to the patient through an agreed patient identification procedure. Where the person who draws up the injection is not the person who injects into the patient, then the handover from one person to another may require an additional step in the identification chain, particularly if the handover is not face-to-face. As both individuals will be operators under IRMER, both should verify in writing they have undertaken their duties in accordance with procedures.

There must also be a written procedure to cover the process of withdrawing the dose from the vial using appropriate ‘non-touch’ aseptic technique and equipment as described in the previous sections. This procedure must state the maximum time limit from withdrawal to administration. It is not recommended that radiopharmaceuticals are diluted as part of the drawing up process but if this practice is to be performed then it must be covered by this or an additional written procedure.

All equipment used during the process of drawing up and administration must be subjected to an appropriate quality assurance regime supported via a set of quality control procedures. This would normally be performed by external contractors and described by means of service level agreements (SLAs) and technical agreements. Such equipment includes laminar flow cabinets, fan filter modules, isolators and dose calibrators.

7.2 Record keeping

Sufficient records must be kept about each administration to enable a full audit trail to be established. This includes the following:

- Documented evidence that all the relevant checks have been performed.
- A record of key information such as administered activity, volume, radiopharmaceutical etc. The time that the dose was withdrawn from the vial should be noted in the records as well as the time of administration so that there is documented evidence that the time difference is within acceptable limits.
- The staff members involved in all steps of the process must be identifiable in the records.
- A unique vial identifier that links the administration to the product. This identifier will also be recorded in the patient administration record and the radiopharmacy records to provide a full trail to all the ingredients used in the manufacture of the product.
- Key information such as radiopharmaceutical, volume, diluent (if used), administered activity and time.
- Evidence that all relevant checks have been performed. This includes a record that equipment maintenance and QC checks have been performed.

7.3 Audit

A regular programme of audit is required to monitor compliance with the facilities and standards specified in this guideline.

8. Training

Staff involved in any aspect of the drawing-up and administration process must be fully trained health professionals with documented evidence of their training. This includes training for those staff performing the equipment QC tests. Where there is no national guidance on training from health professional bodies or statutory bodies, then training should be locally agreed by senior staff with management responsibilities (including the ARSAC holder(s)). Training should be competency based and should be reviewed on a regular basis (e.g. annually).

As the tasks are classed as operator tasks under IRMER, these members of staff need to be formally identified as operators under the IRMER employer's procedures. Training records related to these IRMER operator tasks should be held by the Trust and be available for inspection. In addition, NPSA Alert 20 requires Trusts to ensure the training and competency of clinical staff.

9. Storage and security

The correct storage of radiopharmaceuticals in clinical areas is important to ensure their security and minimise the potential for inadvertent microbial contamination

and chemical degradation. Both sealed and unsealed sources are likely to be kept in the clinical area in which drawing up is performed. It is recommended that the storage area is located close to the work station in order to minimise the risk of accidental breakage during transfer between these areas. Storage in a locked area, cupboard or refrigerator is necessary.

The dedicated clinical area must itself be kept locked when not in use, and consideration must be given to include receiving areas for lead containers and packages being delivered, and empty containers awaiting collection. It is likely that when plans for new hospitals are being considered the local police counter terrorism officers will insist on being consulted on final room layouts. The consideration of CCTV at delivery points should be part of this planning and consultation.

10. Conclusions

Drawing up radiopharmaceuticals from multidose vials must be considered as a higher risk operation compared to direct administration of single use products. Ready prepared products, whether syringes or unit dose vials should be sourced from the supplying Radiopharmacy in the first instance. Where it is deemed that multidose vials are necessary, the following factors should be taken into account.

- The practice of drawing up doses followed by immediate administration is undertaken.
- Existing nuclear medicine departments, if they have the space, should install a contained workstation supplied with Grade A air. This could also be achieved by the installation of a bench-top laminar flow cabinet or a vertical fan filter module.
- Where insufficient space is available, nuclear medicine departments should work towards refurbishing their clinical administration facility, in order to make space for a dedicated drawing up area or room.
- When planning a new nuclear medicine department, the clinical administration area should have an adjacent drawing up room and include a contained workstation (such as benchtop isolator/laminar flow or vertical fan filter module) supplied with grade A air dedicated for drawing up radiopharmaceuticals. Note that this does not mean a full EU GMP Grade A facility, as this would require a Grade B clean room support and a full pharmaceutical environmental monitoring programme.
- Written procedures are in place to ensure that the integrity of products is maintained and that patients receive the correct injection.
- 'Non-touch' aseptic technique is used and all members of staff involved in drawing up

injections have documented approved training with competency assessment.

- Risk assessments exist to support and document the provisions made to ensure that the safety of the patient is protected.

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