Radiopharmaceuticals

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Abstract

Radiopharmacy is a discipline concerned with the preparation and quality control of radiopharmaceuticals. The term radiopharmacy is also used for the pharmacy where these activities are carried out. Radiopharmaceuticals are medicinal products that contain radionuclides (radioactive isotopes). Radionuclides are produced in nuclear reactors or in cyclotrons. The most important radionuclides used in nuclear medicine are ^{99m}technetium and ^{18}fluoride.

Many radiopharmaceuticals are used for diagnostic purposes; some are developed for therapeutic or palliative use. They are administered parenterally, orally or by inhalation. When radiopharmaceuticals are used for diagnostic purposes minute quantities are used. The radiopharmaceutical accumulates in target tissues and emits gamma-radiation that can be detected by imaging instruments. Therapeutic or palliative use requires higher dosages of alpha- or beta-emitting radiopharmaceuticals. Its ionising radiation is directed to damage the target tissue causing minimal damage to other parts of the body.

Radiopharmaceuticals are regulated both as medicinal products and as radioactive substances. Therefore, both medicine legislation and nuclear safety regulations (nuclear energy legislation) are applicable. These regulations dictate both design and layout principles of the radiopharmacy and the general handling and control procedures that should be applied when preparing and dispensing radiopharmaceuticals.

Radiopharmaceuticals used in hospitals are prepared, tested and released under the responsibility of a (radio) pharmacist. In this chapter the most important pharmaceutical aspects of radiopharmaceuticals are highlighted.

Keywords

Radiopharmacy • Radionuclides • Radiopharmaceuticals • Radiolabelling • Nuclear medicine • Alpha-emitters • Beta-emitters • Gamma-emitters • Positron emitters • SPECT • PET

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15.1 Orientation

Radiopharmacy is a discipline concerned with the preparation and quality control of radiopharmaceuticals. Radiopharmaceuticals are defined by the European Pharmacopeia (Ph. Eur.) as "medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose".

Radiopharmaceuticals are regulated both as medicinal products and as radioactive substances. Therefore, both medicine quality regulations (GMP) and safety regulations (nuclear energy legislation) are applicable. Radiopharmaceuticals must be handled (often aseptically) as quickly as possible, with shielding, to avoid unnecessary exposure to radiation.

Most radiopharmaceuticals are used for diagnostic purposes, some for therapeutic or palliative use. They are administered parenterally, orally or by inhalation. When radiopharmaceuticals are used for diagnostic purposes minute quantities are used. The radiopharmaceutical accumulates in target tissues and emits gamma radiation that can be detected by imaging instruments. Therapeutic or palliative use requires higher dosages of alpha- or beta-emitting radiopharmaceuticals. Its ionising radiation is directed to damage the target tissue causing minimal damage to other parts of the body. Alpha or beta emitters are suitable for this purpose because of the limited pathway of their radiation in tissue [1, 2].

Radiopharmaceuticals are used in the hospital department of nuclear medicine or in research institutes. For diagnosis essentially two techniques are used: SPECT (single-photon emission computed tomography) and PET (positron emission tomography). SPECT is an imaging technique detecting gamma rays. In SPECT imaging a gamma camera acquires multiple two dimensional images (also called projections) from multiple angles. With the aid of tomographic reconstruction algorithms a three-dimensional image is calculated.

Positron emission tomography also produces three-dimensional pictures of organs and functional processes in the body. In PET pairs of gamma rays emitted indirectly by a positron-emitting radionuclide are detected. Computer programs reconstruct PET images.

Several techniques from radiology and nuclear medicine have been combined in hybrid imaging techniques, such as SPECT-CT, PET-CT and PET-MRI. In these hybrid systems the use of radiopharmaceuticals (sometimes next to conventional contrast agents) remains essential.

Radiopharmaceuticals used in hospitals are prepared, tested and released under the responsibility of a (radio)pharmacist. In this chapter the most important pharmaceutical aspects of radiopharmaceuticals are highlighted.

15.2 Definitions

ALARA	"As Low As Reasonably Achievable", an occupational safety and health principle pursuing minimal radiation exposure.
Alpha radiation	Ionising radiation by alpha particles (= $^{4}He^{2+}$-ions). In comparison with beta and gamma radiation, alpha radiation has the least penetrating power and the highest linear energy transfer.
Alpha emitter	Radionuclide that decays to a more stable nuclide by emission of an alpha particle.
Annihilation radiation	Two gamma rays with an energy of 511 keV that are emitted at an angle of 180° after collision of a positron with an electron.
Becquerel	Unit of radioactivity: 1 Becquerel (Bq) is equivalent with 1 disintegration per second (kBq = 1,000 Bq, MBq = 10^6 Bq).
Beta radiation	Ionising radiation by $beta^+$ (= positron) or $beta^-$ (= electron) particles.
Beta emitter	Radionuclide that decays to a more stable nuclide by emission of a $beta^+$ (= positron) or a $beta^-$ (= electron) particle.
Computed tomography (CT)	Technology that uses X-rays to produce images (virtual slices), allowing to see inside the body.
Cyclotron	Equipment in which charged particles, after acceleration in a circular pathway, are directed onto a target for evoking a nuclear reaction.
Decay	Spontaneous reaction of a radionuclide to form another (radio)nuclide accompanied by the release of ionising radiation.
Electronvolt (eV)	Kinetic energy gained by an electron when accelerated through a potential field of 1 volt (keV = 1,000 eV).
Gamma radiation	High energy photons that are emitted during radioactive decay.
Gamma emitter	Radionuclide that emits gamma rays during radioactive decay.
Generator	A device in which a daughter radionuclide with a shorter half-life is separated from a mother radionuclide with a longer half-life.
Half-life	The characteristic of a radionuclide that defines the time during which

	the radioactivity of a radionuclide is reduced to half of its original value.
Kit for labelling	Composed set of all non-radioactive reagents in appropriate quantities for the preparation of a specific radiopharmaceutical.
Magnetic resonance imaging (MRI)	A medical imaging technique to investigate the anatomy and physiology of the body using strong magnetic fields.
Nuclear reactor	Installation for the production of radionuclides by nuclear fission of e.g. ^{235}uranium.
PET	Positron emission tomography: an imaging technique that makes use of a radiopharmaceutical that is labelled with a positron emitter (e.g. ^{11}C, ^{13}N, ^{18}F).
Positron	A beta^{+} particle that, after collision with an electron, annihilates to two gamma rays of 511 keV.
Radioactivity	Spontaneous process in which an unstable radionuclide transforms to a more stable (radio)nuclide releasing energy in the form of particles (alpha or beta particles) or photons (gamma rays).
Radiochemical	Any compound containing one of more atoms of a radioactive isotope.
Radiochemical purity	Fraction of the total radioactivity present in the desired radiochemical form.
Radiolabelling	Process of attaching a radionuclide to a non-radioactive molecule.
Radionuclide	An unstable nuclide that decays spontaneously by the emission of particles (alpha or beta particles) or photons (gamma rays).
Radionuclidic purity	Fraction of the total radioactivity present as the desired radionuclide.
Radiopharmaceutical	A pharmaceutical substance that contains one or more radionuclides.
SPECT	Single-photon emission computed tomography: an imaging technique that makes use of a radiopharmaceutical that is labelled with a gamma emitter.

15.3 Radionuclides

Radionuclides (radioactive isotopes) are the most important components of radiopharmaceuticals. Desirable properties of radionuclides in radiopharmaceuticals are relatively short decay times (half-lives from hours to days) and ease of incorporation in the final molecule. The energy of the emitted radiation ranges from about 150 kiloelectronvolt (keV) (gamma-photons for diagnostics) to around 1,000 keV (beta-particles for therapy). The newer imaging technique of positron emission tomography (PET) uses radionuclides with half-lives going down to 2 min, emitting positrons that annihilate to gamma-photons of 511 keV.

Table 15.1 Common radionuclides and their use

Diagnostic use (SPECT)	Diagnostic use (PET)	Therapeutic/ palliative use
^{51}Cr	^{11}C	^{32}P
^{67}Ga	^{13}N	^{89}Sr
^{81m}Kr	^{15}O	^{90}Y
^{99m}Tc	^{18}F	^{131}I
^{111}In	^{68}Ga	^{153}Sm
^{123}I	^{82}Rb	^{177}Lu
^{133}Xe	^{89}Zr	^{188}Re
^{201}Tl	^{124}I	^{223}Ra

Radionuclides either originate from a nuclear reactor or are produced by a cyclotron. The description of the production methods of radionuclides in nuclear reactors and cyclotrons goes beyond the scope of this book and can be found elsewhere [1, 2].

The most important pharmaceutical radionuclide produced by a nuclear reactor is ^{99}molybdenum. This element is the mother radionuclide in a ^{99}Mo/^{99m}Tc-generator (see Sect. 15.6.4). During separation in this generator sodium ^{99m}technetium pertechnetate is formed. ^{99m}Tc-pertechnetate is the most frequently used radiochemical for coupling to a pharmaceutical ligand in the preparation of diagnostic radiopharmaceuticals.

Cyclotrons are found in nuclear industry, but their presence and use in hospitals is increasing. The principal radionuclide from cyclotrons is ^{18}F-fluoride. This radionuclide is often incorporated into ^{18}F-fludeoxyglucose through an automated synthesis procedure. ^{18}F-fludeoxyglucose is the major radiotracer used in PET.

The most frequently used radionuclides and their use are mentioned in Table 15.1.

15.4 Radiopharmaceuticals

15.4.1 Use of Radiopharmaceuticals

A radiopharmaceutical is a radioactive medicinal product for diagnostic, therapeutic or palliative use. Parenteral radiopharmaceuticals usually consist of a radionuclide coupled to another pharmaceutical compound, also called a ligand. Some radionuclides are administered as such. Alternative dosage forms are capsules for oral use or a radioactive gas for inhalation. All dosage forms are shielded, in lead or

tungsten for gamma and positron emitters and in plastics for beta and alpha emitters.

The physical and biopharmaceutical properties of a radiopharmaceutical determine its potential use [1, 2].

The design of radiopharmaceuticals is based upon the physiological function of the target organ. The mechanism of targeting a particular organ can be different, for example physical trapping of particles, binding to structures in tissues or organs or an antigen-antibody reaction. In general, a high target-to-background ratio is pursued.

A radiopharmaceutical emitting alpha or beta radiation can be used for therapeutic or palliative purposes. These types of radiopharmaceuticals deposit their energy on very short distances. For alpha emitters this distance is much shorter than for beta emitters. This high-dose locally accumulated radioactivity is used in radionuclide therapy (pain palliation of bone metastases, therapy for some specific types of cancer).

Some radionuclides are emitting a combined spectrum of radiation. One type of the radiation spectrum (alpha or beta) is used for its therapeutic properties; the other type of the radiation spectrum (gamma) might be used for localisation of the tracer and the targeted tissue or for dosimetry. These radiopharmaceuticals are called theranostics.

Sometimes other medicines are used in combination with the radiopharmaceutical, as co-medication in the diagnostic process, e.g. intravenous diuretics to promote renal clearance, adenosine to induce pharmacological stress and thyroid stimulating hormone in thyroid studies. These pharmacological interventions increase the sensitivity or specificity of a procedure used in nuclear medicine.

15.4.2 Biopharmaceutics

Most radiopharmaceuticals are administered intravenously. After injection, the radioactive substance is distributed fast to the target site thereby avoiding unnecessary radiation dose to the stomach and gut after oral dosing. Scanning may start immediately or after a certain period.

The selective biodistribution and pharmacokinetics of the radiopharmaceutical within the body are determined by the properties of the pharmaceutical agent, the stability of the labelling, the physical and radiochemical properties of the radiopharmaceutical, the purity of the radiopharmaceutical preparation, the pathophysiologic status of the patient and the possible influence of interfering medicines.

By choosing the radionuclide the diagnostic use of the radiopharmaceutical can be determined: gamma emitters or positron emitters can be used for diagnostic procedures by providing static or dynamic images following the distribution of the radiopharmaceutical within the body. For the detection of gamma radiation a classical gamma camera is used, for positron-emitters a PET-camera has to be used. See also next sections.

Adverse effects of radiopharmaceuticals for diagnosis are extremely rare [3]. Radiopharmaceuticals for therapy may have adverse effects, for example bone marrow depression if used for treatment of bone metastases. Radiopharmaceuticals can interact with other (non-radioactive) medicines given to the same patient [4]. Food and glucose in food can disturb the quality of certain types of imaging (interaction of glucose (dextrose) with ^{18}F-FDG in PET imaging).

15.4.3 Parenteral Radiopharmaceuticals

Parenteral radiopharmaceuticals are available as a simple radionuclide in solution, for instance ^{131}I-sodium iodide solution for injection, or are prepared by labelling a non-radioactive pharmaceutical moiety (ligand) with a radionuclide. Many kits or ligands for the preparation of radiopharmaceuticals are available in the form of sterile, freeze-dried powders in an injection vial. These kits are non-radioactive.

Radiopharmaceuticals for parenteral use must comply with the Ph. Eur. monograph for parenteral preparations, so they have to be sterile and with a very low or absent endotoxin concentration. For parenteral administration a sterile injection in a disposable injection syringe is often filled from a multiple dose solution in a glass vial.

15.4.3.1 Technetium-99m Radiopharmaceuticals

^{99m}Technetium labelled radiopharmaceuticals form a majority within all prescribed radiopharmaceuticals. ^{99m}Tc sodium pertechnetate is used for the labelling of the ligand of choice according to fixed preparation procedures. The ligand is a non-radioactive pharmaceutical substance that is part of a “kit for labelling”. Most kits contain additionally a stannous salt that brings the ^{99m}Tc in the right oxidation state for the radiochemical reaction with the ligand. Sometimes the reaction has to be accelerated by increasing the temperature. Many ^{99m}Tc-labelled compounds are prepared using this technique.

15.4.3.2 PET Tracers

PET imaging is performed with positron emitting radiopharmaceuticals. After collision of the emitted positrons with electrons, pairs of gamma-rays are formed that are detected by the PET camera. The most important PET tracer is ^{18}F-Fludeoxyglucose (^{18}F-FDG) with a physical half-life of 110 min. ^{18}F-FDG is nowadays synthesised by nucleophilic substitution of the precursor mannose triflate using fully automated synthesis procedures and cyclotron-produced ^{18}F-fluoride ions. After purification the resulting

^{18}F-FDG is diluted with saline, sterile filtered and dispensed in multiple dose vials or in syringes.

Because FDG accumulates in tissues with a high glucose uptake, ^{18}F-FDG can be used for the imaging of tumours, for the tracing of infections and for neuroimaging. ^{18}F-FDG is also useful for monitoring of therapy response.

15.4.3.3 Complex Parenteral Radiopharmaceuticals

Some radiopharmaceuticals are rather complex dosage forms. Radiolabelled nanospheres, nanoparticles, nanocolloids, peptides, monoclonal antibodies and glass particles for radioembolisation are a few examples. Also autologous blood cells can be radiolabelled, outside or inside the body. The radiolabelling of blood cells is used in routine practice.

15.4.4 Oral Radiopharmaceuticals

Oral radiopharmaceuticals are administered as gelatin capsules. Absorption after oral use is relatively slow so it will take time before the content is distributed in the body and delivered to target organs or tissues (the bone, the heart, the thyroid, brain etc.).

^{123}I and ^{131}I Sodium iodide are examples of radiopharmaceuticals that can be administered in capsules for oral administration.

15.4.5 Radiopharmaceuticals for Inhalation

Some radiopharmaceuticals are administered by inhalation in the form of a radioactive gas. ^{81m}Krypton is an example of a gaseous inhalation radiopharmaceutical that is used in inhalation or ventilation/perfusion studies.

15.5 Legislation

15.5.1 Sources of Legislation

Since radiopharmaceuticals are medicines, the purchasing, preparation, quality control and handling are subject to the same legislation and guidelines as other medicines (see Sect. 35.5). However, radiopharmaceuticals are regulated as radioactive substances as well. Therefore, two sources of legislation: medicine legislation and nuclear safety regulations (e.g. nuclear energy legislation) are applicable. Sometimes this can lead to conflicting situations, see Sect. 15.6.3 for the discussion about pressure hierarchy in pharmaceutical clean rooms, where GMP rules demand relative overpressure and radiation safety rules ask for relative underpressure. The most important regulations for the (small scale) preparation and dispensing of radiopharmaceuticals are summarised below.

15.5.2 Radiopharmaceuticals with a Marketing Authorisation

Like other medicinal products, licensed radiopharmaceuticals are covered by EU Directive 2001/83/EC [5]. The most important requirements are a marketing authorisation and a manufacturing license.

A marketing authorisation is mandatory for the production of radionuclide generators, radionuclide kits and radionuclide precursors.

15.5.3 Radiopharmaceuticals to be Used in Clinical Trials

For all investigational medicinal products (IMPs) used in a clinical trial EU Directive 2001/20/EC ("Clinical Trial Directive") and GMP Annex 13 are applicable [6, 7], see Sect. 35.5.10. The clinical trial directive has recently been replaced by the new and less stringent EU regulation 536/2014 [8, 9]. In this regulation, GMP and a manufacturing license will no longer be required for the preparation of diagnostic radiopharmaceuticals used in clinical trials when they are prepared in a hospital radiopharmacy from licensed sources and used within the Member State.

15.5.4 Good Manufacturing Practice (GMP)

Annex 3 (Manufacture of Radiopharmaceuticals) is the only part of the GMP framework entirely dedicated to radiopharmaceuticals [10]. Preparation of radiopharmaceuticals using authorised generators and kits is excluded from this Annex. The production of radionuclides in reactors and cyclotrons is a physical process and is regarded as a non-GMP activity. Annex 3 describes general GMP principles (quality assurance, personnel, premises and equipment, documentation, production, quality control, reference and retention samples, distribution) in relation to radiopharmaceuticals. As with other medicinal products, other GMP annexes may be applicable, for instance Annex 1 Manufacture of Sterile Medicinal Products [11].

15.5.5 Product Quality

The General Monograph 0125 Radiopharmaceutical preparations provides general information about the preparation and quality control of radiopharmaceuticals [12]. More

than 65 radiopharmaceutical monographs are available in the Ph. Eur., in which specific requirements are elaborated.

Recently a new General Chapter has been drafted on extemporaneous preparation of radiopharmaceutical preparations [13]. This new chapter will provide minimal requirements for kit-based preparations, PET radiopharmaceuticals and radiolabelled blood cells. As with all General Chapters it will not be obligatory, unless mentioned in a product monograph.

15.5.6 Extemporaneously Prepared Radiopharmaceuticals

Legislation for extemporaneous preparation of radiopharmaceuticals is in principle not different from extemporaneous preparation in general (Sect. 35.5). There is a great variation in interpretation and approach in Europe [14]. In some countries radiopharmaceuticals are prepared based on the pharmacy status of the radiopharmacy unit. In other countries radiopharmaceuticals are prepared in laboratories, in university institutions or research laboratories without pharmacy status, with authorisation based on radiation protection legislation only.

Anyway, several guidance documents are available, which can be used as standards. The European Association of Nuclear Medicine (EANM) issued guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals [15, 16]. In these guidelines GMP and radiation safety requirements are interpreted for radiopharmaceuticals not intended for commercial purposes.

Annex 3 of the PIC/S guide to good practices for preparation of medicinal products in healthcare establishments interprets GMP issues for the small-scale preparation of radiopharmaceuticals [17] (see also Sect. 35.5.5).

15.5.7 Legislation on Radiation Protection

Directive 96/29/EURATOM (Basic safety standards) provides safety standards for the protection of health workers and the general public against the dangers of ionising radiation [18]. Directive 97/43/EURATOM (Medical exposure directive) gives rules concerning radiation in relation to medical exposure and provides dose limits [19].

The International Commission on Radiological Protection (ICRP) has issued many recommendations and guidance documents on radiation protection. In addition to European legislation, national and local provisions can be applicable.

Radiation safety is based on general occupational safety and health risk mitigation principles (see also Sect. 26.7): justification (of the use of ionising radiation), ALARA (as low as reasonably achievable; this means aim for the lowest possible exposure) and exposure limits (dose limits for ionising radiation).

15.5.8 Interpretation of Legislation

It is not easy to interpret all above mentioned legislation and to give uniform guidance for each country and each situation. The determination of adequate quality assurance measures, for example the GMP-classification of the clean room, should be the result of a risk assessment [20]. Table 15.2 gives a practical overview of the applicable guidance and the appropriate quality assurance level when preparing radiopharmaceuticals.

15.6 Preparation and Dispensing

15.6.1 Location of Preparation

Preparation and dispensing of radiopharmaceuticals is limited to dedicated radiopharmacies. Radiopharmaceuticals for patient use are usually prepared, controlled and dispensed in a hospital radiopharmacy department, but can also be dispensed on a named patient base by a centralised radiopharmacy ('compounding centre') that operates on a commercial basis or by a centralised hospital pharmacy. The hospital (radio)pharmacist has the final responsibility for the quality of radiopharmaceuticals, also when purchased from an external (commercial) site. The responsible hospital pharmacist has to audit the external site and obtain a quality agreement, clarifying the mutual responsibilities.

Since radiopharmaceuticals are only used in a hospital setting and usually have very short shelf lives, radiopharmacies are often located in or nearby a hospital or imaging centre. Only for radiopharmaceuticals with a longer radioactive half-life the preparing radiopharmacy might be located at longer distance. Some PET radiopharmaceuticals with a very short half-life require the presence of both a cyclotron and a radiopharmacy in the neighbourhood of the imaging centre. ^{82}Rb is a PET radiopharmaceutical that must be prepared in a dedicated rubidium generator next to the patient because of its very short half-life.

Radiopharmaceuticals must be handled (often aseptically) as quickly as possible to avoid unnecessary exposure to radiation.

15.6.2 Prescription and Dose

Diagnostic radiopharmaceuticals are given in extreme low doses in order to minimise radiation exposure. This can be

Table 15.2 Overview of the guidance and main quality assurance issues of the different steps in the extemporaneous preparation of radiopharmaceuticals

Type of activity/ process	Guidance	GMP-classification	Quality control	Microbiological control	Local validation and product dossier
A. Obtaining a radionuclide					
Elution of a licensed generator (in particular, the Mo/Tc-generator)					
Aseptic handling	National guideline	Elution in class A; background: at least class D[a]	At the start of every working day; example: ^{99}Mo-breakthrough)	Microbiological monitoring of the eluate	No validation No product dossier
Elution of an unlicensed generator					
Aseptic handling	National guideline	Elution in class A; background: at least class D[a]	At each elution (extent depending on risk assessment)	Microbiological monitoring of the eluate; endotoxins	Product dossier with validation data on elution and QC; supplier assessment
Production of radionuclides using a cyclotron					
High-technologic process	Non-GMP [10]; radiation safety legislation				
Purchase of a radionuclide (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If unlicensed: assay as active substance (raw material)	Not applicable	If unlicensed: supplier assessment
B. Obtaining a pharmaceutical substance to be labelled					
Purchase of a kit (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If unlicensed: assay as an active substance (raw material)	Not applicable	If unlicensed: supplier assessment
Production of a kit or starting materials for preparation of a radiopharmaceutical					
Production from starting materials (regular pharmacy production)	National guideline	Production and filling: class D if terminally sterilised	Every batch	Environmental monitoring; bioburden; endotoxins	Product dossier with validation data on production and QC
C. Obtaining a radiopharmaceutical					
Preparation of a radiopharmaceutical using a licensed kit					
Aseptic preparation	National guideline	Preparation in class A; background: at least class D	Radiochemical purity according to SmPC; periodically, e.g. once a month or at each new batch	Environmental monitoring	No validation No product dossier
Preparation of a radiopharmaceutical using an unlicensed kit					
Aseptic preparation	National guideline	Preparation in class A; background: class D	At each batch; extent depending on risk assessment	Environmental monitoring	Depending on characteristics: radiochemical/ radiopharmaceutical validation of labelling; limited product dossier
Labelling of blood cells and other complex preparations					
Aseptic preparation	National guideline	Preparation in class A; background: at least class D; dedicated premises (preferred) or separation in time to prevent cross contamination	According to SmPC or own method, at each preparation	Environmental monitoring	If licensed: no validation, no product dossier If unlicensed: product dossier with validation data
Synthesis and purification of (PET) radiopharmaceuticals					
Complex radiochemical synthesis and aseptic preparation	GMP Part II and I including relevant annexes	Preparation in class A; background: depending on risk assessment	According to SmPC or own method, at each preparation	Environmental monitoring	If licensed: no validation, no product dossier If unlicensed: product dossier with validation data
Purchase of a ready to use or ready to administer radiopharmaceutical (licensed or unlicensed)					
Administratively	Not applicable	Not applicable	If not licensed: assay as an active substance (raw material)	Not applicable	If not licensed: supplier assessment

(continued)

Table 15.2 (continued)

Type of activity/ process	Guidance	GMP-classification	Quality control	Microbiological control	Local validation and product dossier
D. Aliquoting[b] of a radiopharmaceutical					
Aliquoting of an extemporaneously prepared or ready to use radiopharmaceutical					
Aseptic handling	National guideline	Aliquoting in clean environment, if administered within 8 h	Not applicable	Not applicable	No validation No product dossier
E. Preparation of a radiopharmaceutical for use in clinical trials[c]					
One or more of the abovementioned	GMP annex 3, 1 and 13	Preparation: class A; background: classification depending on risk assessment	According to IMPD, at each batch, release by QP	Environmental monitoring, extent depending on risk assessment	Manufacturing license required; IMPD with validation data required

[a]Generators for very short living radionuclides (for example a $^{82}Sr/^{82}Rb$-generator) are situated next to the patient, in an unclassified background. The eluate is transferred directly into the patient
[b]Aliquoting is individual dose dispensing from a multidose vial
[c]New clinical trial regulation is less stringent for diagnostic radiopharmaceuticals [9]

achieved by extending the imaging time of the camera. For therapy or palliation (e.g. thyroid gland, bone metastases) higher dosages of radionuclides with high energy transfer are applied.

Diagnostic as well as therapeutic radiopharmaceuticals are prescribed as medicines. The radioactive dosage is usually calculated on the basis of the body weight or (in therapy) the weight and shape of the target organ.

After verification and acceptance of the prescribed dose the prescription is transformed into a standardised preparation instruction (see Sect. 33.5). The requested dose is always corrected upwards for decay of the radionuclide during the time from preparation until administration to the patient.

15.6.3 Layout of the Radiopharmacy Department

For the design of premises reference is made to Sect. 27.2, including aseptic processes and the pressure conflicts that may occur when product safety as well as personnel safety have to be dealt with. A typical radiopharmacy department consists of one or more clean rooms, a quality control room and adjacent rooms such as locks for people and goods, a room for administration/storage, a room for cleaning materials and a waste disposal room [1, 2, 21]. Often the radiopharmacy department is called hot lab, while this term originally refers to the room(s) where radioactive materials are handled.

Ideally the radiopharmacy department in a hospital is situated next to or integrated in the nuclear medicine department. Restricted access to the radiopharmacy department must be assured for both radiation protection and GMP reasons.

The requirements for radiation safety (nuclear energy regulations) as well as aseptic processing (GMP guidelines) must be met. For radiation safety the pressure within the rooms of the radiopharmacy department where radioactive material is processed must be negative relative to the outside world. The level of underpressure needed in the preparation room depends on the maximal amount of radioactivity present in operation and must meet local regulations. A pressure difference of −10 Pa relative to the outside world is a typical value for a radiopharmacy clean room where kits are being labelled and PET radiopharmaceuticals are being handled. However, for the maintenance of aseptic circumstances GMP requires that the pressure in this room must be 10–15 Pa higher than in adjacent rooms of a different GMP class. The airflow must be directed from the cleanest environment towards less clean areas.

The classification of the clean room for preparation of radiopharmaceuticals should be the outcome of a risk assessment and could be class B, C or D [11, 16, 17]. The risk assessment should take into account the use of closed systems, the time between preparation and use and the nature of the product. The critical working zone should be class A and can be realised with a radiopharmacy safety cabinet, an isolator or a hot cell (see Sect. 15.6.4). A compromise to respond to these demands could be an extra airlock between the clean room clothing area (first lock) and the preparation clean room [21]. The first lock has an overpressure of 10–15 Pa to the outside world for keeping out particulate matter (product protection). The second lock has an extra underpressure of −10 to −15 Pa relative to the clean room to realise a deep underpressure (the so-called sink) for radioprotection and ‘GMP-overpressure’ of 10 to 15 Pa between the clean room and this extra lock. See also Fig. 27.1.

In some situations a simpler air pressure regimen, for example an underpressured isolator in an overpressured

clean room might be sufficient to meet all regulations [21]. However, this is subject to local requirements.

The pressure cascade inside the radiopharmacy premises has to be controlled, monitored and documented.

It should be stressed that pressure differences are not a guarantee for safe working conditions. Spreading of radioactivity can easily take place by contaminated shoes, gloves or materials, which only can be prevented by a safe working procedure.

Similarly to conventional clean rooms, qualification and periodic requalification of the clean room conditions, the aseptic workstations and personnel have to be carried out.

The scale-size, organisation and facilities of the radiopharmacy depend on the size and the demand of the nuclear medicine department and can range from simple dispensing of commercial available radiopharmaceuticals to complex synthesis of short-lived PET-radiopharmaceuticals.

In most radiopharmacy departments one or two ^{99m}-technetium generators are in place.

In larger departments facilities for the synthesis of PET radiopharmaceuticals are available for which a local cyclotron may be needed. The use of PET tracers may have advantages in terms of speed, image resolution and radiation burden. Reasons for installing a local cyclotron are the extent of PET diagnostics and research, the demand for very short-lived PET radiopharmaceuticals (e.g. based on ^{13}N and ^{15}O) and the lack of FDG availability from commercial suppliers.

In some departments facilities are in place for the labelling of peptides or proteins (e.g. antibodies) and blood cells. When handling blood cells cross contamination or mix-up must be prevented by working in a separate dedicated room.

15.6.4 Equipment in the Radiopharmacy

A radiopharmacy has dedicated equipment for synthesis, preparation and quality control of radiopharmaceuticals. The workbench for the safe and aseptic preparation of radiopharmaceuticals is often a sufficiently lead shielded radiopharmacy safety cabinet with downflow HEPA filtered laminar air providing a GMP class A working zone. The exhaust air is filtrated and expelled outside the radiopharmacy to the roof on top of the building. The cabinet has built-in radiation protection by installed lead plates in the walls and in the working field, a horizontally movable lead containing glass window, lead shielded instruments for radiation measurement and waste containment and special equipment for automatic preparation and dispensing such as a barcode scanner, printer, screen and mouse pad.

A hot cell is a lead shielded locked containment chamber with underpressure, often used for handling highly radioactive radionuclides and products. Hot cells are usually equipped with manipulators to perform all operations by an operator from outside or a robot inside. When the chamber is a GMP class A working zone, the material is introduced by the operator from a separate class B chamber, giving access to the class A working area. Materials enter the class B chamber from a GMP class C clean room environment.

An isotope dose calibrator is shaped as a cylinder and is often built in beneath the working area in the safety cabinet. It measures the radioactivity of a prepared dose in a vial or syringe. Each individual radionuclide can be measured accurately. Other equipment to measure radioactivity are scintillation counters (e.g. the NaI well counter) and semiconductor-based instruments (e.g. the Germanium detector).

A survey counter is a gas filled detector used to detect spilled radioactive materials that can be hazardous for the operators or may disturb accurate dose measurements. Survey counters can be mounted at critical places to measure the radiation level in rooms continuously. A hand-foot-clothing monitor is a suitable and obligatory instrument to detect possible contamination before leaving the area where radioactive materials are handled.

A thin layer chromatography (TLC) scanner is used for the quality control of a radioactive labelled product. It firstly separates the different radiochemical forms by chromatography and subsequently measures the radiation of the spot of the intended radiopharmaceutical and the unwanted by-products (see Sect. 15.6.7 quality control).

A fume cupboard provides safe working conditions when heating is needed, as some radiopharmaceuticals must be heated in a water bath for some time to finish the labelling. A fume cupboard is also used with the preparation of radioactive diagnostic pancakes and when working with organic volatile solvents as in thin layer chromatography for the quality control of radiopharmaceuticals.

15.6.4.1 Radionuclide Generators

Radionuclide generators are loaded by the manufacturer with a mother radionuclide. This radionuclide decays continuously to a daughter radionuclide with suitable properties for the preparation of radiopharmaceuticals. These generators can be used on site for a period of a week to several months, depending on the type of generator [1, 2].

The radiopharmacist is responsible for the proper use and pharmaceutical quality of radionuclide generators. Most radionuclide generators have to be eluted with a non-radioactive infusion fluid such as sterile sodium chloride 0.9 %. The most commonly used generator is the ^{99}Mo/^{99m}Tc- generator, which is described more in detail.

15.6.4.2 ^{99}Molybdenum/^{99m}Technetium Generator

The daily preparation of ^{99m}Tc-compounds requires the use of a ^{99}Mo/^{99m}Tc generator (see Fig. 15.1). A technetium

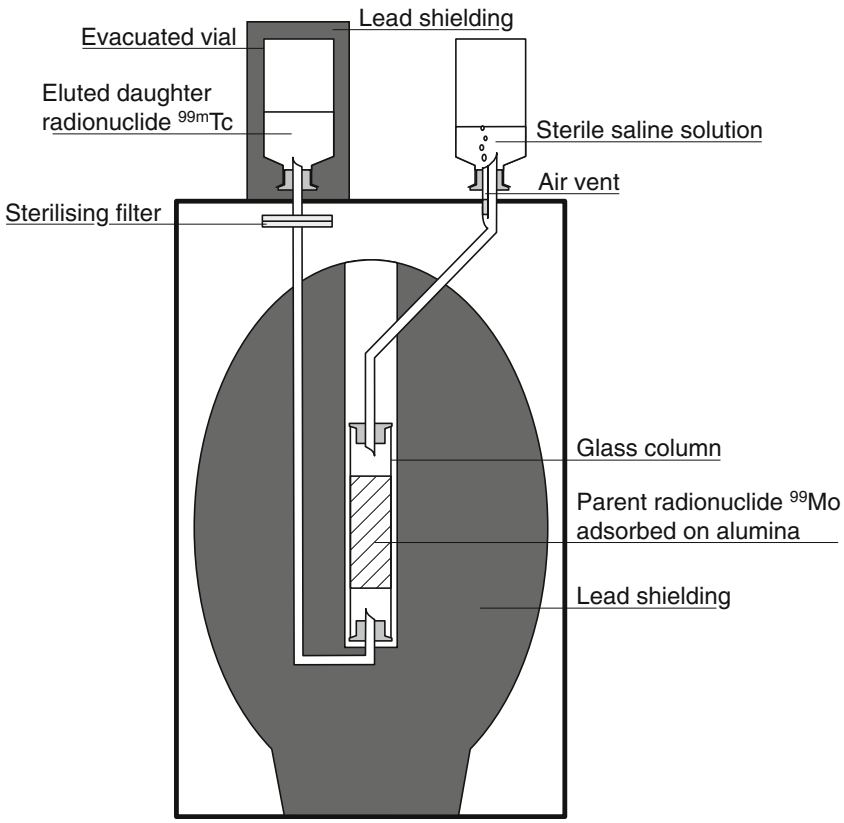

Fig. 15.1 Structure of a ^{99}Mo/^{99m}Tc generator. ©P.M.Berkemeyer

generator is made up of a glass column containing the reactor fission product molybdenum-99 adsorbed on alumina. ^{99}Mo has a half-life of 66 h and decays to ^{99m}Tc having a half-life of 6 h. The glass column is fitted within a lead container for radiation protection. The ^{99m}Tc is eluted from the column by a sterile saline solution into an evacuated sterile empty glass vial. The underpressure in the evacuated vial is the driving force. The resulting sterile solution of sodium pertechnetate is called the eluate. The sterile eluate can be used for radiolabelling of ligands or for preparation of a solution for injection. The ^{99m}technetium generator is typically eluted once or twice a day. After elution, the ^{99m}Tc-activity has to build up again by decay of the mother radionuclide to the daughter radionuclide. After delivery from the supplier the new generator has the highest activity, every day the activity decreases. After 1–2 weeks, the generator is returned to the reactor site for regeneration.

The quality of the generator system should be monitored every working day. Quality control consists of performing the ^{99}Mo breakthrough test (radionuclidic purity) and assaying the aluminium content, the pH, sterility and endotoxin level of the eluate. The radiochemical purity test is a routine test to quantify the different (wanted and unwanted) chemical forms of the radionuclide (e.g. $^{99m}TcO_4^-$ and $^{99m}TcO_2$). Not all above mentioned tests have to be performed on a daily basis. The extent and frequency of quality control of generator systems has to be determined by risk assessment.

15.6.5 Preparation and Handling

Radiopharmaceuticals for use in a hospital are prepared or aliquoted, labelled and dispensed for each individual patient. Usually no stock production or storage of radionuclides takes place in the radiopharmacy because of their short shelf lives due to radioactive decay. Most radiopharmaceuticals are administered within a working day.

The preparation and aliquoting of radiopharmaceuticals can be performed by pharmacy technicians, nuclear technicians or analysts, but is always the responsibility of a (radio)pharmacist. Gowning with clean room clothing is similar to gowning for other clean rooms (see Sect. 31.3.4). Disposable gloves are used in all rooms where radioactive materials are handled to prevent radioactive contamination of the hands. Personal dosimeters must be worn during all operations with radioactive materials. When handling radioactive materials, exposure must be minimised by limiting the handling time, maximising the distance to the source (e.g. by using a tong or forceps) and the use of shielding.

Most radiopharmaceuticals are administered intravenously and must therefore be sterile. Since terminal

sterilisation is usually not possible due to the radionuclide's short half-life, these products have to be prepared following aseptic procedures. The most appropriate procedure is the closed system technique. In this procedure the starting materials and medical devices are sterile and processed in a clean room without direct contact with the environment.

The most common preparation process is the so-called kit preparation, which comprises the following steps:

- Aseptical elution of the generator.
- Quality control of the eluate (see Sect. 15.6.7).
- Aseptic transfer of a measured eluate dose to the kit vial for incubation; the radiopharmaceutical is synthesised, sometimes under heating.
- Quality control of the radiopharmaceutical (see Sect. 15.6.7).
- Aliquoting (aseptic transfer of the radiopharmaceutical) into ready to administer dosage delivery devices. This includes the measurement of the calculated dose taking into account the half-life of the radionuclide and the time up to administration.
- Release and dispensing (see Sect. 15.5.7).

The reconstitution and quality control should follow the instructions of the manufacturer, the Ph. Eur. monograph or a locally validated preparation process and assay.

Just as with other aseptic preparation processes, a program of environmental monitoring and personal qualification for aseptic operation has to be carried out, see Sect. 31.6.

15.6.5.1 Radioactive Stock and Waste Management

At all times the identity and amount of radionuclides and radiopharmaceuticals in the radiopharmacy department must be known. This also applies to the radioactive waste. All places where radioactive materials (including waste) are stored must be protected from fire and unauthorised access.

Radioactive waste is produced in everyday practice within the radiopharmacy department as part of the preparation process. Examples are radioactive needles and syringes, residuals in vials and radioactive tissues.

In case of spilling radioactive materials, a safe procedure has to be followed to remove them. This leads to an extra amount of radioactive waste.

Radioactive waste must be sorted by the half-life of the radionuclide so that it can be stored separately. Radioactive waste from short-lived radionuclides is often disposed of by the so-called decay in storage method. The waste is set apart for a certain time period and the residual radioactivity is measured. If the level of radioactivity is as low as the background, the material can be seen as normal hospital waste and is disposed of in closed hospital waste containers. The waste of short-lived radionuclides can often be stored during the working day in a lead shielded container, built in the safety cabinet. Longer living radionuclides must be stored in dedicated lead shielded storage cabinets that may be placed in a separated waste disposal room with negative pressure. Also expired generators may be stored there, waiting for transportation. An authorised firm can take the longer living radioactive residuals to a special storage site.

15.6.6 Packaging and Labelling

Like other preparations, radiopharmaceuticals must be labelled with the required information. In most situations, the label has to be attached to the shielding needed for radiation protection.

Apart from the general requirements (see Sect. 37.3) the label has to bear the following items:

- Dose in combination with the calibration time (usually the time of administration)
- Radioactivity symbol

15.6.7 Quality Control and Release

The necessity and extent of quality control of radiopharmaceuticals depends on the situation.

The quality assurance and quality control of commercially available radionuclides, non-radioactive labelling kits and ready-to-use radiopharmaceuticals as well as their release are the responsibility of the manufacturer.

The quality assurance, quality control and release of radiopharmaceuticals prepared in the radiopharmacy and their radionuclide precursors are the responsibility of the radiopharmacist.

Sometimes real time or complete quality control is not reasonably possible, especially when the radioactive dose is extremely high (e.g. loading of generators with mother radionuclide) or when the half-life of the radionuclide is very short. In those cases all feasible quality control tests are finalised after release, but always before administration to the patient. This two-step release requires a strict recall procedure in order to prevent administration when the delayed quality control results do not meet the requirements.

The frequency of quality control of hospital prepared radiopharmaceuticals may be determined on the basis of a risk assessment. When using licensed generators and kits a quality control may be limited to the first vial of every new batch, for example.

Quality control tests can be divided in physico-chemical tests (mainly radionuclidic and radiochemical purity) and biological tests (sterility, endotoxins).

A visual assessment of the appearance of the product (e.g. the colour or clarity of the solution) may be difficult because of the radiation protection (e.g. lead glass). A visual

check of the radioactive solution without radiation protection may be too dangerous. Preparations containing colloids are not clear.

15.6.7.1 Radionuclidic Purity

A radiopharmaceutical has adequate radionuclide purity when the fraction in the form of the wanted radionuclide is high enough to meet the specifications. Impurities in the finished radiopharmaceutical may arise from impurities in the target material or from fission in the reactor. Radionuclide generators could also release unwanted impurities, for example the mother nuclides. When using a ^{99m}Tc-generator the ^{99}Mo breakthrough has to be measured in the eluate. In the eluate of a ^{82}Rb-generator ^{82}Sr and ^{85}Sr breakthrough have to be checked. Impurities must be limited because they may impart the quality of scintigraphic images. In case of different biodistribution of the impurities this also may lead to increased radiation dose to the patient, which is of course undesirable and unacceptable.

15.6.7.2 Radiochemical Purity

A radiopharmaceutical has adequate radiochemical purity when the fraction in the form of the wanted chemical form is high enough to meet specifications. Radiolysis (degradation due to own radiation) and the usual factors that affect stability (light, oxidation, reduction, pH shifts), may cause incomplete or slow labelling, degradation and create radiochemical impurities. Thin layer chromatography is the most widely used technique for the analysis of radiochemical purity. HPLC techniques may also be used, for instance for the assessment of the radiochemical purity of PET radiopharmaceuticals.

15.6.7.3 Non-radioactive Impurities

Sometimes non-radioactive impurities are present in radiopharmaceuticals or their precursors. To avoid undesired effects of these impurities (instability, sometimes toxicity) their content should be limited. Limits of well-known impurities can be found in Ph. Eur. monographs.

15.6.7.4 Sterility

Finished parenteral products prepared in the radiopharmacy department must be sterile. Based on a risk analysis one may conclude that the risk of non-sterility is very low for standard radiopharmaceutical kit preparations. The risk of contamination is somewhat higher for the eluate from radionuclide generators, especially when they are used for a long period. The injection bottle on top of a ^{99m}Tc generator (sterile sodium chloride solution for injection) is changed aseptically each day; however, the inside of the generator system is not sterilised nor disinfected. For that reason it is recommended to control the microbiological quality of the generator system on a regular basis. For a ^{99m}Tc generator system this can be done at the end of the life cycle. Small volumes of the eluate are used for assuring the microbiological quality of the generator system and its elution process.

15.6.7.5 Endotoxins

The Ph. Eur. gives limits for radiopharmaceuticals in general but for some individual radiopharmaceutical preparations as well. In most radiopharmacy departments the endotoxin content of radiopharmaceutical preparations is not tested before injection. In some situations, e.g. development of a new preparation process or when using generators for longer periods of time (weeks to some months) endotoxin testing may be useful (see further Sect. 19.3.4).

15.6.7.6 Quality Control of Purchased Ready to Use Preparations

If purchased radiopharmaceuticals are used without further processing (e.g. ^{99m}Tc-radiopharmaceuticals in syringes, ^{18}F-FDG in syringes or vial, ^{123}I in capsules), their receipt and supply to the nuclear medicine department is an administrative process. On receipt the certificate of analysis is checked under responsibility of the pharmacist and the radiopharmaceuticals are registered. In most situations no physical or chemical quality control is necessary. It is important to purchase only from a certified supplier. However, auditing and qualifying the supplier may be necessary.

References

1. Saha GB (2010) Fundamentals of nuclear pharmacy, 6th edn. Springer, New York
2. Theobald T (ed) (2011) Sampson's textbook of radiopharmacy, 4th edn. Pharmaceutical Press, London
3. Hesslewood SR, Keeling DH (1997) Frequency of adverse reactions to radiopharmaceuticals in Europe. Eur J Nucl Med 24(9):1179–82
4. Schreuder N (ed) (2013) Radiofarmaca Medicatiebewaking. www.radiofarmacie.nl
5. The European Parliament and the Council of the European Union (2001) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union L(311):67–128
6. The European Parliament and the Council of the European Union (2001) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Off J Eur Union L(121):34–44
7. European Commission. Eudralex Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use – Annex 13 Investigational Medicinal Products. http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf. Accessed 14 July 2014

8. Decristoforo C, Peñuelas I, Elsinga P, Ballinger J, Windhorst A, Verbruggen A et al (2014) Radiopharmaceuticals are special, but is this recognized? The possible impact of the new Clinical Trials Regulation on the preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging 41:2005–2007
9. European Parliament and Council of the European Union (2014) Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Off J Eur Union L(158):1–76. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=EN. Accessed 14 July 2014
10. European Commission. Eudralex Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use – Annex 3 Manufacture of Radiopharmaceuticals. http://ec.europa.eu/health/files/eudralex/vol-4/2008_09_annex3_en.pdf. Accessed 14 July 2014
11. European Commission. Eudralex Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use – Annex 1 Manufacture of Sterile Medicinal Products. http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf. Accessed 14 July 2014
12. Ph. Eur. Radiopharmaceutical preparations 01/2014:0125. European Pharmacopoeia, 8th edn. Council of Europe, Strasbourg
13. EDQM (2014) General Chapter 5.19. Extemporaneous preparation of radiopharmaceutical preparations. Pharmeuropa 26:1–10. http://pharmeuropa.edqm.eu/TextsForComment/NetisUtils/srvrutil_getdoc.aspx/0L3atCJKrELmrCJamC4KkQ7Hj//51900E.pdf. Accessed 14 July 2014
14. Decristoforo C, Peñuelas I (2009) Towards a harmonized radiopharmaceutical regulatory framework in Europe? Q J Nucl Med Mol Imaging 53:394–401
15. EANM Radiopharmacy Committee. Guidelines on current good radiopharmacy in the preparation of practice radiopharmaceuticals. http://www.eanm.org/publications/guidelines/gl_radioph_cgrpp.pdf. Accessed 14 July 2014
16. Elsinga P, Todde S, Peñuelas I, Meyer G, Farstad B, Faivre-Chauvet A et al (2010) Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging 37(5):1049–62
17. Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme. PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments. PE 010–4. http://www.picscheme.org/publication.php?p=guides. Accessed 14 July 2014
18. Council of Europe (1996) Council Directive 96/29/EURATOM of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation. Off J No L 159:1–114
19. Council of Europe (1997) Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom. Off J No L 180:22–7
20. Lange R, Ter Heine R, Decristoforo C, Peñuelas I, Elsinga PH, Van der Westerlaken MM, Hendrikse NH (2015) Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach. Nucl Med Commun 36(5):414–422
21. Technologists Committee EANM. The Radiopharmacy – A Technologist's Guide. http://www.eanm.org/publications/tech_guidelines/docs/tech_radiopharmacy.pdf. Accessed 14 July 2014