



RADIOPHARMACEUTICALS
SUPPLEMENTARY INFORMATION
Final text for addition to *The International Pharmacopoeia*
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Texts within this section of *The International Pharmacopoeia* do not constitute part of the standards of the Pharmacopoeia. They consist of explanatory and other supplementary texts provided for guidance and information of users of *The International Pharmacopoeia*.

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Introduction

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis and/or therapy.

The facilities and procedures for the production, use, and storage of radiopharmaceuticals are subject to licensing by national and/or regional authorities. This licensing includes compliance both with regulations governing pharmaceutical preparations and those governing radioactive materials. Additional regulations may apply for issues such as transportation or dispensing of radiopharmaceuticals.

Each producer or user must be thoroughly cognizant of the national requirements pertaining to the articles concerned. Regulations concerning pharmaceutical preparations include the application of current Good Manufacturing Practices (GMP). Guidelines are available in Quality assurance of pharmaceuticals, Volume 2: Good manufacturing

practices and inspection (WHO, Geneva, 2004); for the current WHO recommendations consult the WHO Medicines website (<http://www.who.int/medicines>). Regulations governing radioactive materials include those on safe handling and production of radioisotopes. See International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (IAEA, Vienna, 2003, CD-ROM Edition) Safety Series No. 115/CD, Radiological Protection for Medical Exposure to Ionizing Radiation Safety Guide (IAEA, Vienna, 2002) Safety Standard Series No. RS-G-1.5 and the Operational Guidance on Hospital Radiopharmacy : A Safe and Effective Approach (IAEA, Vienna, 2008 - http://www-pub.iaea.org/MTCD/publications/PDF/Pub1342_web.pdf). Consult the IAEA website for the current Safety Standards and publications (<http://www-ns.iaea.org/standards/>).

Safety considerations

Radiopharmaceuticals are radioactive and can pose a risk to the personnel involved in handling them during *inter alia* manufacture, storage, transport, compounding, testing, dispensing and administration, to the patients to whom they are administered and to the environment.

All personnel involved in any part of the above operations are required to have appropriate specific additional training. All personnel with access to the areas where these operations are carried out, for example, maintenance and support staff such as cleaners should receive specific instruction and appropriate supervision whilst in the operational areas. Risk to patients should be minimized. It is essential to ensure that reproducible and clinically reliable results will be obtained. All operations should be carried out or supervised by personnel who have received expert training in handling radioactive materials.

Specialized techniques are required to minimize the risks to personnel. All procedures in which radiopharmaceuticals are handled must be designed and carried out in compliance with the **ALARA principle**, that is to ensure that exposure to radiation is *as low as reasonably applicable*. Three key components of the ALARA principle are **time** (reduce time of exposure), **distance** (the greater the distance, the lower the risk) and **shielding** (appropriate shielding is essential at all stages of handling).

Radiation shielding Adequate shielding must be used to protect all personnel from ionizing radiation. Additionally, when testing radiopharmaceuticals instruments must be suitably shielded from background radiation.

Alpha and beta radiations are readily shielded because of their limited range of penetration, although the production of Bremsstrahlung by the latter must be taken into

account. The range of alpha and beta particles varies inherently with their kinetic energy. The alpha particles are mono-energetic and have a range of a few centimetres in air. The absorption of beta particles, owing to their continuous energy spectrum and scattering, follows an approximately exponential function. The range of beta particles in air varies from centimetres to metres.

The secondary radiation produced by beta radiation upon absorption by shielding materials is known as Bremsstrahlung and resembles soft X-rays in its property of penetration. The higher the atomic number or density of the absorbing material, the greater the energy and probability of the Bremsstrahlung produced. Elements of low atomic number produce low-energy Bremsstrahlung, which is readily absorbed; therefore, materials of low atomic number or of low density, such as aluminium, glass, or transparent plastic materials, are used to shield sources of beta radiation.

Attenuation of gamma radiation in matter is exponential and is expressed in terms of half-value layers. The half-value layer is the thickness of shielding material necessary to decrease the intensity of radiation to half its initial value. A shield of 7 half-value layers is of a thickness that will reduce the intensity of radiation to less than 1% of its unshielded intensity of activity. Gamma radiation is commonly shielded with material of high atomic number such as lead and tungsten.

The intensity of gamma radiation is reduced according to the inverse square of the operational distance between the source and the point of reference. Radioactive materials of several gigaBecquerel (GBq) strength can be handled safely in the laboratory by using proper shielding and/or by arranging for the maximum practicable distance between the source and the operator by means of remote-handling devices.

Preparation of Radiopharmaceutical preparations: Additional guidance

Manufacture of radiopharmaceutical injections

Addition of antimicrobial preservatives As noted in the general monograph radiopharmaceutical injections are commonly supplied in multidose containers. Moreover, the general monograph states that the requirement of the general monograph for Parenteral preparations that such injections should contain a suitable antimicrobial preservative in a suitable concentration does not necessarily apply to radiopharmaceutical preparations. A reason for this exemption is that many common antimicrobial preservatives (for example, benzyl alcohol) are gradually decomposed by the effect of radiation in aqueous solutions. The rate of decomposition is dependent upon a number of factors, including the nature of the radionuclide and the radioactivity concentration of the solution. It is therefore not always possible to prescribe an effective antimicrobial preservative for a radiopharmaceutical injection and for certain preparations the addition of an agent is undesirable.

Compounding

Compounded radiopharmaceuticals are not for sale and are not to be advertised. Compounding includes formulation of radiopharmaceutical reagent kits from raw ingredients for radiopharmaceuticals preparation, adding reagents to approved/unapproved commercial kits to modify or enhance performance of radiopharmaceuticals (shelf life extension, fractionation) and/or synthesis from raw materials. Compounding should follow recognized pharmacopoeial protocols whenever available; approval by institutional committee is otherwise required. The process of compounding radiopharmaceuticals must be under the supervision and responsibility of recognized nuclear physician or suitably qualified professional, ideally a radiopharmacist.

Within the radiopharmaceutical industry the range of associated risk of product failure varies from manufacturing, compounding and dispensing. Compounding is limited to clinical practice according to medical doctor's prescription or requisition for a specific patient. Patent-protected radiopharmaceuticals should not be compounded. When, however, patented reagent kits cannot be readily obtainable from a commercial source, limited compounding shall be done to meet the urgent medical needs of an identified individual patient; in this case the prescriber shall be informed that a reagent kit will be compounded to replace the commercial product. See Operational Guidance on Hospital Radiopharmacy (IAEA, Vienna, 2008) STI/PUB/1342. Consult the IAEA website for other current publications on Nuclear Medicine (including radiopharmaceuticals) (<http://www-pub.iaea.org/MTCD/publications/SubjectAreas.asp>).

Dispensing

Dispensing a radiopharmaceutical preparation is distinct from compounding in that a radiopharmaceutical preparation is prepared with the use of approved/authorized commercially available components. . These usually consist of a kit for radiopharmaceutical preparation together with a radionuclide precursor or an elute from a radionuclide generator . All aspects are undertaken in accordance with the instructions provided by the manufacturers and suppliers of the components.

Testing of Radiopharmaceutical preparations: Additional guidance

End-user testing

End-user testing is an important step in the quality management of radiopharmaceutical preparations and for the safety of patients especially for those radiopharmaceutical preparations that are dispensed or compounded in the end-user facility (for example, nuclear medicine clinics). Application of the tests specified in the relevant monograph may not be possible at this stage either because of the short half-life of the radioisotope or due to other analytical limitations. The use of alternative, simple, tests that adequately identify the radiopharmaceutical preparation is therefore advisable.

Such tests fulfil a similar role to the Basic tests provided for pharmaceutical substances and dosage forms which are published by WHO¹ to provide simple and readily applicable methods for confirmation of identity especially useful when a fully equipped quality control laboratory and/or analytical expertise are not available and when indicative and rapid control is necessary.

¹ For current publications in the series consult the WHO Medicines website (<http://www.who.int/medicines>).

If non-licensed or non-approved/registered radiopharmaceutical preparations under national rules are used, a detailed certificate of analysis or certificate of compliance is essential. In addition, the essential tests which give sufficient assurance of quality must be undertaken to allow safe use in patients.

Thin-layer chromatography of common radiopharmaceuticals

The following table gives an indication of thin layer chromatographic tests that may be suitable as end-user tests for identifying certain radiopharmaceuticals.

In chromatographic tests included within the monographs of the International Pharmacopoeia, the type of TLC plate or coating material to be used is stated but reference to commercial sources of these chromatographic supports is not given within the monograph. Where such information is given in the table below, it is intended to indicate a commercially available material that has been found to be suitable but does not imply that a different but equivalent commercial brand may not be used. Whatever chromatographic support is chosen, the person carrying out the analysis is responsible for ensuring that the chromatographic system is suitable.

Radiopharmaceutical	Stationary phase	Mobile phase	Rf	Rf
			Unbound radionuclide	Bound radionuclide
¹⁴ C-urea	cellulose	butanol-water-acetic acid (12:5:3)	0	0.6
^{123/131} I-hippuran	silica gel	chloroform-acetic acid (9:1)	0.0	0.2-0.3
^{123/131} I-MIBG	silica gel	ethyl acetate-ethanol (1:1)	0.6	0.0
¹¹¹ In-DTPA	ITLC-SG	10% ammonium acetate-methanol (1:1)	0.1	1.0
¹¹¹ In-octreotide	ITLC-SG	0.1 M citrate buffer pH 5	1.0	0.0
¹⁸ F-FDG	silica gel	acetonitrile-water (95:5)	0.0	0.45
¹²³ I- ioflupane	ITLC-SG spot must be dry	chloroform-methanol (9:1)	0.0	1.0
¹²³ I-iomazenil	silica gel	ethyl acetate-ammonia (200:1)	0.0	0.7
¹²³ I-iomazenil	silica gel	chloroform-acetic acid-water (65:35:5)	0.0	0.3
¹³¹ I-iodocholesterol	silica gel	chloroform-ethanol (1:1)	0.0	0.66

Radiochemical Purity Measurement Systems of Radiopharmaceuticals: Thin-layer chromatography of technetium-99m radiopharmaceuticals

Stationary phases:

ITLC-SG	Instant thin-layer chromatography, silica gel, e.g. Pall life Sciences
3MM	Whatman 3MM chromatography paper
No 1	Whatman No 1 chromatography paper
silica gel	Silica gel 60, e.g. Merck
alumina	aluminium oxide, e.g. Bakerflex
cellulose	cellulose, e.g. Merck

Mobile phases:

butanone = 2-butanone = methyl ethyl ketone = MEK
 saline = 9g/l solution of sodium chloride
 1 M sodium acetate = 82 mg/mL anhydrous sodium acetate
 or 136 mg/ml sodium acetate trihydrate
 0.1 M citrate = 21 mg/ml monosodium citrate dihydrate
 1 M ammonium acetate = 77 mg/ml ammonium acetate
 Mixtures of volatile solvents should be made freshly each day

Thin-layer chromatography of technetium-99m radiopharmaceuticals

The following table gives an indication of thin layer chromatographic tests that may be suitable for identifying certain technetium-99m radiopharmaceuticals.

In chromatographic tests included within the monographs of the International Pharmacopoeia, the type of TLC plate or coating material to be used is stated but reference to commercial sources of these chromatographic supports is not given within the monograph. Where such information is given in the table below, it is intended to indicate a commercially available material that has been found to be suitable but does not imply that a different but equivalent commercial brand may not be used. Whatever chromatographic support is chosen, the person carrying out the analysis is responsible for ensuring that the chromatographic system is suitable.

Radiopharmaceutical	Stationary phase	Mobile phase	Rf	Rf	Rf
			RH-Tc (Tc-colloidal)	TcO ₄	Tc-bound
^{99m} Tc-pertechnetate	ITLC-SG	MEK, acetone or saline	0.0	1.0	-
^{99m} Tc-MDP	ITLC-SG or 3MM	MEK or acetone	0.0	1.0	0.0

^{99m} Tc-MDP	ITLC-SG	1 M sodium acetate or saline	0.0	1.0	1.0
^{99m} Tc-DTPA	ITLC-SG or 3MM	MEK or Acetone	0.0	1.0	0.0
^{99m} Tc-DTPA	ITLC-SG or 3MM	saline	0.0	1.0	1.0
^{99m} Tc-colloid	ITLC-SG or 3MM	acetone or saline	0.0	1.0	0.0
^{99m} Tc-DMSA	3MM	MEK or acetone	0.0	1.0	0.0
^{99m} Tc-MAA	ITLC-SG or 3MM	MEK, acetone or saline	0.0	1.0	0.0
^{99m} Tc-pyrophosphate	ITLC-SG or 3MM	MEK or acetone	0.0	1.0	0.0
^{99m} Tc-pyrophosphate	ITLC-SG	Water	0.0	1.0	1.0
^{99m} Tc-HSA	ITLC-SG or 3MM	MEK or acetone	0.0	1.0	0.0
^{99m} Tc-HSA	ITLC-SG strip should be pre-saturated with human serum albumin and dried	ethanol-ammonia-water (2:1:5)	0.0	1.0	1.0
^{99m} Tc-HIG or IgG	ITLC-SG or 3MM	acetone, saline, or 0.1 M citrate	0.0	1.0	0.0
^{99m} Tc(V)-DMSA	ITLC-SG	butanone	0.0	1.0	0.0
^{99m} Tc(V)-DMSA	ITLC-SG	saline	0.0	1.0	1.0
^{99m} Tc(V)-DMSA	silica gel	butanol-acetic acid-water (3:2:3)	0.0	0.8	0.5
^{99m} Tc-IDAs	3MM spot must be dry	butanone	0.0	0.9	0.0
^{99m} Tc-IDAs	ITLC-SG	water or 50% acetonitrile	0.0	1.0	1.0
^{99m} Tc-sestamibi	Alumina Pre-spot with ethanol; do not allow spot to dry	ethanol	0.0	0.0	1.0
^{99m} Tc-tetrofosmin	ITLC-SG spot must be dry	acetone-dichloromethane (35:65)	0.0	1.0	0.5
^{99m} Tc-MAG3	ITLC-SG	ethyl acetate-butanone (3:2)	0.0	1.0	0.0
^{99m} Tc-MAG3	ITLC-SG	50% acetonitrile	0.0	1.0	1.0
^{99m} Tc-exametazime	ITLC-SG	butanone	0.0	1.0	1.0
^{99m} Tc-exametazime	ITLC-SG	saline	0.0	1.0	0.0
^{99m} Tc-exametazime	No 1	50% acetonitrile (freshly prepared)	0.0	1.0	1.0
^{99m} Tc-sulesmurab	ITLC-SG or 3MM	acetone, saline, or 0.1 M citrate solution	0.0	1.0	0.0
^{99m} Tc-depreotide	ITLC-SG	saturated solution of	0.0	1.0	0.0

		sodium chloride			
^{99m} Tc-depreotide	ITLC-SG	1 M ammonium acetate-methanol (1:1)	0.0	1.0	1.0

Substitutions:

- in most cases, 2-butanone (methyl ethyl ketone, MEK) can be substituted for acetone
- in most cases, water can be substituted for saline
- in most cases, Whatman No 1 can be substituted for Whatman 3MM paper
- acid citrate dextrose solution (ACD) can be substituted for 0.1 M citrate
