Chapter 12

RADIOPHARMACY PRACTICES

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Introduction

Ready availability of a good range of radiopharmaceuticals is an important prerequisite for the organization of nuclear medicine service. Table 1 gives details of the radiopharmaceutical preparations which are currently used in nuclear medicine and their main applications.

With the exception of cyclotron-produced short-lived positron emitting radionuclides and their compounds, which are employed in positron-emission-tomography (PET) in advanced countries, all the radiopharmaceuticals listed in this Table are of interest to developing countries for providing cost-effective and practicable diagnostic and therapeutic nuclear medicine procedures.

The major part of nuclear medicine applications - covering more than 80% of all in-vivo applications - is accounted for by preparations of ^{131}I and $^{99}Tc^{m}$. The favourable nuclear characteristics of ^{131}I and $^{99}Tc^{m}$ and the versatile chemistry of the elements I and Tc, have enabled the development of many labelled compounds, and have given the pride of place for these two radionuclides in radiopharmacy.

Radiopharmaceutical preparations of relatively long-lived radionuclides (with half-lives ranging from few days to few months) are available from many commercial suppliers; in addition, national atomic energy organisations in many countries have undertaken programmes for their production and supply to meet the national needs. $^{99}Tc^{m}$ is available in the form of generators which consist of the parent ^{99}Mo retained on a column of alumina from which the $^{99}Tc^{m}$ is eluted out with normal saline. Other generator systems which enable the separation of the daughter $^{99}Tc^{m}$ from the parent ^{99}Mo by selective solvent extraction or sublimation are also in use in some countries. $^{99}Tc^{m}$ is obtained from the generator in the form of pertechnetate solution; from the pertechnetate the $^{99}Tc^{m}$ is reduced to a lower valency cationic state and is then converted into various labelled pharmaceuticals.

Preparation of short-lived radiopharmaceuticals produced from generators is usually undertaken in the hospital itself in a facility - called hospital radiopharmacy or a centralised radiopharmacy if it caters to the needs of more than one user hospital. Such centralized service may also undertake bulk imports of longer-lived radiopharmaceuticals and radiochemicals, dispensing and dose preparation, preparation of labelled compounds, quality control and training.

This chapter describes the specifications of the commonly used radiopharmaceuticals, preparation of dosage forms of longer-lived products, in-house preparation of "kits" for short-lived generator-produced radiopharmaceuticals, their formulation and quality control. Relevant aspects of good radiopharmacy practice, organisation of a radiopharmacy facilities

are briefly reviewed keeping in view the requirements and conditions prevailing in developing countries.

^{131}I-radiopharmaceuticals

In the initial years of nuclear medicine ^{131}I was the work-horse and radiopharmaceuticals of ^{131}I were more frequently employed than those of any other radionuclide. ^{131}I radiopharmaceuticals are still widely used in many developing countries for imaging with rectilinear scanners which form the main-stay of nuclear medicine in these countries rather than the expensive gamma cameras which are still not available. Sodium iodide ^{131}I in the form of aqueous solution or absorbed on anhydrous sodium phosphate or other suitable absorbent in gelatin capsules is widely used for thyroid investigations and therapy of thyrotoxicosis and thyroid cancer. The specifications and characteristics of these products are given in appendices.

Sodium iodide ^{131}I

Sodium iodide ^{131}I in solution form suitable for oral or intravenous human administration is obtained by chemical processing of reactor irradiated tellurium targets. In addition to ^{131}I, other isotopes of iodine (^{127}I and ^{129}I) are also produced by this irradiation. The formation of these isotopes dilutes the specific activity of the ^{131}I.

Labelled pharmaceuticals of ^{131}I

The ease with which iodine in its oxidised state labels many organic compounds has proved very useful for preparation of many ^{131}I labelled compounds of interest in nuclear medicine. Labelling of proteins is achieved by iodine substitution for hydrogen at the tyrosine unit; the imidazole ring of histidine is also labelled at higher levels of substitution of iodine involving several atoms of iodine per molecule of protein.

Radioisotopes of iodine can also be readily incorporated into many iodo-organic compound (example - Rose Bengal, Hippuran, Diodrast etc.) by exchange of radioiodine for stable iodine. Many compounds whose molecular structure has a double-bond linkage in the carbon chain such as unsaturated fats and fatty acids can be readily iodinated with elemental iodine or iodine monochloride, yielding the diiodo or iodochloro derivatives of these compounds. In the use of these labelled compounds, it is important to ensure that the label remains firmly attached during storage of the product and for the duration of the patient study. The presence of "unbound ^{131}I" is a source of error in tracer investigations using ^{131}I labelled radiopharmaceuticals and it is essential to have quality control analysis to estimate the percentage of free iodine ^{131}I activity in all ^{131}I labelled products.

The specifications and characteristics of the commonly used ^{131}I labelled radiopharmaceuticals are given in Appendices. These products are available in multidose forms from several commercial and other large-scale producers.

$^{99}Tc^{m}$ radiopharmaceuticals

$^{99}Tc^{m}$ is the work-horse of nuclear medicine and is expected to continue to be so in the foreseeable future also.

$^{99}Tc^{m}$ generator

The main source of $^{99}Tc^{m}$ for hospitals is a "generator" or "cow" which consists of a system where the parent ^{99}Mo is retained and the 99mTc is "milked out" at periodic intervals. Two types of generators are commonly used:

(a) The "column generator" which is available from many commercial suppliers and consists of a chromatographic alumina column on which very high specific activity ^{99}Mo (usually produced by the fission of ^{235}U and present in the chemical form of molybdate) - the $^{99}Tc^{m}$ which is produced by the decay of the parent (and present in the form of pertechnetate) is eluted out with normal saline solution.

(b) The "solvent extraction generator" where the parent ^{99}Mo (usually of medium and low specific activity, produced by direct irradiation of natural Mo) in the form of molybdate in alkaline solution is extracted with an organic solvent (usually pure methyl ethyl ketone - MEK) which selectively extracts the pertechnetate. The MEK extract is evaporated to dryness and the pertechnetate is leached out with normal saline solution. Solvent extraction generators for $^{99}Tc^{m}$ are in regular use in a few countries which produce the parent ^{99}Mo using their local irradiation facilities.

The advantageous features of the 'column generator' include ease of operation, rapid recovery of $^{99}Tc^{m}$ with high yield and purity (usually in a sterile, pyrogen-free isotonic saline solution), compact size, attractive presentation and ready availability from many commercial suppliers. The disadvantages include high cost, occasional problems of poor elution yields and impure $^{99}Tc^{m}$ with long-lived radionuclide contamination. In view of the relatively short half-life of the parent ^{99}Mo, regular imports of these generators may pose difficulties of transport delays, in transit decay loss and uncertain availability.

The preparation of column generators involves a very complex technology firstly to produce the parent fission-product ^{99}Mo with high purity and specific activity and, secondly, to fabricate a reliable generator system which will assure a sterile pyrogen free eluate. The production and purification of fission product ^{99}Mo involve the handling of large quantities of long-lived fission product wastes, the storage and disposal of which pose serious problems which may be beyond the infrastructural capability of many developing countries. In view of these disadvantages and problems, many developing countries have focused attention on the development of alternate technologies for $^{99}Tc^{m}$ generators involving the use of low and medium specific activity ^{99}Mo produced by the direct irradiation of natural Mo-containing targets in medium flux research reactors which are available in these countries.

The advantageous features of the solvent extraction technology for $^{99}Tc^{m}$ include low cost of production, since indigenously produced medium and low specific activity ^{99}Mo can be used for the extraction. The process also involves production of the minimum of radioactive waste (essentially only spent ^{99}Mo solution) which does not pose serious problems of storage and disposal. Further, the process yields $^{99}Tc^{m}$ of high radioactive concentration and purity. Several designs of apparatus have been employed in various centres for the solvent extraction process and large centralised generators as well as small portable units suitable for operation in hospital radiopharmacies have been in use. The disadvantages of the solvent extraction procedure include the rather lengthy and complicated operations involved which are time-consuming as against the simple direct elution of the column generator. The possible fire hazard associated with the use of an inflammable solvent such as MEK, and the need to have an adequately ventilated fumehood to evaporate off the MEK phase are other handicaps. The operation of the solvent extraction process demands highly trained personnel. Further, problems have been encountered occasionally due to incomplete evaporation of MEK, formation of labelled organic impurities arising from condensation products of MEK, and poor extraction yields.

Two other types of generators which are under development are of interest to developing countries. The first is based on a low temperature sublimation of technetium oxide from irradiated molybdenum containing targets and the second is based on elution of $^{99}Tc^{m}$ from a matrix containing ^{99}Mo in the form of a gel.

$^{99}Tc^{m}$ labelled radiopharmaceuticals

General aspects

The starting material for the preparation of $^{99}Tc^{m}$ radiopharmaceuticals is $^{99}Tc^{m}$-pertechnetate obtained from a ^{99}Mo- $^{99}Tc^{m}$ generator. Essentially a $^{99}Tc^{m}$ labelled radiopharmaceutical preparation is a compound of Tc or a complex formed with a specific ligand by $^{99}Tc^{m}$ at an oxidation state lower than +7. The exact composition and structure of many of these compounds (complexes) are not known with certainty. Depending on the reaction conditions, in some of the $^{99}Tc^{m}$ -ligand systems several complexes with different biological behaviour may be formed.

In all $^{99}Tc^{m}$ labelling procedures, $^{99}Tc^{m}$ pertechnetate of high purity is reduced to a lower oxidation state using a suitable reducing agent. This is followed by formation of a stable complex(es) with the ligand or by binding to suitable particles etc. The reduction of the $^{99}Tc^{m}$ pertechnetate is advantageously carried out using stannous ions. The high reduction efficiency of Sn(II), ease of handling and low toxicity have made the $^{99}Tc^{m}$- (VII)-Sn(II)-ligand systems the most widely used for labelling.

The sequence of steps in the labelling procedure is:

(a) Preparation of the Sn(II) complex of the ligand,

(b) reduction of $^{99}Tc^{m}O_4$ with the Sn(II) complex with simultaneous binding of the reduced $^{99}Tc^{m}$ to the ligand compound.

Having fixed the amount of the ligand, the other conditions and parameters are carefully standardised to get the optimum labelling yield, radiochemical purity and reproducibility. The important parameters to be optimised include amount of Sn(II), pH of the reaction, effect of trace impurities such as Al(III), MoO4=, H2O2 and ^{99}Tc and heating, if required. At present, there is no simple physicochemical method for separating the different components and polymers arising out of the complexation of $^{99}Tc^{m}$ with various ligands. It has been generally observed that the overall biological distribution and behaviour of the ligand-complex and polymer mixtures obtained under meticulously controlled optimum conditions are adequate for the intended diagnostic applications and a rigorous purification of the labelled complex from small amounts of homologues and polymers is not an essential prerequisite for their clinical applications. It is, however, essential that the reaction conditions are carefully standardised to obtain a product with satisfactory biodistribution in experimental animals. The specifications for the acceptable biodistribution pattern for several $^{99}Tc^{m}$ labelled radiopharmaceuticals are given in appendix. Once these optimum experimental conditions are established, they should be followed carefully with appropriate quality controls on all ingredients used (including the ligands and $^{99}Tc^{m}$ pertechnetate) and analysis of the final product by chromatographic and biodistribution studies.

Labelling kits

The labelled radiopharmaceutical formulations of $^{99}Tc^{m}$ are prepared by reacting the corresponding ligand and other ingredients with the $^{99}Tc^{m}$ pertechnetate obtained in a sterile, pyrogen-free form. The ligand and other ingredients are usually prepared, tested and kept in a ready-to-use form in what are known as "kits". The "kits" contain the required amount of the non-radioactive precursor of the $^{99}Tc^{m}$ radiopharmaceutical along with requisite quantities of sterile, pretested essential ingredients. The kit is designed to enable the simple and convenient preparation of the radiopharmaceutical in a closed system, often by a single-step addition of the pertechnetate $^{99}Tc^{m}$ to the "cold" ingredients contained in a vial.

The most popular form of kits is based on stabilising the stannous ions by freeze drying against air oxidation and hydrolysis. Even though other forms of kits like liquid or frozen solutions under inert atmosphere have also been used, the freeze dried kits have an advantage of their long shelf life, the procedural reliability and ease of reconstitution into a clear solution, or suspension (in case of labelled colloids or particles) suitable for parenteral administration. The long shelf life of the kits, (of the order of 6 months) makes it possible to carry out thorough quality control before human use.

Conveniently formulated freeze-dried kits for the most widely used radiopharmaceuticals of $^{99}Tc^{m}$ are available from many commercial sources. However, they are expensive. In most cases the kit costs constitute about 50% of the total cost of a dose of the radiopharmaceutical for a patient. It is practicable and cost-effective to undertake preparation of kits in a centralized radiopharmacy and the equipment and the facilities for such a programme are not too expensive. (see further under "organization of a central radiopharmacy facility").

Procedures for preparing freeze dried kits for a few $^{99}Tc^{m}$ radiopharmaceuticals have been described in this chapter. The composition of the kit preparations for specific agents described in the literature vary somewhat with respect to the amounts of ingredients, pH, and other additives. Each one of them could result in a product acceptable for the intended use. A comparative study of such procedures with a view to standardisation of a single acceptable formulation has not yet been attempted. The procedures given in this chapter have been used over many years for kit preparation with acceptable results. Nevertheless they cannot be claimed as the only procedures or the best procedures. Similarly, the $^{99}Tc^{m}$ radiopharmaceuticals described here have been included primarily with a view to help radiopharmacists in developing countries engaged in kit preparation to start the programme and produce them with the resources available. It is also to be kept in mind that many of these kits are finding newer applications other than the originally intended ones (such as $^{99}Tc^{m}$ pyrophosphate for myocardial infarct imaging, $^{99}Tc^{m}$ glucoheptonate for lung tumour imaging, and $^{99}Tc^{m}$ DTPA for in vivo labelling of red blood cells). The same logic applies to the analytical procedures described here and variations, such as in chromatographic systems and choice of animals etc. have also been reported.

In-house preparation of kits

General:

The procedures described in this section outline the details of the preparation of kits with a batch size of 100 vials. The batch size can be decreased or increased by proportional decrease or increase in the quantities or volumes of reagents. However, while increasing the batch size over 500 or so it has been observed that special precautions are needed, such as cooling the reaction mixture after addition of stannous chloride, purging with inert gas and dispensing into precooled vials. In-process control of stannous ions becomes particularly important in such batches.

Shelf life of the kits and formulations:

The freeze dried kits obtained by the procedures described usually have a shelf life of six months. However, it would be necessary to determine the shelf life of the kits under local conditions. It is recommended that while undertaking the production of kits, in the initial stages a few kits are retained for collecting stability data on kits. It is also advisable to imitate some improper handling of the kits, as it might occur during transportation or storage, by applying stress conditions such as enhanced temperature or exposure to light of a few batch control samples, and then study the behaviour of the kits under these conditions.

Quality assurance programme in kit preparation:

Since the ingredients of the kits for $^{99}Tc^{m}$ formulations are administered intravenously in humans after the formulation processing, a well designed quality assurance programme should be implemented keeping in mind the scale of operations and their intended use in small volumes, as diagnostic agents. Since $^{99}Tc^{m}$ radiopharmaceuticals contain very low

concentration of ingredients of not well defined molecular structure, an unequivocal analysis with conventional chemical methods cannot be performed. Hence, the quality assurance programme should involve clear description of the raw materials, premises, facilities, and equipment, preparation procedures, product control and documentation. The batch size should include sufficient samples for all the control tests, taking into account the possibility of their repetition. Batch control samples should be maintained through the shelf life of the batch for examining the complaints if any received about the quality of the product. Proper record should be maintained of any complaints of improper quality of the product which should be investigated and remedial measures taken. Similarly the shelf life (in vitro stability) of the $^{99}Tc^{m}$ formulations obtained using the kits is recommended to be determined experimentally using the locally available $^{99}Tc^{m}$ pertechnetate and prevailing conditions. The shelf life indicated in the Chapter are not very rigid and are to be taken as guidelines only.

Kits for individual $^{99}Tc^{m}$ Radiopharmaceuticals.

Only few kit preparations are described in detail below just to give an idea to the reader what is involved in making the kits indigenously. A good chemist or a pharmacist is supposed to make them after an appropriate training. An IAEA TECDOC giving details of preparation of kits currently in use in a nuclear medicine laboratory is under preparation.

Kit for $^{99}Tc^{m}$ MDP Injection

Batch size: 100 (100 ml dispensing solution)

CHEMICALS: The main chemicals used are:

(a) Methylene diphosphonic acid (MDP)

(b) Stannous chloride dihydrate

(c) Hydrochloric acid

(d) 1 N Sodium hydroxide solution

(e) water for injection

(f) Ascorbic acid

ACCESSORIES: The main accessories required for kit preparation are:

(a) Sterilised glassware (beakers, pipettes, measuring cylinders, etc.)

(b) Sterilised vials, split-type rubber closures

(c) Sterilised membrane filtration assembly fitted with 0.22 μm (or 0.45 μm) filter

(d) Aluminium caps

(e) Capping and decapping tools

PREPARATION OF STOCK SOLUTION:

This solution should be prepared just prior to kit preparation

Solution of stannous chloride, 8% (w/v):
400 mg of stannous chloride to be dissolved in 0.5 ml of conc. hydrochloric acid and warmed if necessary to get a clear solution. Final volume to be made to 5 mL with water for injection.

(a) 500 mg of MDP and 50 mg ascorbic acid to be dissolved in 80 mL of water for injection. Some drops of 1 N sodium hydroxide solution to be added to get a clear solution.

(b) 0.60 mL of the stannous chloride solution to be added dropwise to the above solutions.

(c) The pH of the solution to be adjusted to 6 to 7 by dropwise addition of 1 N sodium hydroxide solution.

(d) The final volume to be adjusted to 100 mL with water for injection.

(e) The solution to be sterilised by filtration.

(f) The filtered solution to be dispensed in 1 mL quantities into sterilised vials and fitted with dry sterilised rubber closures.

(g) The vials to be transferred to a freeze-dryer and lyophilized for 24 hours.

(h) The vials to be sealed under vacuum or under dry, filtered nitrogen gas.

(i) The vials to be stored at 2-10°C with the following label affixed to each vial:

Kit for 99mTc MDP Injection Code; ... Batch No.: .... Cons. No.: .... 5 mg of MDP 0.5 mg of $SnCl_2.2H_2O$ 0.5 mg of Ascorbic Acid To be stored at 2-10°C

Kits for other $^{99}Tc^m$ radiopharmaceuticals

Kits for other radiopharmaceuticals of $^{99}Tc^m$ are prepared by a similar stepwise procedure: the quantities of ligand, $SnCl_2$, pH of final solution and dilution are shown in Table II. The main accessories required for kit preparation and the procedures for freeze-drying and labelling of the final vials are as indicated for $^{99}Tc^m$-MDP.

Kit for $^{99}Tc^m$ Sulphur Colloid Injection

Batch size: 100 kits with three components each

CHEMICALS: The main chemicals used are:

(a) Sodium dihydrogen orthophosphate dihydrate

(b) Disodium hydrogen orthophosphate dodecahydrate

(c) Sodium thiosulfate pentahydrate

(d) Hydrochloric acid

(e) 1 M sodium hydroxide solution

(f) Water for Injection

(g) Nitric acid

(h) Rhenium metal

(i) 3.5% Infusion solution of gelatine for intravenous administration

ACCESSORIES: As in the case of MDP kits.

PREPARATION OF STOCK SOLUTION:

(a) 0.3 N Hydrochloric Acid solution:
2.8 mL of conc. hydrochloric acid to be diluted to 100 mL with water for injection.

(b) Solution of Sodium thiosulphate, 10% (w/v):
5.0 gm sodium thiosulphate pentahydrate to be dissolved in about 40 mL of water for injection. Final volume to be made to 50 mL with water for injection.

(c) Solution of Rhenium, 2.0% (w/v):
300 mg of rhenium metal to be dissolved in about 0.3 mL of conc. nitric acid. The solution to be warmed for 4-5 minutes and pH adjusted to about 7 using 1 M sodium hydroxide solution. Final volume to be adjusted to 15 mL with water for injection.

(d) Phosphate buffer, pH 7.4:
13.6 g of disodium hydrogen orthophosphate dodecahydrate and 1.2 g of sodium dihydrogen orthophosphate dihydrate to be dissolved in 80 mL of water for injection. Final volume to be adjusted to 100 mL with water for injection.

KIT PREPARATION:

Component A:

(a) The 0.3 N hydrochloric acid solution (Stock Solution a) to be dispensed in 0.5 mL quantities into sterilised vials and capped with sterilised rubber closures and clean aluminium caps. The vials to be sterilised in an autoclave.

(b) The following label to be affixed to each vial:

> Kit for 99mTc Sulphur Colloid Injection
> Code: ... Batch No.: .... Cons. No.: ....
> Component A (Reaction vial)
>
> 0.5 mL solution of dilute hydrochloric acid
> Expiry date: ....

Component B:

(a) 130 mL of 3.5% (w/v) solution of gelatin for infusion, 15 mL of the solution of sodium thiosulphate, 10% (Stock Solution (b) and 8 mL of the rhenium solution (Stock Solution (c) to be mixed well in a beaker.

(b) The solution to be dispensed in 1 mL quantities into sterilised vials and capped with sterilised rubber closures and clean aluminium caps. The vials to be then sterilised in an autoclave.

(c) The following label to be affixed to each vial:

> Kit for 99mTc Sulphur Colloid Injection
> Code: ... Batch No.: .... Cons. No.: ....
> Component B
>
> 1 mL solution containing gelatine, thiosulphate and perrhenate
> Expiry date: ....

Component C:

(a) The phosphate buffer, pH 7.4 (Stock Solution (d) to be dispensed in 1 mL quantities into sterilised vials and capped with sterilised rubber closures and clean aluminium caps. The vials to be then sterilised in an autoclave.

(b) The following label to be affixed to each vial:

> Kit for 99mTc Sulphur Colloid Injection
> Code: ... Batch No.: .... Cons. No.: ....
>
> Component C
>
> 1 mL phosphate buffer, pH 7.4
> Expiry date: ....

Formulation processing of $^{99}Tc^{m}$ radiopharmaceuticals

Formulation processing of $^{99}Tc^{m}$ labelled radiopharmaceuticals is carried out under aseptic conditions by transferring sterile, pyrogen-free pertechnetate solution into the vial containing the kit ingredients. The contents are mixed well, allowed to stand for a few

minutes in some cases at an elevated temperature. The transfer should be carried out using sterile, preferably disposable syringes and needles. Appropriate radiation shielding should be provided during the operations. The stepwise details of formulation processing for a few $^{99}Tc^{m}$ formulations are given below:

Formulation of $^{99}Tc^{m}$ Sulphur Colloid Injection

(a) Two to three mL of $^{99}Tc^{m}$ sodium pertechnetate injection should be added to Component A containing vial.

(b) To the above vial 0.5 mL of Component B should be added. The contents should be mixed well and heated in a boiling water bath (vent needle without connection to the solution) for about five minutes till a brownish colloidal suspension is formed.

(c) The vial should be cooled and 0.5 mL Component C should be added to the vial and mixed well.

(d) The vial should be fixed with a label with a radioactive symbol and giving the details of the formulation such as:

99mTc Sulphur Colloid Injection Batch No.: .... Date: .... Vol.: .... Activity/mL: .... at ..... Use before ..... hrs. Shake well before use

Formulation of $^{99}Tc^{m}$ DTPA Injection

(a) The kit vial should be allowed to attain ambient temperature after removing from refrigerator.

(b) Two to three mL of $^{99}Tc^{m}$ sodium pertechnetate injection should be added to the kit contents and mixed well. The contents be allowed to stand for ten minutes.

(c) The vial should be fixed with a label with a radioactive symbol and giving the details of the formulation such as:

99mTc DTPA Injection Batch No.: .... Date: .... Vol.: .... Activity/mL: ..... at ..... Do not use later than ..... hrs.

Other generator systems and radiopharmaceuticals derived from these generator-produced isotopes:

The only other generator system of some interest for developing countries is the ^{113}Sn-$^{113}In^{m}$ generator. This generator consists essentially of a column of hydrous zirconium oxide on which high specific activity ^{113}Sn (in the form of a chloro complex) is adsorbed. The ^{113}In activity is eluted out with very dilute HCl (pH N 2.0). The ^{113}Sn break through in an acceptable generator is less than 0.01% ^{113}Sn at the time of elution. The high cost of this generator system and the poor nuclear characteristics of ^{113}In (particularly for use with a gamma camera) have limited the use of this generator system.

In view of the long half-life (115.1d) of ^{113}Sn, the ^{113}Sn-$^{113}In^{m}$ has a useful shelf-life of at least six months. It is necessary to ensure that the generator is protected against microbial contamination during its long shelf-life and the hundreds of elutions which can be performed during its useful life period. It is desirable to house the generator in a laminar air flow (LAF) unit. It is a good practice to elute the generator at least once a week (irrespective of its use) and it is essential that the operating and maintenance instructions for the generator recommended by the supplier are rigorously adhered to. Some suppliers recommend the replacement of the elution tube at intervals (two to three months) because of the possible corrosive effect of dilute HCl on the needle.

Quality control of the ^{113}Sn-^{113}In generator consists of:

(a) Evaluation of ^{113}Sn break through. The permissible limit of ^{113}Sn activity in $^{113}In^{m}$ is not more than 0.3 kBq ^{113}Sn per MBq of $^{113}In^{m}$ at the time of administration. This is estimated by allowing the $^{113}In^{m}$ eluate to decay for 2 days and then evaluating the ^{113}Sn activity by measuring the daughter activity of $^{113}In^{m}$ using a ^{133}Ba reference source. A gamma spectrometer with a single-channel analyzer or a simple gamma scintillation counter may be used for the assay.

(b) Test for zirconium break-through: Soluble zirconium may be eluted out of the generator and the acceptable upper limit is 10 μg per patient dose.

(c) Tests for sterility and apyrogenicity: The $^{113}In^{m}$ eluate should be tested to confirm sterility and apyrogenicity by the standard procedures.

Quality assurance and quality control

General aspects

Quality assurance procedures and quality control measures have to be built into a programme of indigenous production of radiopharmaceuticals. The quality control system should be comprehensive, yet simple, inexpensive and practicable at the level of production

envisaged. The sequence of operations covered under quality assurance and quality control encompass the following:

(a) Control of raw materials (documented specifications, analysis and certification of pooled stocks, periodic analysis of bulk stocks and stability studies while stored under optimum conditions).

(b) In process control and supervision of various production parameters (pH, temperature of reaction, concentration of reactants, role of impurities, etc.).

(c) Control of additives, preservatives, diluents, carriers etc.

(d) Quality control analysis of the final products.

These operations are an integral and essential part of Good Pharmaceutical Practices which are briefly outlined in a subsequent Section.

Quality control of raw materials

The raw materials required for the preparation of medical radioisotopes and radiopharmaceuticals in a hospital radiopharmacy consist mainly of the following:

(a) Miscellaneous chemicals and reagents such as methyl ethyl ketone (MEK) for extraction of $^{99}Tc^{m}$ from molybdate solutions, buffers, ingredients of buffer systems, vehicles, additives, etc.;

(b) Sodium iodide ^{131}I solution, reducing agent free and of high radioactive concentration for the preparation of ^{131}I-labelled radiopharmaceuticals;

(c) Generators of $^{99}Tc^{m}$, $^{113}In^{m}$;

(d) Ligands/ingredients for kit preparation.

Quality Control of Generators

The generators for $^{99}Tc^{m}$ and ^{113}In are generally procured from reputed suppliers who provide their detailed specifications and operating instructions. Typical details of a commercially available generator are given in Appendix X.

Quality controls of such generators consist of the following:

(a) Examination of the label affixed on the package and the package insert (leaflets) giving details of the generator and its operation. The activity of $^{99}Tc^{m}$ expected from the elution of the generator and the characteristics of the eluate should be recorded.

(b) Trial elutions of the generator should be carried out soon after its receipt and also at periodic intervals during its useful storage life to assay or confirm the following:

(i) Clarity of the eluate solution

(ii) Total $^{99}Tc^{m}$ activity and radioactive concentration of the eluate

(iii) Sterility and apyrogenicity

(iv) Suitability of the eluted $^{99}Tc^{m}$ for preparation of labelled radiopharmaceuticals

(v) Adequacy of shielding and integrity of packaging of the generator

When generators based on solvent extraction separation or sublimation of $^{99}Tc^{m}$ are employed, the performance characteristics of these systems and the purity of the separated $^{99}Tc^{m}$ should be ascertained in the same manner.

Similar quality control tests are required to be carried out on $^{113}In^{m}$ generators. In view of the long shelf-life of these generators (six to eight months) it is necessary to carry out analysis of the eluates at carefully scheduled periodic intervals to confirm the purity of the eluted ^{113}In and good performance of the generator.

Quality control of ligands and ingredients used for kit preparation.

The ligands and chemicals used in the kit preparation should be of high purity. However, for many of these ligands it may be difficult to lay down standards specifically for use in kit preparation, since, sufficient data on the effect of trace chemical impurities present in them on the behaviour of $^{99}Tc^{m}$ kit preparations is not available. The general approach adopted here is to use the specifications available in recognised pharmacopia wherever available or the specifications prescribed for AR grade reagents are adopted. In case no specifications are readily available, as in case of a few ligands to be synthesised, the user should lay down their specifications. It may be difficult to carry out confirmatory analysis for such specifications in a small set up for radiopharmaceutical preparation. In such a case the tests may be done in a reputed outside laboratory or alternately materials certified for the purity requirements may be obtained from reputed sources.

The following protocols suggested for the analysis of methylene diphosphonic acid (MDP) could serve as an example of the quality control analysis of ligands used in kit preparation:

Methylene diphosphonic acid (MDP)

(a) white crystalline powder

(b) MW 176.000

(c) melting point: 197-199°C

(d) For kit preparation, a product certified more than 97% purity should be used.

Keeping in mind the final intended use, it is recommended to evaluate the product for its radiochemical purity and biodistribution after having prepared a kit and the corresponding $^{99}Tc^{m}$ radiopharmaceutical.

Quality control of kits.

Quality control of kits includes test of appropriate physical appearance, pH of reconstituted solution, determination of stannous ions, test of sterility and apyrogenicity, as well as in-vitro stability of the $^{99}Tc^{m}$ radiopharmaceuticals. The best proof of their appropriateness with the intended use will be provided by biodistribution studies of the kit-prepared $^{99}Tc^{m}$ radiopharmaceuticals. Specifications for the reconstituted $^{99}Tc^{m}$ radiopharmaceuticals obtained by adding pertechnetate solution to a kit vial, have been published in monographs in pharmacopoeias, e.g. British Pharmacopoeia 1988, European Pharmacopoeia, and the United States Pharmacopoeia (USP XX).

Typical specifications and quality assurance analysis for a kit for $^{99}Tc^{m}$ Sulphur Colloid are outlined below:

Description:

Kit for $^{99}Tc^{m}$ Sulphur Colloid is a set of reagent vials as specified on the labels of the vials. When used with $^{99}Tc^{m}$ sodium pertechnetate for Injection according to the instruction of the kit, these would give a sterile and pyrogen free suspension suitable for imaging the reticuloendothelial system after intravenous injection.

Components of the kit:

Component A:

A vial containing a clear, colourless solution of 0.5 mL of 0.3 N hydrochloric acid

Component B:

A vial containing a clear, pale yellow solution of 29.9 mg gelatin, 10 mg sodium thiosulphate pentahydrate and 1 mg rhenium as sodium perrhenate in 1 mL

Component C:

A vial containing a clear colourless solution of 136 mg Na2HPO4.2H2O and 12 mg $NaH_2PO_4.2H_2O$ in 1 mL

Assay for main ingredients in the vials:

The amount of main ingredients in the components A, B and C will be confirmed by monitoring and double-checking the amount of starting materials used in the kit preparation, and the volumes.

Identification of the kit:

(a) A nonradioactive formulation of the product should be carried out by the procedure described under "formulation" using 0.9% NaCl solution instead of sodium $^{99}Tc^m$ pertechnetate. The resulting product will be a brownish colloidal suspension.

(b) The results of radiochemical purity and biodistribution tests taken together for a $^{99}Tc^m$ sulphur colloid injection prepared with the kit should be taken as an identification test for the kit.

pH: The pH of the nonradioactive preparation should be between five and eight as measured by a pH meter.

Sterility:

Sterility tests should be preformed using a nonradioactive preparation as described above, using sterile pyrogen free 0.9% NaCl solution. The product should be confirmed to be sterile before release for human use.

Pyrogen test:

Pyrogen tests should be carried out on rabbits using an inactive colloid preparation using sterile pyrogen free 0.9% NaCl solution. The product should be confirmed to be pyrogen free before human use.

Formulation of $^{99}Tc^m$ Sulphur Colloid Injection

The formulation should be carried out without opening the kit components and using aseptic practices. The transfer should be carried out using sterile (preferably disposable) syringes and needles. Appropriate radiation shielding should be provided during these operations.

(a) Two to three mL of $^{99}Tc^m$ sodium pertechnetate injection will be added to Component A contained in the vial.

(b) To the above vial 0.5 mL of Component B will be added. The contents will be mixed well and heated in a boiling water bath (with a vent needle without connection to the solution) for about five minutes till a brownish colloidal suspension is formed.

(c) The vial will be cooled and 0.5 mL Component C will be added to the vial and mixed well.

(d) The vial will be fixed with a label with a radioactive symbol and giving the details of the formulation such as:

99mTc Sulphur Colloid Injection Batch No.: .... Date: .... Vol.: .... Activity/mL: .... at ..... Use before ..... hrs. Shake well before use

Description:

$^{99}Tc^{m}$ sulphur colloid injection is a sterile, pyrogen free colloidal suspension, brownish in colour, stabilised by gelatin, suitable for intravenous administration.

pH: will be between five and eight as checked by pH paper.

Radiochemical purity:

This will be determined shortly after preparation of the radiopharmaceutical, and for the evaluation of its in-vitro stability every hour up to 4 hours, by ascending paper chromatography using 85% v/v aqueous methanol on Whatman No. 1 paper. $^{99}Tc^{m}$ sulphur colloid will remain at spotting point and $^{99}Tc^{m}$ pertechnetate will move with an Rf value of about 0.6. The radioactivity corresponding to $^{99}Tc^{m}$ sulphur colloid will be not less than 92% of the total activity.

Biological Distribution:

This should be done as described in the next chapter.

The acceptable biodistribution characteristics for the sulphur colloid injection and for several other $^{99}Tc^{m}$ radiopharmaceuticals are given in the next chapter.

Storage:

(a) The nonradioactive kit for $^{99}Tc^{m}$ sulphur colloid injection should be stored at room temperature (approx. 23°C). Shake well before use.

(b) The radioactive formulation $^{99}Tc^{m}$ sulphur colloid injection should be stored at room temperature with adequate shielding.

Expiry:

(a) The kit should be used not later than 3 months after satisfactory completion of all the quality control tests or 4 months after kit production.

(b) The radioactive formulations $^{99}Tc^{m}$ sulphur colloid injection is recommended to be used as early as possible but not later than 4 hours after preparation.

Good Pharmaceutical Practices (GPP)

General

GPP is broadly defined as a comprehensive system, designed, documented and implemented such that the finished products will be of a quality appropriate for their intended use. GPP guidelines are well known and accepted in the pharmaceutical industry. Preparation of radiopharmaceuticals has to be carried out according to these general guidelines which concern the premises, equipment, hygiene, starting materials, preparations, labelling, packaging, storage, the quality control system, and documentation. Besides implementing GPP, the preparation and use of radiopharmaceuticals are subject to legal regulations by national authorities.

Personnel

The personnel deployed for radiopharmaceutical preparation and testing should be well qualified and trained. They should be graduates in either chemistry or pharmacy with additional training in radiochemistry and preparation and testing of radiopharmaceuticals. In many places formal, regular training in these areas is not available. It is often necessary to provide on-the-job training in centres producing radiopharmaceuticals. A new recruit to the facility should be given adequate on-the-job training before deploying for these activities. It is desirable to divide the responsibilities for of product preparation and their quality control between two independent persons.

Premises

Radiopharmaceutical preparation must be performed in premises of defined cleanliness. According to GPP, for the manufacturing of drugs that are intended to be sterile but cannot

be sterilised in their final containers, separate enclosed areas, specifically designed for the purpose, should be provided. This area should be provided with air supply which is filtered through a microbes retaining filter. Entry to this area should be through an air-lock. Provision of Laminar Air-Flow (LAF) benches, which provide a sterile atmosphere, is essential for preparing and dispensing of injectable solutions, kits, etc. In addition, the area in which the LAF benches are installed should be designed to facilitate easy maintenance.

The typical premises for preparation, dispensing and quality control of radiopharmaceuticals may consist of three rooms of approximate size 6 x 6 m each, and additional areas of packaging, storage and service. It is suggested that all preliminary work such as cleaning and sterilisation of glassware, containers, closures, filters and preparation of bulk solutions for the kits are performed in the room adjacent to the preparation and dispensing room. The two areas may be interconnected by hatches for material transfer. All surfaces in the area should be designed to facilitate cleaning and disinfection. To keep the contamination in the dispensing room to a minimum, equipment should be reduced to the minimum necessary. It is advisable to house equipment such as LAF benches, freeze-drying unit etc. in such a way that only the working areas are accessible to the dispensing room.

A periodic sanitation programme, for the premises indicating cleaning procedures and cleaning schedules, should be designed and implemented. The contamination level in the room as well as dispensing areas should be monitored at regular intervals.

Equipment

In addition to standard laboratory equipment, such as work benches and storage cabinets, essential equipment for radiopharmaceutical dispensing, kit preparation and quality control work includes LAF bench, freeze-dryer, deep-freezer, membrane filtration device, semi-micro balance, autoclave for sterilisation, and dry-air steriliser.

Laminar Air Flow (LAF) Bench

Standard LAF benches, either of the vertical or horizontal air flow type can be used as far as they meet the requirements as outlined in BRITISH STANDARD 5295 Class I. After the installation of a LAF bench the conformation to the standard must be verified prior to use. The LAF bench should be disinfected before use by swabbing with an appropriate disinfectant. The performance of the LAF bench should be regularly checked by measurement of air velocity and periodic exposure of nutrient agar culture plate in the working area to detect microbial contamination in air.

Membrane filtration device

Pre-sterilised disposable membrane filtration devices or reusable filtration devices made of either plastic or glass or stainless steel could be used. The membrane filter should not be used more than once. For filtration of nitrogen gas for purging solutions or for sealing the vials under nitrogen atmosphere, membrane filters meant for gas filtration should be used.

Lyophilizer

A shelf-type freeze drying unit capable of accommodating about 200 vials of 10 mL capacity each can be typically used. The unit should have facilities for stoppering the vials under vacuum or nitrogen gas by mechanical means. The other operational features are:

(a) mechanical condenser capable of reaching temperatures of less than - 40°C,

(b) in ice-removing capacity of more than 2 kg in 24 hrs operation,

(c) capacity for retaining a vacuum of less than 50 mtorr without load,

(d) facility for cooling and heating the shelf from -40°C to +40°C by a circulating fluid,

(e) facility for monitoring the above parameters as well as the product temperature. On installation of the equipment and every time prior to loading of the samples the freeze dryer should be operated without load and the performance of the machine with respect to the above parameters checked. Freeze drying is an intricate process and careful standardisation of the various parameters is essential to get a good product.

Containers and Closures

Container

For dispensing the radiopharmaceutical formulations, kits and reagents USP type-I flint neutral glass vials of 10 mL capacity are commonly used. The vials should be obtained from reputed sources certified for conformity to USP specification. Cleaning and sterilisation protocols for the vials should be established and followed. A typical protocol is given in Appendix XI to serve as a guideline. Other glassware such as beakers, measuring cylinders, graduated pipettes, glass rods, filters, flasks, etc. made of good quality boro-silicate glass should be used. They should also be cleaned and sterilised as per established protocol such as given in Appendix XII for glass vials.

Rubber stoppers.

Rubber stoppers with split end for use in freeze drying operations should be purchased from reputed sources certified for conformity to the physical and the chemical tests described in pharmacopoeia. Cleaning and sterilising protocols for rubber stoppers should be established and followed. A typical such procedure is given in Appendix XIII for guidance.

Process

$^{99}Tc^{m}$ labelling kits

The general procedure for the preparation of $^{99}Tc^{m}$ labelling kits essentially consists of the following simple steps:

(a) Weighing and dissolution of stannous chloride in dilute hydrochloric acid.

(b) Weighing and dissolution of the ligand in water or dilute alkali.

(c) Addition of the required amount of stannous chloride solution to the ligand solution with constant stirring.

(d) Adjustment of the pH to the required value using a pH meter.

(e) Sterilisation of the above solution by membrane filtration.

(f) Dispensing of this solution aseptically into sterile vials.

(g) Lyophilisation.

The steps in the lyophilisation process are:

(i) freezing the dispensing solution - this can be done either in the freeze dryer itself or outside in a deep freezer.

(ii) cooling the condenser to less than -40°C.

(iii) evacuating the system to less than 0.1 torr.

(iv) providing controlled heat input to the product during the freeze drying cycle.

(v) Sealing the vials under vacuum or under nitrogen gas in the freeze dryer after completion of the drying cycle.

To obtain a product of reliable and reproducible quality, the process parameters should be continuously monitored throughout the cycle, and properly recorded for every batch.

The normal lyophilisation cycle is for 24 hours. However, when the salt concentration is high and when the volume taken in the vial is more than 1 mL the cycle may have to be extended to 48 hours. The physical appearance of the final product very much depends on the solid content in the starting solution. If it is too less, during the drying cycle the dry powder may crumble and light particles may escape from the vials. Normally this problem

can be taken care of by ensuring sufficient solid content in the dispensing solution. Some workers have found addition of inert substances like inositol, dextrose etc. helpful in the freeze drying process.

Normally the product will be dry following the freeze-drying cycle given under the individual procedures. A qualitative test should be carried out approximately one week after freeze drying, by observing the kit contents. No change in the physical appearance of the product such as shrinkage or presence of water droplets should be seen.

Quality Control.

Good Quality Control Practices form an integral part of GPP and cover quality controls of all raw materials, their certification, control of process parameters including environmental microbial levels, and comprehensive quality controls of the finished products including physicochemical, radiochemical, biological, microbiological and immunological evaluation and stability studies. The quality controls of radiopharmaceuticals, generators and kits have been described in detail in an earlier Section.

Records and Record Keeping

Documentation and record keeping of the various stages of the preparation, dispensing of radiopharmaceuticals and kit preparation including maintenance of premises, processing of formulations, processing of the kits, results of test procedures, and the supply of the kits is an essential aspect of Good Pharmaceutical Practices. A master copy of the compilation of all preparation procedures and testing methods for various products as well as their specifications should be prepared and made available for reference to the personnel involved in the preparation and analysis. These procedures may be periodically reviewed in the light of the in-house experience and developments reported in the literature. Any modifications in the existing procedures should be accepted as routine practice only after its satisfactory validations and should be authorised by the Head of the unit. These should be effectively communicated to all persons involved in the production and quality control work as well as the user.

Log books, preferably printed, giving details of all processing and analysis should be maintained. Typically this should include details of raw materials, containers, glassware, processing details, batch number, identification numbers, history of use, test results and any other relevant information.

The raw materials, chemicals and ligands for use in preparation should preferably be given in-house batch numbers after acceptance by due analysis. Complete record of their procurement, use, analysis and disposal should be maintained in a log book. In addition, the original label on the containers giving the manufacturers batch number, date of analysis, etc. should be affixed on the container to clearly indicate that the reagent is for use in radiopharmaceutical production. Since the quantities of reagents and ligands used in kit preparation are small and to avoid contaminating the bulk reagents and ligands by frequent handling, it may be advantageous to redistribute them in smaller vials, close them air-tight

and store them safely. Once identified for use in production it is preferable to store them in safe custody thereby avoiding mix up with other chemicals.

Batch Control Samples

A sufficient number of samples from each batch should be kept aside under safe custody during the lifetime of the product. In case of receipt of complaints of unsatisfactory performance of the product, the batch control samples can be used to check the product quality and identify reasons for the poor performance.

Organization of a central radiopharmacy facility

A centralised radiopharmacy could undertake the following services:

(a) Bulk imports of ready to use radiopharmaceuticals such as ^{131}I sodium iodide, preparations of ^{51}Cr, ^{59}Fe, ^{32}P etc. and their dispensing and distribution to user hospitals.

(b) Bulk imports of $^{99}Tc^{m}$ generators and their distribution.

(c) Preparation of kits for $^{99}Tc^{m}$ radiopharmaceuticals.

(e) Preparation of "instant $^{99}Tc^{m}$ formulations" and their supply to user hospitals.

(f) Preparation and distribution of $^{99}Tc^{m}$ generators from imported ^{99}Mo.

An economically designed centralised radiopharmacy, handling and processing the various products listed above and the activity levels shown in Table III (Appendix III) should have a total constructed area of about 400 m^2 and a staff of three scientific and three technical personnel. At the optimum level of operation this centralised radiopharmacy would be able to prepare and supply 4000 to 5000 consignments of various radiopharmaceutical preparations per annum which would be adequate for 15 000 to 20 000 patient procedures. The operating costs of such a centralised radiopharmacy (inclusive of staff salaries, running costs and costs of raw materials) would be about US $60 000 per year, while the import costs of the radiopharmaceuticals processed and supplied from the facility per year would exceed US $150 000. With marginal increases in space and staff, the range of products and levels of activity handled in this facility could be substantially scaled up. The experience of several developing countries has shown that local production and/or distribution of medical radiopharmaceuticals results in substantial savings in foreign exchange and ensures the provision of a more streamlined nuclear medicine service. The raw material costs of such a programme ranges from 10-15% of the overall production costs, the staff salaries account for about 15%, while the operating costs of laboratory and equipment and the depreciation provision account for about 20-25%. Indigenous kit production costs have been found to be less than 5% of the import costs.

Legislative Aspects

A wide range of radiopharmaceuticals is now regularly used in nuclear medicine and many of these products have been included in the pharmacopoeia of advanced countries. The specifications and testing procedures for these products which have been documented in the Pharmacopoeia have been finalised and accepted after extensive studies had been carried out concerning their physicochemical, radiochemical and biological aspects of purity, and clinical utility and efficacy.

The special characteristics and properties of radiopharmaceuticals (as against conventional pharmaceutical products) such as their radioactivity, short shelf-life and the fact that the large majority of these products are diagnostic agents with no pharmacological action have been duly recognised. A special provision has been made in the pharmacopoeia that injectable radiopharmaceuticals may be used on patients by the intending nuclear medicine practitioner before the tests for their sterility are completed as such tests require 14 days for completion which is too long compared to the half-life of most of the medically important radionuclides.

Many developing countries have been importing radiopharmaceutical preparations meeting the specifications and purity criteria outlined in the USP/BP/EP and produced by suppliers in UK, USA, France, Germany, Australia, etc. There are a few radiopharmaceutical products which are not yet documented in the Pharmacopoeia, however, these are in regular use in many advanced countries and are processed and supplied by reputed commercial suppliers. Many developing countries have also been using these products with beneficial results in their nuclear medicine services.

While considering the legislative practices for radiopharmaceutical products in developing countries, the following special characteristics and features of these products and their human applications may have to be kept in view:

(a) Most radiopharmaceutical products contain extremely small quantities of chemical ingredients (a few micrograms to a few milligrams of mostly well known chemicals).

(b) The large majority of radiopharmaceutical products are used essentially as diagnostic agents. These have no pronounced pharmacological action. The radionuclides involved in these preparations are of low and medium toxicity.

(c) Most radiopharmaceutical preparations are administered in small quantities and often only once or on a small number of occasions on the same patient. Repeated administrations are not involved in most cases.

(d) Radiopharmaceutical preparations are supplied only to highly qualified experts who are aware of their special characteristics and end applications. They are not available for sale from pharmacies as is the case with many conventional pharmaceutical products.

(e) The dosage, route of administration and the clinical indications for their use are well established and documented for most radiopharmaceuticals. The contraindications and side effects of their use are also well documented.

(f) Over the years, radiopharmaceuticals have been administered to millions of patients the world over and only a very small number of adverse reactions have been reported which could be attributed to their administration. The adverse reactions have been mostly confined to allergies and a small number of other idiosyncratic reactions of a mild nature.

While the legislation practices regarding medical and pharmaceutical products are a matter of national policy, it would be a logical and practical approach to accord legislative clearance and acceptance to all radiopharmaceutical products which are listed in the well known pharmacopoeia (USP, BP, EP, IP). A general clearance for human use may also be accorded for other products which are in regular use in advanced countries though these products are not yet officially recognised in the Pharmacopoeia.

The overall objective of the legislative process should be to ensure the safe, efficacious and cost effective use of well recognised radiopharmaceutical products for patient care and to promote their indigenous production and widespread applications.

Appendix I

TABLE I. COMMONLY USED RADIOPHARMACEUTICALS AND THEIR MAIN APPLICATIONS.

Serial No.	Radiopharmaceutical	Main medical application/s
1.	Chromic (^{51}Cr) Chloride Injection	Determination of loss of serum protein into the GI tract (by direct i.v. injection)
2.	Sodium chromate (^{51}Cr) Solution	In-vitro labelling of red blood cells for red cell volume, and red cell survival
3.	Cyano cobalamin (^{57}Co) Solution	GI absorption tests
4.	Cyano cobalamin (^{57}Co) Capsules	GI absorption tests
5.	Cyano cobalamin (^{58}Co) Solution	GI absorption tests
*6.	Indium (^{111}In) Bleomycin Injection	Localisation of tumours in a variety of neoplastic conditions
*7.	Indium (^{111}In) chloride	For preparation of ^{111}In labelled proteins and cells, and monoclonal antibodies for immuno-scintigraphy
*8.	Indium (^{111}In) calcium DTPA Injection	CSF studies, cisternography and ventriculography
*9.	Indium (^{111}In) oxine solution	For labelling blood cells
*10.	Sodium iodide (^{123}I) capsules	Investigation of thyroid function and thyroid scintigraphy
*11.	Sodium orthoiodo (^{123}I) hippurate injection	Scintigraphic investigation of kidney function
*12.	Metaiodobenzyl guanidine (^{123}I) injection	Diagnosis of increased localised catecholamine metabolism. Also for localization and diagnosis of active catecholamine metabolic tumours and their metastases (ex. pheochromocytoma and neuroblastoma)

TABLE I. (cont.)

Serial No.	Radiopharmaceutical	Main medical application/s
13.	Sodium orthoiodo (^{125}I) hippurate injection	Determination of effective renal plasma flow (EPRF)
14.	Sodium iodo thalamate (^{125}I) injection	Determination of glomerular filtration rate (GFR)
15.	Iodinated (^{125}I) human serum albumin injection	Blood volume determination
16.	Iodinated (^{125}I) human fibrinogen injection	Detection of deep vein thrombosis of the legs
17.	Sodium orthoiodo (^{131}I) hippurate injection	renography
18.	Sodium orthoiodo (^{131}I) hippurate injection containing less than 0.5% non-bound ^{131}I	Determination of EPRF
19.	Sodium iodide ^{131}I solution	thyroid uptake, and localisation of thyroid cancer metastases, therapy of thyrotoxicosis and thyroid cancer
20.	Sodium iodide ^{131}I injection	thyroid uptake, and localisation of thyroid cancer metastases, therapy of thyrotoxicosis and thyroid cancer
21.	Sodium iodide ^{131}I capsules (diagnostic)	thyroid uptake
22.	Sodium iodide ^{131}I capsules (therapeutic)	Therapy of thyrotoxicosis and thyroid cancer
23.	Meta-iodo benzylguanidine (^{131}I) (m-1BG) solution (diagnostic)	Adrenal medulla scintigraphy in investigations of pheo-chromocytoma, neurobastoma and for the assessment of adrenal medullary hyperplasia
24.	Meta-iodo benzylguanidine (^{131}I) (m-1BG)	Treatment of malignant pheochromocytoma and neuroblastoma
25.	Ferric Citrate (^{59}Fe) injection	Investigation of iron metabolism
26.	Sodium phosphate (^{32}P) injection	Treatment of polycythemia vera and related disorders

TABLE I. (cont.)

Serial No.	Radiopharmaceutical	Main medical application/s
27.	Strontium (^{89}Sr) chloride injection	Palliative treatment of bone metastases
28.	Indium (^{113m}In) DTPA injection	Brain scintigraphy
29.	Indium (^{113m}In) colloid-mannitol stabilized or gelatin stabilized	Liver scintigraphy
30.	Technetium-99m EHIDA	Scintigraphic imaging of the hepatobiliary system
31.	^{99m}Tc gluconate	Diagnostic scintigraphy of the kidney or brain
32.	^{99m}Tc R.B.C.	Diagnostic imaging of blood pools
33.	^{99m}Tc DMSA	Diagnostic imaging of kidney
34.	^{99m}Tc DTPA	Measurement of GFR, functional study of kidney and/or brain
35.	^{99m}Tc dl-HMPAO	Diagnosis of abnormalities of regional cerebral blood perfusion; also for leucocyte labelling
36.	^{99m}Tc MAA	Lung imaging
37.	^{99m}Tc-MDP	Bone scintigraphy
38.	Xenon (^{133}Xe) gas	Lung ventilation studies
39.	Xenon (^{133}Xe) injection	Lung perfusion studies, cerebral blood flow studies
40.	Yttrium (^{90}Y) silicate injection	Intrapleural or intraperitoneal injection treatment of malignant disease

* These radionuclides are produced by target irradiation in a cyclotron or similar accelerator.

TABLE II. PREPARATION OF ^{99m}Tc LABELLING KITS

Name of kit	Quantity of Ligand	Volume of solution in step 1	Quantity of $SnCl_2$ used	pH Step 3	Final volume step 4	Storage Temperature of kits.
$^{99}Tc^m$ -MDP	500 mg MDP, 50 mg ascorbic acid	80 mL	0.6 mL	6-7	100 mL	2-10° C
$^{99}Tc^m$ -EHDP	1 g EHDP	80 mL	1.25 mL	6-7	100 mL	2-10° C
$^{99}Tc^m$ - Pyro-phosphate (PYP)	1.5 g Tetra-Na-pyrophos. deca- hydrate	80 mL; warm if necessary	1.25mL	6-7	100 mL	2-10° C
$^{99}Tc^m$ DTPA	3.5 g DTPA mix with 10 mL 1N NaOH.	80 mL; warm if necessary	2.5 mL	6-7	100 mL	2-10° C
$^{99}Tc^m$ - gluconate	20 g sodium gluconate	160 mL	1.25 mL	6-7	200 mL	2-10° C
$^{99}Tc^m$ - gluco-heptonate	20 g sodium glucoheptonate	160 mL	1.25 mL	6-7	200 mL	2-10° C
$^{99}Tc^m$ DMSA	100 mg DMSA; 5 mL 1N NaOH	80 mL	0.5 mL	2.5 (with 1N HCl)	100 mL	2-10° C
$^{99}Tc^m$ - EHIDA	1 g EHIDA 40 mL 0.1N NaOH	40 mL	0.5 mL	5.5-6 (pH water)	100 mL	2-10° C
$^{99}Tc^m$ - Bromo trimethyl IDA	1 g 10 mL 1N NaOH	10 mL	0.25 mL	6-6.5	100 mL	2-10° C
$^{99}Tc^m$ - phytate	1 g Sodium phytate	80 mL	1.25 mL	6-7	100 mL	2-10° C

Appendix III

TABLE III. OPTIMUM QUANTITIES OF MEDICAL RADIONUCLIDES WHICH MAY BE PROCESSED/HANDLED IN A MEDIUM LEVEL CENTRALISED RADIOPHARMACY

Serial No.	Radionuclide and pharmaceutical form	Frequency of processing or handling	Activity per batch
1.	^{99}Mo-$^{99}Tc^{m}$ generators	Twice in a week	500 G Bq
2.	$^{99}Tc^{m}$ pertechnetate	Once or Twice a day	1 G Bq of each product
3.	^{131}I as sodium iodide solution and capsules	Once a week	5 G Bq of each product
4.	^{131}I labelled compounds (Rose Bengal, Hippuran, MIBG, etc.)	As required	500 G Bq
5.	^{125}I as sodium iodide for protein iodination,	Once in 2 weeks	100 G Bq
6.	^{125}I labelled compounds (Rose Bengal, Hippuran, MIBG, etc.)	Once in 2 weeks	5 G Bq or as solution
7.	$^{57}Co/^{58}C$ labelled cyanocobalamin	As required	100 M Bq
8.	Miscellaneous medical products (labelled forms of ^{51}Cr, ^{59}Fe, ^{75}Se, ^{32}Pek)	As required	1 G Bq of each product
9.	^{113}Sn-$^{113}In^{m}$ generator	Once in 2 months	5 G Bq

Appendix IV

CHARACTERISTICS AND SPECIFICATIONS OF SODIUM IODIDE ^{131}I SOLUTION

1. Sodium iodide ^{131}I in aqueous solution containing a suitable buffer (sodium carbonate-bicarbonate)

2. Multidose packing in penicillin-type glass vials

3. Clear colourless solution, may have a light brown colour occasionally (due to effect of radiation)

4. Contains sodium thiosulphate added as a preservative (reducing agent)

5. Radioactive concentration 40-400 MBq/mL

6. Radiochemical purity $I^- > 97\%$

7. Radionuclidic purity $^{131}I > 99.9\%$

8. pH: 7 - 9.5

9. Content of $Na_2S_2O_3$ 0.001-0.02 mg/MBq ^{131}I

10. Content of stable iodine (< 0.02 mg/MBq of ^{131}I at the time of (for therapeutic purposes)) patient administration

11. Storage: at room temperature with adequate shielding

12. Useful shelf-life: 4 weeks

Appendix V

CHARACTERISTICS AND SPECIFICATIONS OF DIAGNOSTIC ^{131}I-SODIUM IODIDE CAPSULES

1. Sodium iodide ^{131}I adsorbed on a solid adsorbent such as anhydrous sodium phosphate and contained in a gelatin capsule
2. 1-6 capsules may be packed together in penicillin-type vials which may contain a dessicant in a separate sachet
3. Single dose capsule
4. Activity per capsule 0.5-5 MBq/capsule
5. Radiochemical purity of $^{131}I^-$ > 97%
6. Radionuclidic purity ^{131}I > 99.9%
7. Maximum variation in activity of individual capsules in a batch $\pm$ 5%
8. Sodium phosphate content per capsule 50-200 mg
9. Storage: at room temperature with adequate shielding
10. Useful shelf-life: 2 weeks

Appendix VI

CHARACTERISTICS AND SPECIFICATIONS OF THERAPEUTIC SODIUM IODIDE ^{131}I CAPSULES

1. Sodium iodide ^{131}I adsorbed on a solid adsorbent such as anhydrous lactose or sodium phosphate and contained in a gelatin capsule

2. The capsules may be individually packed in penicillin-type vials which may contain a dessicant in a separate sachet

3. Single dose capsules - for therapy of thyrotoxicosis or thyroid cancer

4. Activity per capsule: 40-4000 MBq/capsule

5. Radiochemical purity: $I^- > 97$ %

6. Radionuclidic purity: $^{131}I > 99.9$%

7. Storage: at room temperature with adequate shielding

8. Useful shelf-life: 2 weeks

Appendix VII

CHARACTERISTICS AND SPECIFICATIONS OF ^{131}I-HIPPURAN INJECTION

1. Hippuran (sodium ortho iodo hippurate) ^{131}I in isotonic solution suitable for intravenous human administration

2. May contain a bacteriostatic agent (0.9% Benzyl alcohol solution)

3. Multidose packing in penicillin-type (amber-coloured) glass vials

4. Clear colourless solution, may have a light brown colour occasionally (due to effect of radiation)

5. Radioactive concentration: 4-20 MBq/mL

6. Content of Hippuran: 1-5 mg/mL

7. pH: 6-8

8. Radiochemical purity: $I^- < 2$ %
(less than 1% for some applications)
^{131}I as ortho iodo benzoic acid < 2 %

9. Storage: at 2-10°C in amber coloured glass vials with appropriate shielding

10. Useful shelf-life: 3 weeks

Appendix VIII

CHARACTERISTICS AND SPECIFICATIONS OF RADIOIODINATED (^{131}I) HUMAN SERUM ALBUMIN INJECTION

1. Radioiodinated (^{131}I) human serum albumin in isotonic solution suitable for intravenous human administration

2. May contain a bacteriostatic agent (0.9% Benzyl alcohol solution)

3. Multidose packing in penicillin-type (amber-coloured) glass vials

4. Clear colourless solution, may have a light brown colour occasionally (due to effect of radiation)

5. Radioactive concentration: 4-20 MBq/mL

6. Content of human serum albumin: 1-50 mg/mL

7. pH: 6-8

8. Radiochemical purity: Inorganic iodine ^{131}I $< 2\%$

9. Storage: At 2-10^{0}C in amber coloured glass vials with appropriate shielding

10. Useful shelf-life: 3 weeks

Appendix IX

CHARACTERISTICS AND SPECIFICATIONS OF META-IODOBENZYLGUANIDINE (^{131}I) (m-IBG) SOLUTION-DIAGNOSTIC

1. Sterile, aqueous solution, containing 9 mg/mL of sodium chloride and 10 mg/mL of benzyl alcohol
2. Multidose packing in penicillin-type vials
3. pH 4.0-7.0
4. Radioactive concentration: 9-20 MBq/mL
5. Specific activity: 30-200 MBq/mg, m-IBG
6. Storage: at 2-8°C
7. Useful shelf-life: 3 days

CHAPTER 12

Appendix X

CHARACTERISTICS AND SPECIFICATIONS OF INDIUM (^{113m}In) STERILE GENERATOR

Tin-113 absorbed on an ion-exchange material contained in a robust plastic column, with puncturable rubber end seals. The sealed unit is sterilized by heating with bactericide. Sterile indium-113m in aqueous solution is obtained by elution with the sterile eluent provided. The shielded generator is despatched with full instructions and accessories for 60 elutions.

1.	Activities available:	Generators containing 200 MBq to 5 GBq of ^{113}Sn.
2.	Purity:	Eluate contains less than 3.7 kBq, as tin-113 and less than 0.74 Bq, as other impurities per 37 MBq, ^{113}In at the time of calibration. Total heavy metal impurities present in the eluate do not exceed 5 μg/ml.
3.	pH:	pH of eluate is 1.4 $\pm$ 0.1.
4.	Storage:	Store at 15-25°C.
5.	Expiry:	The generator should not be used later than 6 months after the reference date.
6.	Description:	The kit provides pre-dispensed sterile reagents which, when used with the eluate from Indium [^{113m}In] Sterile Generator in the recommended manner, produces a sterile solution containing carrier-free indium-113m in the form of a strong DTPA chelate complex. The solution is ready for immediate intravenous injection as a diagnostic brain scanning agent. The kit contains reagents for five individual preparation units. Each prepared unit will provide several patient doses, the number being dependent on the total activity added.

7.	Content:	Each preparation unit contains two components: Component A - Sterile complexant 1 ml of sterile aqueous solution containing 1-60 mg of diethylenetriamine penta-acetic acid and 1.02 mg acetic acid. The solution is contained in a 10 ml neutron glass vial with puncturable rubber insert seal. Component B - Sterile buffer 1.3 ml of sterile aqueous solution.
8.	Storage:	Store at 15-25°C
9.	Expiry:	Normally at least 6 weeks from day of despatch as stated on the label.
10.	Indication:	The indium-113m brain scanning kit is indicated for brain scintigraphic studies following preparation by the method described below.
11.	Preparation Procedure:	Carrier-free indium-113m eluted from an indium [113mIn] sterile generator is complexed with diethylenetriamine penta-acetic acid (DTPA). The pH of the solution is then adjusted to neutrality by addition of a buffer.

Appendix XI

CLEANING AND DISINFECTION OF PREMISES

1. The floors of the laboratory should be cleaned daily by mopping with a disinfectant solution such as Dettol (or other disinfectants as specified in the authorized disinfectant list).

2. The walls, the bench tops and doors should be cleaned similarly once a week.

3. The rooms should be exposed to formaldehyde vapour once a week by keeping formaldehyde/potassium permanganate mixture in Petri dishes in the room during the weekend.

4. The equipment such as freeze drying unit should be cleaned by wiping with aqueous alcohol regularly once a week and just prior to use.

Monitoring:

1. Nutrient agar plates should be exposed for one hour at a few places in the room and the dispensing area.

2. Sterile fluid thioglycolate medium or tryptocase soya broth should be filled and sealed in sterile vials under the same conditions as in the production of radiopharmaceuticals. They should then be incubated and examined for any microbial growth.

This should be carried out prior to preparation of each batch of products and the record of the results should be maintained.

Appendix XII

CLEANING OF GLASS VIALS

1. _____ No. of _____ capacity flint vials should be carefully selected and cleaned with 0.1% Teepol by brushing individually or by ultrasonic cleaning for 30 minutes.

2. These should then be cleaned in running tap water to remove Teepol.

3. After this, these should be all immersed in 15% v/v nitric acid (C.P.) and kept overnight.

4. Next day these should be removed from acid and washed to remove acid completely.

5. At this stage, these should be checked with indicator paper to confirm no acid contamination in them.

6. Then these vials should be individually rinsed twice with double distilled water and kept inverted in a clean container and sterilized by dry heat at 180°C for 2 hrs or 160°C for 6 hrs.

Appendix XIII

CLEANING OF RUBBER CLOSURES

1. _____ Nos. of rubber closures should be carefully selected and cleaned with tap water to remove visible dust and extraneous particles.

2. Then they should be immersed in 1% Teepol solution and scrubbed thoroughly.

3. They should then be rinsed with tap water till they are completely free from Teepol.

4. They should be soaked in 10% w/v sodium hydroxide solution and allowed to remain overnight.

5. Next day they should be removed from alkali and washed with running tap water till they are free from alkali.

6. Further these closures should be soaked in 20% v/v hydrochloric acid and allowed to remain for 24 hours.

7. Next day the acid should be drained off completely and these rubber closures should be washed with double distilled water till acid is completely removed (rinsing should be checked for absence of any acidity).

8. They should be autoclaved in double distilled water for 30 minutes under 15 p.s.i. pressure.

9. They should then be rinsed with double distilled water and then put in cleaned beakers and kept in hot air oven at 70^0C for drying.

10. They should then be stored in a clean atmosphere.

11. For use in production they should be sterilized by one of the following methods:

    Sterilization:

    (a) Radiation sterilization: Seal in polythene bags and sterilize by gamma radiation (2.5 Mrad dose).

    (b) Autoclaving: Rinse with double distilled water, seal in polypropylene bags and autoclave at 15 p.s.i. (121^0C) for 30 minutes. Dry in hot air oven at 70^0C. To be used within one week after autoclaving.

Appendix XIV

SPECIAL EQUIPMENT AND MATERIALS REQUIRED FOR SETTING UP A RADIOPHARMACY

1.	Laminar flow work bench	1
2.	Pyrogen-free water unit	1
3.	Electronic analytical balance	1
4.	pH Meter	1
5.	Medium-capacity freeze drying unit	1
6	Steam sterilizer	1
7.	Dry air sterilizer	1
8.	Incubator	1
9.	Centrifuge	1
10.	Well-type scintillation counter with detector and spectrometer	1
11.	Portable survey meter (beta gamma)	1
12.	Portable beta-gamma contamination monitor	1
13.	Radioisotope dose calibrator	1
14.	Shielding materials (lead bricks, viewing glasses)	As required
15.	Millepore filters	
16.	Automatic pipettes for small volumes	
17.	Special chemicals	
18.	Small tongs, handling tools	
19.	Radioactive standards and long-lived reference sources	
20.	Chromatography paper	
21.	Glassware (vials, chromatography jars, pipettes, etc.)	
22.	Fume hood/beta gamma box	1

Appendix XV

CHARACTERISTICS AND SPECIFICATIONS OF INDIUM [^{113m}In] COLLOID LIVER SCANNING KIT

1.	Description	The kit provides pre-dispensed sterile reagents which, when used with the eluate from Indium [^{113m}In] Sterile Generator in the manner described, produces a sterile solution containing carrier-free indium-113m labelled colloid. The solution is ready for immediate intravenous injection as a diagnostic liver scanning agent. The kit contains reagents for five individual preparation units. Each prepared unit will provide several patient doses, the number being dependent upon the total activity added.
2.	Contents	Each preparation unit contains two components: Component A - Sterile stabilized carrier. 1 ml of sterile aqueous solution containing 4.8 μg of ferric chloride (FeCl3.6H2O) and 50 mg of mannitol. The solution is contained in a 10 ml neutral glass vial with a puncturable rubber insert seal. Component B - Sterile buffer 1.3 ml of sterile aqueous solution containing 43.3 mg of sodium dihydrogen phosphate and 68.5 mg of disodium hydrogen phosphate. The solution is contained in a neutral glass ampoule.
3.	Storage	Store at 15-25°C.
4.	Expiry	Normally at least 6 weeks from date of despatch as stated on the label.