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RADIOPHARMACEUTICALS

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Contents

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 with 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 web site (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 and Radiological Protection for Medical Exposure to Ionizing Radiation Safety Guide (IAEA, Vienna, 2002) Safety Standard Series No. RS-G-1.5. Consult the IAEA website for the current Safety Standards and publications (http://www-ns.iaea.org/standards/).

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Radiopharmaceuticals

This general monograph is intended to be read in conjunction with the individual monographs on radiopharmaceutical preparations. A radiopharmaceutical preparation that is subject of an individual monograph in The International Pharmacopoeia *complies with the general requirements stated below and with the general monograph for the relevant dosage form (most commonly that for Parenteral preparations) as modified by any of the requirements given below and by any specific instruction included in the individual monograph.*

Additional information

- **See Annex for terminology applied to radiopharmaceuticals**

Shelf-life The shelf-life (expiry period) of a radiopharmaceutical preparation depends primarily on the physical half-life of the radioisotope, the radiochemical stability and the content of longer-lived radionuclidic impurities in the preparation under consideration. Many radiopharmaceutical preparations contain radioisotopes with very short half-lives and such preparations therefore have very short shelf-lives. Such preparations require an expiry date and time to be indicated. For example, technetium based preparations and positron emission tomography (PET) preparations are normally intended to be used within less than12 hours (some within minutes) of preparation.

At the end of the expiry period, the radioactivity will have decreased to the extent where insufficient radioactivity remains to serve the intended purpose or where the dose of active ingredient must be increased so much that undesirable physiological responses occur. In addition, chemical or radiation decomposition may have reduced the radiochemical purity to an unacceptable extent. In addition the radionuclidic impurity

content may be such that an unacceptable radiation dose would be delivered to the patient.

The shelf-life of a multidose radiopharmaceutical preparation, after aseptic withdrawal of the first dose, will also depend on microbiological considerations. For radiopharmaceutical preparations containing radioisotopes with long half-lives, microbiological considerations may take precedence over those based on the physical half-life of the radioisotope. For example, once the first dose has been aseptically withdrawn from a multidose container of a iodine-containing injection, the container should be stored at a temperature between 2° and 8°C and the contents used within 7 days.

Definition

Radiopharmaceuticals can be divided into four categories:

Radiopharmaceutical preparation A radiopharmaceutical preparation is a medicinal product in a ready-to-use form suitable for human use that contains a radionuclide. The radionuclide is integral to the medicinal application of the preparation, making it appropriate for one or more diagnostic or therapeutic applications.

Radionuclide generator A system in which a daughter radionuclide (short half-life) is separated by elution or by other means from a parent radionuclide (long half-life) and later used for production of a radiopharmaceutical preparation.

Radiopharmaceutical precursor A radionuclide produced for the radiolabelling process with a resultant radiopharmaceutical preparation.

Kit for radiopharmaceutical preparation In general a vial containing the non-radionuclide components of a radiopharmaceutical preparation , usually in the form of a sterilized, validated product to which the appropriate radionuclide is added *or* in which the appropriate radionuclide is diluted before medical use. In most cases the kit is a multidose vial and production of the radiopharmaceutical preparation may require additional steps such as boiling, heating, filtration and buffering. Radiopharmaceutical preparations derived from kits are normally intended for use within 12 hours of preparation.

Manufacture

The manufacturing process for radiopharmaceutical preparations should meet the requirements of Good Manufacturing Practice.

The manufacturer is responsible for ensuring the quality of his products, and especially for examining preparations of short-lived radionuclides for long-lived impurities after a suitable period of decay. In this way, the manufacturer ensures that the manufacturing processes employed are producing materials of appropriate quality. In particular, the radionuclide composition of certain preparations is determined by the chemical and

isotopic composition of the target material (see below) and trial preparations are advisable when new batches of target material are employed.

When the size of a batch of a radiopharmaceutical preparation is limited to one or few units (for example, certain therapeutic preparations or very short-lived preparations) parametric release of the product manufactured by a fully validated process is the method of choice. When the half-life is very short (for example, less than 20 minutes), the administration to the patient is usually on-line within a validated production system.

Radionuclide production In general ways of manufacturing radionuclides for use in radiopharmaceutical preparations are:

Nuclear fission Nuclides with high atomic number are fissionable and a common reaction is the fission of uranium-235 by neutrons in a nuclear reactor. For example, iodine-131, molybdenum-99 and xenon-133 can be produced in this way. Radionuclides from such a process must be carefully controlled in order to minimize the radionuclidic impurities.

Charged particle bombardment Radionuclides may be produced by bombarding target materials with charged particles in particle accelarators such as cyclotrons.

Neutron bombardment Radionuclides may be produced by bombarding target materials with neutrons in nuclear reactors . The desired nuclear reaction will be influenced by the energy of the incident particle and by the isotopic composition and purity of the target material.

Radionuclide generator systems Radionuclides of short half-life may be produced by means of a radionuclide generator system involving separation of the daughter radionuclide from a long-lived parent by chemical or physical separation.

Starting materials (including excipients) In the manufacture of radiopharmaceutical preparations, measures are taken to ensure that all ingredients are of appropriate quality, including those starting materials, such as precursors for synthesis, that are produced on a small scale and supplied by specialized producers or laboratories for use in the radiopharmaceutical industry. The actual quantity of radioactive material compared with quantities of excipients is normally very small therefore excipients can greatly influence the quality of the radiopharmaceutical preparation.

Target materials The composition and purity of the target material and the nature and energy of the incident particle will determine the relative percentages of the principal radionuclide and other potential radionuclides (radionuclidic impurities) and thus ultimately the radionuclidic purity. For very short lived radionuclides including the ones present in most positron emission tomography tracers (PET) tracers the determination of the chemical state and purity of radionuclide before patient use is difficult. Therefore before clinical use of these radionuclides, extensive validations and strict operational conditions are essential. Strict control of

range of specified quantity and quality is also essential. Any subsequent change in operational conditions should be re-validated.

Each batch of target material must be tested and validated in special production runs before its use in routine radionuclide production and manufacture of the preparation, to ensure that under specified conditions, the target yields a radionuclide in the desired quantity and quality.

Carriers A carrier, in the form of inactive material, either isotopic with the radionuclide, or non-isotopic, but chemically similar to the radionuclide, may be added during processing and dispensing of a radiopharmaceutical preparation to permit ready handling. In some situations it will be necessary to add carrier to enhance chemical, physical or biological properties of the radiopharmaceutical preparation. The amount of carrier added must be sufficiently small for it not to cause undesirable physiological effects. The mass of an element formed in a nuclear reaction may be exceeded by that of the inactive isotope present in the target material or in the reagents used in the separation procedures.

Carrier-free Radioactive preparations in which no carrier is intentionally added during the manufacture or processing may be referred to as *carrier-free*. The designation *no-carrier-added* is sometimes used to indicate that no dilution of the specific activity has taken place by design, although carrier may be present due to the natural presence of a non-radioactive element or compound accumulated during the production of the radionuclide or preparation of the compound in question.

Carrier-free specific activity can be determined by a consideration of the relationship between activity A, the number of radioactive atoms present N and the decay constant λ where $\lambda = 0.693/T_{1/2}$.

$$A = N\lambda = N\left(\frac{0.693}{T_{1/2}}\right)$$

The specific activity of radioactive materials that are not carrier-free can be determined by measuring both the radioactivity and the total amount of the element or compound of interest. Accurate determination, where a material has a high specific activity, may be difficult due to limitations in obtaining an accurate determination of the amount of the substance present by standard physical or chemical analysis.

Production of Radiopharmaceutical preparation Radiopharmaceutical preparations may contain the types of excipients permitted by the general monograph for the relevant the dosage form.

Sterilization Radiopharmaceutical preparations intended for parenteral administration are sterilized by a suitable method (see 5.8 Methods of sterilization). Whenever possible, terminal sterilization is recommended, although for many radiopharmaceutical preparations, the nature of the preparation is such that filtration is the method of choice.

All sterilization processes are validated.

When the size of the batch of a radiopharmaceutical is limited to one or few samples (e.g. therapeutic or very short-lived radiopharmaceutical preparations) parametric release of the product manufactured by a fully validated process is the method of choice. When the half-life is very short (e.g. less than 20 minutes), the administration of the radiopharmaceutical to the patient is generally on-line with a validated production system.

Addition of antimicrobial preservatives Radiopharmaceutical injections are commonly supplied in multidose containers. 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. The nature of the antimicrobial preservative, if present, is stated on the label or, where applicable, that no antimicrobial preservative is present.

Radiopharmaceutical injections for which the shelf-life is greater than one day and that do not contain an antimicrobial preservative should be supplied in single-dose containers. If, however, such a preparation is supplied in a multidose container, it should be used within 24 hours of aseptic withdrawal of the first dose.

Radiopharmaceutical injections for which the shelf-life is greater than one day and that do contain an antimicrobial preservative may be supplied in multidose containers. After aseptic withdrawal of the first dose, the container should be stored at a temperature between 2° and 8°C and the contents used within 7 days.

Warning/Caution: Adequate shielding[1] must be used to protect laboratory personnel from ionizing radiation. Instruments must be suitably shielded from background radiation.

[1]See Supplementary information chapter on Radiopharmaceuticals and 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 and Radiological Protection for Medical Exposure to Ionizing Radiation Safety Guide (IAEA, Vienna, 2002) Safety Standard Series No. RS-G-1.5. Consult the IAEA website for the current Safety Standards and publications (http://www-ns.iaea.org/standards/).

Identity tests

Tests for identity of the radionuclide are included in the individual monographs for radiopharmaceutical preparations. The radionuclide is generally identified by its half-life or by the nature and energy of its radiation or by both as stated in the monograph.

Half-life measurement The preparation to be tested should be tested after appropriate dilution to avoid dead time losses using an ionization chamber, a Geiger-Muller counter, a scintillation counter or a semiconductor detector. The activity must be sufficiently high to allow detection during several estimated half-lives. The measured half-life should not deviate by more than 5% from the half-life stated in the individual monograph..

Radionuclidic purity

Requirements for radionuclidic purity are specified in two ways:

1. By expression of a minimum level of radionuclidic purity. Unless otherwise stated in the individual monograph, the gamma-ray spectrum, should not be significantly different from that of a standardized solution of the radionuclide before the expiry date is reached.
2. By expression of maximum levels of specific radionuclide impurities in the individual monographs. In general, such impurities are those that are known to be likely to arise during the production of the material – for example, thallium-202 ($t_{1/2}$=12.23d) in the preparation of thallium-201 ($t_{1/2}$ =73.5h).

Radiochemical purity

Radiochemical purity is assessed by a variety of analytical techniques such as liquid chromatography, paper chromatography, thin-layer chromatography and electrophoresis. After or during separation, the distribution of radioactivity on the chromatogram is determined. Different measuring techniques are used depending on the nature of the radiation and the chromatographic technique. The quantity of substance applied to the chromatographic support (paper, plate or column) is often extremely small (because of the high sensitivity of detection of the radioactivity) and particular care has to be taken in interpretation with regard to the formation of artefacts. The addition of carriers (i.e. the corresponding non-radioactive compounds; see above under Manufacture) for both the radiopharmaceutical itself and the suspected impurities is sometimes helpful. There is, however, a risk that when a carrier of the radiopharmaceutical is added it may interact with the radiochemical impurity, leading to underestimation of these impurities. In cases where simple chromatographic methods fail to characterize the labelled compound satisfactorily, high performance liquid chromatography could be useful. In some cases, it is necessary to determine the biological distribution of the radiopharmaceutical in a suitable test animal.

Chemical Purity

Chemical purity refers to the proportion of the preparation that is in the specified chemical form regardless of the presence of radioactivity; it may be determined by accepted methods of analysis.

The chemical purity of a preparation is often no guide to its radiochemical purity. Preparations, especially those resulting from exchange reactions (for example, a preparation of o-iodohippuric acid in which some of the iodine atoms are replaced by atoms of iodine-131), may be of high chemical purity but may contain impurities of high specific activity (that is, a tiny weight of an radiochemical impurity may be associated with a relatively large amount of the radionuclide).

In general, chemical impurities in preparations of radiopharmaceuticals are objectionable only if they are toxic or if they modify the physiological processes that are under study or if they result in undesirable interactions (e.g. aluminium can induce flocculation of Tc-99m sulphur colloid). Special attention is necessary for impurities with a

pharmacologically active or pharmacodynamic effect even for very low amounts (for example, receptor ligands). Where appropriate, the stereo-isomeric purity has to be verified. In general, the type of limits for inorganic impurities such as arsenic and heavy metals that are specified in monographs for pharmaceutical substances are also valid for radiopharmaceuticals.

pH

When required, measure the pH of non-radioactive solutions as described under 1.13 Determination of pH. For radioactive solutions the pH may be measured using paper pH indicator strips, provided that the pH strips have been validated using an appropriate range of non-radioactive buffers.

Sterility

A number of monographs for radiopharmaceuticals contain the requirement that the preparation is sterile. Such preparations comply with 3.2 Test for sterility. Special difficulties arise, however, in carrying out the test for sterility for radiopharmaceutical preparations because of the short half life of most radionuclides, small size of batches and the radiation hazards. The half-life of many radiopharmaceuticals is so short that, while the sterility test may be initiated prior to release, it will be completed retrospectively.

When the size of the batch of a radiopharmaceutical is limited to one or few samples (e.g. therapeutic or very short-lived radiopharmaceutical preparations), sampling the batch may not be possible.

Bacterial endotoxins/ pyrogens

Where appropriate, an individual monograph for a radiopharmaceutical preparation requires compliance with 3.4 Test for bacterial endotoxins. Validation of the test is necessary to exclude any interference or artefact due to the nature of the radiopharmaceutical. The levels of radioactivity should be standardized as some types of radioactivity and radionuclides, especially high levels of activities, can interfere with the test. The pH of some radiopharmaceutical preparations will require to be adjusted to pH 6.5-7.5 to achieve optimal results.

Where it is not possible to eliminate interference with the test for bacterial endotoxins due to the nature of the radiopharmaceutical, compliance with 3.4 Test for pyrogens may be specified.

Labelling

Every radiopharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

The label on the primary container should include:

- a statement that the product is radioactive *or* the international symbol for radioactivity
- the name of the radiopharmaceutical preparation;
- where appropriate, that the preparation is for diagnostic or for therapeutic use;
- the route of administration;
- the total radioactivity present at a stated date and, where necessary, time; for solutions, a statement of the radioactivity in a suitable volume (for example, in MBq per ml of the solution) may be given instead;
- the expiry date and, where necessary, time;
- the batch (lot) number assigned by the manufacturer;
- for solutions, the total volume.

The label on the outer package should include:

- a statement that the product is radioactive *or* the international symbol for radioactivity
- the name of the radiopharmaceutical preparation;
- where appropriate, that the preparation is for diagnostic or for therapeutic use;
- the route of administration;
- the total radioactivity present at a stated date and, where necessary, time; for solutions, a statement of the radioactivity in a suitable volume (for example, in MBq per ml of the solution) may be given instead;
- the expiry date and, where necessary, time;
- the batch (lot) number assigned by the manufacturer;
- for solutions, the total volume;
- any special storage requirements with respect to temperature and light;
- where applicable, the name and concentration of any added microbial preservatives or, where necessary, that no antimicrobial preservative has been added;

Note: The shipment of radioactive substances is subject to special national and international[3] regulations as regards to their packaging and outer labelling.

[3]See Radiation ProtectionProgrammes for the Transport of Radioactive Material Safety Guide (IAEA, Vienna, 2007) for further details. Consult the IAEA website (http://www-ns.iaea.org/standards/) for the current guidance ."

Storage

Radiopharmaceuticals should be kept in well-closed containers and stored in an area assigned for the purpose. The storage conditions should be such that the maximum radiation dose rate to which persons may be exposed is reduced to an acceptable level.
Care should be taken to comply with national regulations for protection against ionizing radiation.

Radiopharmaceutical preparations that are intended for parenteral use should be kept in a glass vial, ampoule or syringe that is sufficiently transparent to permit the visual inspection of the contents. Glass containers may darken under the effect of radiation.

ANNEX

TERMINOLOGY

Nuclide

A unique atom characterized by its atomic number (number of protons in the nucleus) and its atomic mass number (total number of neutrons and protons in the nucleus) and having stability such that its lifetime is measurable. All atoms sharing the same atomic number are the same element.

Isotopes

Atoms of the same element with different atomic mass numbers are called isotopes.

Radioactivity

The property of certain nuclides of emitting radiation by the spontaneous transformation of their nuclei into those of other nuclides.

EXPLANATORY NOTE. The term "disintegration" is widely used as an alternative to the term "transformation". Transformation is preferred as it includes, without semantic difficulties, those processes in which no particles are emitted from the nucleus.

Radioactive decay

The property of unstable nuclides during which they undergo a spontaneous transformation within the nucleus. This change results in the emission of energetic particles or electromagnetic energy from the atoms and the production of an altered nucleus.

EXPLANATORY NOTE. The term "disintegration" is widely used as an alternative to the term "transformation". Transformation is preferred as it includes, without semantic difficulties, those processes in which no particles are emitted from the nucleus.

Units of radioactivity

The activity of a quantity of radioactive material is expressed in terms of the number of spontaneous nuclear transformations taking place in unit time. The SI unit of activity is the becquerel (Bq), a special name for the reciprocal second (s^{-1}). The expression of activity in terms of the becquerel therefore indicates the number of transformations per second.

The historical unit of activity is the curie. The curie (Ci) is equivalent to 3.7×10^{10} Bq. The conversion factors between becquerel and curie and its submultiples are given in Table.

Table. Units of radioactivity commonly encountered with radiopharmaceuticals and the conversions between SI units and historical units

Number of atoms transforming per second	SI unit: becquerel (Bq)	historical unit: curie (Ci)
1	1 Bq	27 picocurie (pCi)
1000	1 kilobecquerel (kBq)	27 nanocurie (nCi)
1×10^6	1 megabecquerel (MBq)	27 microcurie (μCi)
1×10^9	1 gigabecquerel (GBq)	27 millicurie (mCi)
37	37 Bq	1 (nCi)
37,000	37 kBq	1 (μCi)
3.7×10^7	37 MBq	1 (mCi)
3.7×10^{10}	37 GBq	1 Ci

Half-life period

The time in which the radioactivity decreases to one-half its original value.

EXPLANATORY NOTE. The rate of radioactive decay is constant and characteristic for each individual radionuclide. The exponential decay curve is described mathematically by the equation:

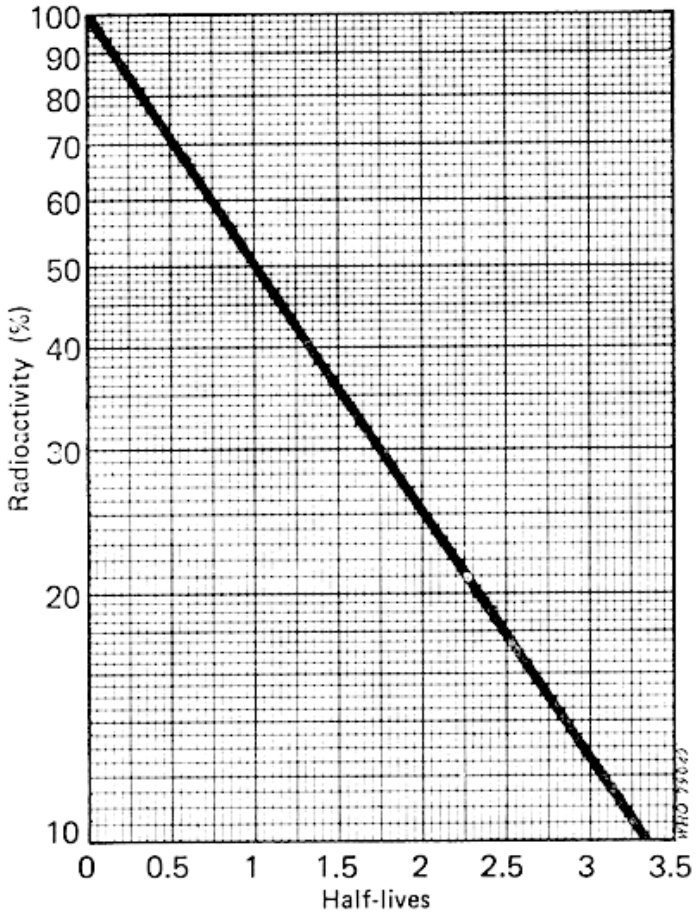
$$N = N_o e^{-\lambda t}$$

where N is the number of atoms at elapsed time t, No is the number of atoms when t = 0, and λ is the disintegration constant characteristic of each individual radionuclide. The half-life period is related to the disintegration constant by the equation:

$$T_{\frac{1}{2}} = \frac{0.693}{\lambda}$$

Radioactive decay corrections are calculated from the exponential equation, or from decay tables, or are obtained from a decay curve plotted for the particular radionuclide involved (see Fig. 1).

FIG. 1. MASTER DECAY CHART



Physical half-life

The physical half-life of a radionuclide ($T_{½}$ p) is the time in which the amount of radioactivity decreases to one half of its original value. Although the time of decay of an individual atom can not be determined, large numbers of atoms will obey statistical considerations and calculations of activity versus time can be carried out. The rate of decay for a collection of atoms (N) of the same radionuclide is constant and characteristic for each individual radionuclide. The exponential decay is described by the equation:

$$N = N_O e^{-\lambda t}$$

Where N is the number of atoms after an elapsed time t. N_0 is the number of atoms at time t = 0 and λ is the decay constant characteristic for a given nuclide. This relationship is commonly referred to as the decay law equation. Where the activity of a quantity of radioactive substance is known at a certain time its activity at any other time can be determined by using the decay law relationship. The physical half-life is related to the decay constant by the equation:

$$T_{1/2} = \frac{0.693}{\lambda}$$

In addition to the use of the decay law formula radioactivity can be determined at different times using decay tables or decay curves plotted for the specific radionuclide.

Biological half-life

The biological half-life ($T_{½}b$) of a radiopharmaceutical is the time taken for the concentration of the pharmaceutical to be reduced 50% of its maximum concentration in a given tissue, organ or whole body, not considering radioactive decay.

Effective half-life

The effective half-life ($T_{½}e$) is the actual half-life of a radiopharmaceutical in a given tissue, organ or whole body and is determined by a relationship including both the physical half life and biological half-lives. The effective half-life is important in calculation of the optimal dose of radiopharmaceutical to be administered and in monitoring the amount of radiation exposure. It can be calculated from the formula:

$$T_{1/2e} = \frac{T_{1/2p} x T_{1/2b}}{T_{1/2p} + T_{1/2b}}$$

Where $T_{1/2p}$ and $T_{1/2b}$ are the physical and biological half-lives respectively.

Radionuclidic purity

The radionuclidic purity of a preparation is that percentage of the total radioactivity that is present in the form of the stated radionuclide.

EXPLANATORY NOTE. Some radionuclides decay into nuclides that are themselves radioactive: these are referred to as mother (or parent) and daughter radionuclides respectively. Such daughter radionuclides are often excluded when calculating the radionuclidic purity; for example, iodine-131 will always contain its daughter xenon-131 m, but this would not be considered an impurity because its presence is unavoidable.

In employing the definition, the radioactivity must be measured in appropriate units: that is, in the number of nuclear transformations that occur in unit time (in terms Becquerels). If, for example, a preparation stated to be iodine-125 is known to contain 99MBq of iodine-125 and 1MBq of iodine-126, and no other radionuclide, then the preparation is said to be of 99% radionuclidic purity. It will be noted that the relative amounts of iodine-125 and iodine-126, and hence the radionuclidic purity, will change with time. An expression of radionuclidic purity must therefore contain a statement of the time, such as: “Not more than 1% of the total radioactivity is due to iodine-126 at the reference date stated on the label”.

It is clear that, in order to give a statement of the radionuclidic purity of a preparation, the activities (and hence the identities) of every radionuclide present must be known. There are no simple and certain means of identifying and measuring all the radionuclidic impurities that might be present in a preparation. An expression of radionuclidic purity must either depend upon the judgement of the person concerned, or it must be qualified

by reference to the method employed, for example: "No radionuclidic impurities were detected by gamma scintillation spectrometry using a sodium iodide detector."

Radioactive concentration

The radioactive concentration of a solution refers to the amount radioactivity per unit volume of the solution. As with all statements involving radioactivity, it is necessary to include a reference date and time of standardization. For radionuclides with a half-life period of less than one day, a more precise statement of the reference time is required.

In addition, the term radioactive concentration is generally applied to solutions of a radioactive solute. The radioactive concentration of a solution refers to the amount of radioactivity per unit volume of the solution. An example of units for radioactive concentration would be megaBecquerels per millilitre (MBq/ml). Since the radioactive concentration will change with time due to decrease in the nuclide radioactivity it is always necessary to provide a reference time. For short lived radionuclides the reference time will be more precise including time of day in addition to date.

Specific radioactivity (or specific activity)

The specific activity of a preparation of a radioactive material is the radioactivity per unit mass of the element or of the compound concerned.

The specific activity of a given radioisotope refers to the disintegration rate per unit mass of the element. For example, a fresh solution of ^{99m}Tc will have a specific activity of:

$$A_s = NxA$$

Where A_s=specific activity, and N=the number of ^{99m}Tc atoms in one gram of pure technetium. N is calculated as:

$$N=6.023 \times 10^{23} \text{ (atoms/mole)/(99 grams/mole)}$$

However, the following note must be taken into consideration to calculate the specific activity of a formulated compound.

EXPLANATORY NOTE. It is usual to specify the radionuclide concerned and also it is necessary to express the time thus: "100MBq of iodine-131 per mg of MIBG at 12.00 hours GMT on 1 January 2006".

Specific radioactivity is often not determined directly but is calculated from knowledge of the radioactive concentration of the solution and of the chemical concentration of the radioactive compound. Thus, if a solution contains x MBq of ^{131}I per ml, and if the ^{131}I is entirely in the chemical form of MIBG of which the concentration is y mg per ml, then at that time the specific activity is:

x/y mCi of iodine-131 per mg of MIBG.

Where necessary, the radiochemical purity of the preparation (see below) must be taken into account.

The term employed in radiochemical work is “specific activity”. As the word, “activity” has other connotations in a pharmacopoeia, the term should, where necessary, be modified to “specific radioactivity” to avoid ambiguity.

Radiochemical purity

The radiochemical purity of a preparation is that percentage of the stated radionuclide that is present in the stated chemical form. As radiochemical purity may change with time, mainly because of radiation decomposition, the result of the radiochemical purity test should be started at given date and if necessary hour indicating when the test was carried out. The radiochemical purity limit should be valid during the whole shelf-life.

EXPLANATORY NOTE. If, for example, a preparation of ^{99m}Tc-DTPA is stated to be 99 % radiochemically pure, then 99% of the technetium-99m is present in the form of DTPA (diethylenetriamine-pentaacetic acid) complex. Radiochemical impurities might include such substances as reduced-hydrolysed ^{99m}Tc or free ^{99m}Tc-pertechnetate anion

The possible presence of radionuclide impurities is not taken into account in the definition. If the radionuclide impurity is not isotopic with the stated radionuclide, then it cannot possibly be in the identical chemical form. If the radionuclide impurity is isotopic with the stated radionuclide, it could be, and indeed is likely to be, in the same chemical form.

Radiochemical impurities may arise during the preparation of the material or during storage, because of ordinary chemical decomposition or, what is often more important, because of radiation decomposition (that is, because of the physical and chemical effects of the radiation-radiolysis).

Critical Organ

The Critical Organ is the organ or tissue which receives the highest radiation dose. This may not be the target tissue and therefore the dose to the critical organ will determine the maximum safe dose which can be administered. This is primarily of importance with respect to therapeutic radiopharmaceuticals.

Physical characteristics of clinically relevant radionuclides.

Information on the physical characteristics of key radionuclide used in nuclear medicine is provided in the following table.

For more detailed information on physical characteristics including parent half-life, daughter half-life, decay mode, energy, end-point energy intensity, dose and daughter nucleus refer to IAEA nuclear data base (http://www.nndc.bnl.gov/nudat2/ and http://hpschapters.org/northcarolina/nuclide_information_library.php3).

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TABLE 1. PHYSICAL CHARACTERISTICS OF RADIONUCLIDES

Nuclide	Half-life period[a]	Type of decay[b]	Particle energies and transition probabilities		Electromagnetic transitions		
			energy MeV	transition probability	photon energy MeV	photons emitted	transitions internally converted
Caesium-137	30.1 a	β^-	0.512	94.6%			
			1.174	5.4%			
					.....		
					via 2.6 min ^{137m}Ba		
					0.662	85.1%	9.5%
					0.032-0.038	8% (Ba K X-rays)	
Carbon-11	1223.1 s	β^+	0.960	99.76	0.511	*from annihilation*	
Carbon-14	5730 a	β-	0.158	100 %	-	-	
Chromium-51	27.7 d	e.c.		100%	0.320	9.83%	
					0.005-0.006	~22% (V K X-rays)	
Cobalt-57	270 d	e.c.		100%	0.014	9.4%	78.0%
					0.122	85.2%	2.0%
					0.136	11.1%	1.5%
					0.570	0.02%	
					0.692	0.16%	
					others	low intensity	
					0.006-0.007	~55% (Fe K X-rays)	
Cobalt-58	70.8 d	β^+	0.475	15.0%	0.511	from β^+	

		e.c.		85.0%	0.811	99.4%	
					0.864	0.7%	
					1.675	0.5%	
					0.006-0.007	~26% (Fe K X-rays)	
Cobalt-60	5.27 a	β^-	0.318	99.9%	1.173	99.86%	0.02%
			1.491	0.1%	1.333	99.98%	0.01%
					others	<0.01%	
Dysprosium-165	2.32 h	β-, γ	0.205	0.1 %	0.046	2.5 %	
			0.290	1.6 %	0.047	4.6%	
			1.190	14.6 %	0.053	1.8 %	
			1.285	83.4 %	0.094	3.5%	
					0.279	0.5 %	
					0.361	0.8 %	
					0.545	0.16 5	
Erbium-169	9.4 d	β-, γ	0.341	45 %	0.008	0.15 %	
			0.350	55 %			
Fluorine-18	111 min	β+, K	0.649	97 %	*0.511*	*from annihilation*	
Gallium-67	78.3 h	e.c.		100%	0.091	3.6%	0.3%
					0.185	23.5%	0.4%
					0.209	2.6%	0.02%
					0.300	16.7%	0.06%

					0.394	4.4%	0.01%
					0.494	0.1%	
					0.704	0.02%	
					0.795	0.06%	
					0.888	0.17%	
					0.008-0.010	43% (Zn K X-rays)	
					.....		
					via 9.2 μs ^{67m}Zn		
					0.093	37.6%	32.4%
					0.008-0.010	13% (Zn K X-rays)	
Holmium-166	27.3 h	β-, γ	0.191	0.2 %	0.007	7.6 %	
			0.394	1 %	0.048	2.8 %	
			1.773	48 %	0.049	5.0 %	
			1.854	51 %	0.055	2.0 %	
					0.080	6.2 %	
					1.379	0.9 %	
					1.581	0.18 %	
					1.662	0.12 %	
Indium-111	2.81 d	e.c.		100%	0.172	89.6%	10.4%
					0.247	94.0%	6.0%
Indium-113m	99.5 min	i.t.		100%	0.392	64.9%	35.1%

					0.024-0.028	24% (In K X-rays)	
Iodine-123	13.2 h	e.c.		100%	0.159	83.0%	16.3%
					0.347	0.10%	
					0.440	0.35%	
					0.506	0.26%	
					0.529	1.05%	
					0.539	0.27%	
					0.027-0.032	~86% (Te K X-rays)	
Iodine-124	4.1 d	β+, γ, K	1.53		*0.511*	*from annihilation*	
			2.13		*and*		
						66 %	
					0.605	12 %	
					0.644	14 %	
					0.730	1.0 %	
					1.320	4.2 %	
					1.510	14 %	
					1.695	2.0 %	
					2.09		
					2.26	1.5 %	

Iodine-125	60.0 d	e.c.		100%	0.035	7%	93%
					0.027-0.032	138% (Te K X-rays)	
Iodine-131	8.06 d	β^-	0.247	1.8%	0.080	2.4%	3.8%
			0.304	0.6%	0.284	5.9%	0.3%
			0.334	7.2%	0.364	81.8%	1.7%
			0.606	89.7%	0.637	7.2%	
			0.806	0.7%	0.723	1.8%	
		1.3% of ^{131}I decays via 12 d ^{131m}Xe					
(Xenon-131m)		i.t.		100%	0.164	2%	98%
		(percentages relate to disintegrations of ^{131m} Xe)					
Iron-59	44.6 d	β^-	0.084	0.1%	0.143	0.8%	
			0.132	1.1%	0.192	2.8%	
			0.274	45.8%	0.335	0.3%	
			0.467	52.7%	0.383	0.02%	
			1.566	0.3%	1.099	55.8%	
					1.292	43.8%	
					1.482	0.06%	
Krypton-81m	13 s	γ	-	-	0.193	82 %	
Lutetium-177	6.71 d	β-, γ	0.175	12.3%	0.071	0.16 %	
						6.3 %	
			0.384	9.0 %	0.113		
				78.7 %		11.0%	
			0.497		0.208		
						0.2 %	
					0.250	0.2 %	

					0.321		
Molybdenum-99	66.2 h	β^-	0.454	18.3%	0.041	1.2%	4.8%
			0.866	1.4%	0.141	5.4%	0.7%
			1.232	80%	0.181	6.6%	1.0%
			others	0.3%	0.366	1.4%	
					0.412	0.02%	
					0.529	0.05%	
					0.621	0.02%	
					0.740	13.6%	
					0.778	4.7%	
					0.823	0.13%	
					0.961	0.1%	
					.....		
					via 6.02 h ^{99m}Tc in equilibrium		
					0.002	~0%	93.9%
					0.141	83.9%	10.0%
					0.143	0.03%	0.8%
Nitrogen-13	10 min	β+	1.19		*0.511*	*from annihilation*	
Oxygen-15	2.04 sec	β+	1.723		*0.511*	*from annihilation*	
Phosphorus-32	14.3 d	β^-	1.709	100%			
Rhenium-186	88.9 h	β-, γ, K	0.939	22.0 %	0.123	0.7 %	
			1.076	71.0 %	0.137	9.5 %	

					0.631	1.9 %
					0.768	0.8 %
Rhenium-188	18 h	β-, γ	1.964	25.3 %	0.155	14.9 %
			2.119	71.4 %	0.477	1.0 %
					0.633	1.2 %
					0.635	0.14
					0.673	0.11 %
					0.829	0.41 %
					0.931	0.56 %
					1.13	0.7 %
					1.306	0.01 %
Rubidium-81	4.7 h	β+, γ, K	0.33		0.253	
			0.58		0.450	
		daughter	1.05		1.10	

		^{81m}Kr					
Samarium-153	47 h	β-, γ	0.26	0.1 %	0.0058	11.8 %	
			0.632	34.1 %	0.0409	17.2 %	
			0.702	44.1 %	0.0415	31.2 %	
			0.81	21.0 %	0.0470	12.2 %	
					0.0696	5.1 %	
					0.103	28.3 %	
					0.422	0.2 %	
Selenium-75	118.5 d	e.c.		100%	0.066	1.1%	0.3%
					0.097	2.9%	3.0%
					0.121	15.7%	0.7%
					0.136	54.0%	1.6%
					0.199	1.5%	
					0.265	56.9%	0.4%
					0.280	18.5%	0.2%
					0.401	11.7%	
					others	<0.05% each	
					0.010-0.012	~50% (As K X-rays)	
					.....		
					via 16.4 ms ^{75m}As		
					0.024	0.03%	5.5%
					0.280	5.4%	

					0.304	1.2%	0.1%
					0.010-0.012	~2.6% (As K X-rays)	
Strontium-89	50.5 d	β-, (γ)	0.582	0.01 %	0.909	0.01 %	
				99.98 %			
			1.491				
Technetium-99m	6.02 h	i.t.		100%	0.002	~0%	99.1%
					0.141	88.5%	10.6%
					0.143	0.03%	0.87%
		.....					
		Daughter ^{99}Tc					
Thallium-201	73.5 h	e.c.		100%	0.031	0.29%	10.1%
					0.032	0.25%	9.6%
					0.135	2.9%	8.9%
					0.166	0.13%	0.2%
					0.167	8.81%	16.0%
Tin-113	115 d	e.c.		100%	0.255	21%	0.1%
					0.024-0.028	73% (In K X-rays)	
		.....					
		Daughter ^{131m}In					
Tritium (^{3}H)	12.35 a	β^-	0.0186	100%			
Tungsten-188	69.5 d	β-,	0.3		0.227		
					0.291		
		daughters					
		$^{188m+188}$Re					

Xenon-131m	11.9 d	i.t.		100%	0.164	2%	98%
					0.029-0.035	~52% (Xe K X-rays)	
Xenon-133	5.25 d	β^-	0.266	0.9%	0.080	0.4%	0.5%
			0.346	99.1%	0.081	36.6%	63.3%
					0.160	0.05%	
					0.030-0.036	~46% (Cs K X-rays)	
Xenon-133m	2.26 d	i.t.		100%	0.233	8%	92%
					0.029-0.035	~59% (Xe K X-rays)	
		.....					
		Daughter ^{133}Xe					
Ytterbium-169	32.0 d	e.c.		100%	0.021	0.21%	12.3%
					0.063	45.16%	50.4%
					0.094	0.78%	12.3%
					0.110	3.82%	56.2%
					0.117	0.04%	
					0.118	1.90%	3.2%
					0.131	11.42%	13.5%
					0.177	17.31%	17.7%
					0.198	26.16%	25.7%
					0.240	0.12%	
					0.261	1.74%	
					0.308	11.04%	0.7%
Yttrium-90	64.5 h	β-	2.281	100 %	-	-	

[a] μs = microsecond; ms = millisecond; s = second; min = minute; h = hour; d = day; a = year.

[b] e.c. = electron capture; i.t. = isomeric transition.

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