Consultation documents

The International Pharmacopoeia

Radiopharmaceuticals: General monograph

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/13.542/Rev.1, March 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

1.1 Introduction

Radiopharmaceuticals, as the name suggests, are pharmaceutical formulations consisting of radioactive substances (radioisotopes and molecules labelled with radioisotopes), which are intended for use either in diagnosis or therapy.

Radiopharmaceuticals are essential components of nuclear medicine practice; a modality where radiopharmaceuticals are administered to patients for diagnosing, managing and treating a large number of diseases.

In imaging, the unique properties of $\gamma$-rays emitted from the radioactive isotopes allow the radiopharmaceutical to be traced or imaged non-invasively, thus providing functional information of the target tissue or organ. In therapy, the $\beta$-ray energy from the radioisotope is delivered to the target tissue to partially or completely destroy the diseased tissues.

Radiopharmaceuticals are unlike conventional pharmaceuticals in many respects. The most striking feature is the property of the radionuclide, which disintegrates or decays with time, often resulting in a limited shelf-life of the product. The physical half-life of the radionuclides used in radiopharmaceuticals is generally short, and hence the final preparation needs to be carried out before administration to the patient. Hence, the concept of the "hospital radiopharmacy" unit to prepare radiopharmaceuticals has become a practice in nuclear medicine departments in hospitals. At the hospital radiopharmacy a trained radiopharmacist prepares the various radiopharmaceutical formulations and tests each formulation for its quality (quality control). The formulations are then provided to a nuclear medicine physician for administration into the patient for investigation or for therapy.

Radiopharmaceuticals are either ready to use (available from suppliers) or prepared in-house from "cold kits" and radioisotopes from generators, or synthesized from radioisotopes and suitable precursors as with cyclotron-produced radioisotopes. Some centres synthesize the necessary ligands at their hospital radiopharmacy and formulate the radiopharmaceuticals. All are subjected to the required quality control tests, to ensure that the formulations fulfill radiological and pharmaceutical safety and efficacy in accordance with the specifications laid down.

The use of radioactive material necessitates careful and safe handling of these products by trained and authorized personnel, in an approved/authorized laboratory facility as per the guidelines of Atomic Energy Regulatory Board (AERB) in India.
1.2 Definitions and terminology

*chemical purity*
Chemical purity of a chemical substance is the percentage of the chemical of interest in the specified chemical form. In the monographs on radiopharmaceutical preparations, chemical purity of the active ingredient is indicated and controlled by specifying limits on chemical impurities.

*half-life period*
The time in which a given quantity of a radionuclide decays to half its initial value is termed as half-life ($T_{1/2}$).

*isotopes*
Isotopes of an element are nuclides with the same atomic number “Z” but different mass numbers “A”. They occupy the same place in the periodic table and have similar chemical properties.

*isotopic carrier*
An isotopic carrier is a stable isotope of the element either present or added to the radioactive isotope of the same element. Often the radionuclides contain isotopic carriers and their content depends on the route/method followed for the production of the radionuclide.

*kit for radiopharmaceutical preparation*
It is a set of non-radioactive reagents to be reconstituted and/or combined with radionuclides following the protocol suggested by the manufacturer for preparing the final radiopharmaceutical formulations, prior to its administration. Such kits are also often referred to as “cold kits”, as they are devoid of radioactivity.

*nuclide*
An elemental species characterized by (a) its mass number “A”, (the sum of the number of protons and neutrons in its nucleus), (b) its atomic number “Z” (number of protons which is also same as number of electrons in a neutral atom) and also by (c) its nuclear energy state.

*period of validity or shelf-life of the radiopharmaceutical*
The time during which specifications described in the monograph are complied with by the radiopharmaceutical denoting the shelf-life of the radiopharmaceutical preparation. Any radiopharmaceutical preparations including the cold kits have limited shelf-life, which needs to be clearly stated on the label as the expiry date, and if necessary, the time.

*radioactive concentration*
This refers to the radioactivity of a radionuclide per unit volume of the radioactive preparation.

*radioactivity*
The phenomenon of emission of radiation owing to the spontaneous transformation or disintegration of a radionuclide is known as “radioactivity”. However, the term “radioactivity” is also used to express the physical quantity (activity or strength) of this phenomenon. The radioactivity of a preparation is the number of nuclear disintegrations or transformations per unit time.

*radiochemical purity*
The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest in a stated chemical form, to the total radioactivity of that radionuclide present in the preparation, is referred to as “radiochemical purity”. In the context of radiopharmaceuticals, radiochemical purity is an important quality parameter which needs to be within the stipulated limits. The relevant radiochemical impurities are listed with their limits in the individual monographs for each radiopharmaceutical.
**radionuclide**
Nuclides containing an unstable arrangement of protons and neutrons that transform spontaneously to either a stable or another unstable combination of protons and neutrons with a constant statistical probability by emission of radiation. These are said to be radioactive and are called radionuclides. The initial unstable nuclide is referred to as the "parent radionuclide" and the nuclide after transformation as the "daughter nuclide". Such a transformation is also known as "radioactive transmutation" or "radioactive disintegration" or "radioactive decay".

**radionuclide generator**
Any system or device incorporating a fixed parent radionuclide from which is produced a daughter radionuclide by elution or by any other method and used in radiopharmaceutical preparation, e.g. the most widely used radionuclide generator in radiopharmacy is the $^{99}$Mo-$^{99m}$Tc generator.

**radionuclidic purity**
The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest to the total radioactivity of the radioactive preparation is referred to as “radionuclidic purity”. In the context of radiopharmaceuticals, radionuclidic purity is an important quality parameter and it is mandatory that the radionuclidic impurities are within the stipulated limits. Such radionuclidic impurities arise during the radionuclide production and are, hence, dependent on the production route. In the context of radiopharmaceuticals the acceptable limits for the possible radionuclides are listed in the individual monographs.

**radiopharmaceutical**
Any medicinal or pharmaceutical product which, when ready for use, contains one or more radionuclides (radioactive isotopes) intended for human use, either for diagnosis or therapy.

**radiopharmaceutical precursor**
It is a chemical compound or ligand used in the synthesis of the radiopharmaceutical preparation. It could either be an inactive chemical compound or a radiolabelled intermediate produced for the preparation of radiopharmaceutical formulation, prior to administration.

**specific radioactivity**
The radioactivity of a radionuclide per unit mass of the element or of the chemical form of the radioactive preparation is referred to as the “specific radioactivity”, sometimes also referred as “specific activity”.

**total radioactivity**
The radioactivity of the radionuclide per unit of the dispensed formulation (vial, capsule, ampoule, generator, etc.) is the total radioactivity, which is an important parameter in dispensing and administration of the radioactive material to the patient as well as from the regulatory requirement for safe handling of the radioactive materials in a facility.

**units of radioactivity**
In the International System (SI), the unit of radioactivity is one nuclear transmutation per second and is expressed in Becquerel (Bq), named after the scientist Henri Becquerel. The old unit of radioactivity was Curie (Ci), named after the scientists Madame Marie Curie and Pierre Curie, the pioneers who studied the phenomenon of radioactivity. One Ci is the number of disintegrations emanating from 1 g of Radium-226, and is equal to $3.7 \times 10^{10}$ Bq. Absolute radioactivity measurements require a specialized laboratory, but identification and measurement of radiation can be carried out relatively by comparing with standardized preparations provided by reference laboratories recognized by international or national authorities. (With all statements involving radioactivity, it is necessary to include a reference date of measurement in case of radionuclides with a half-life less than 30 days. The time of
standardization should be expressed to the nearest hour. For radionuclides with a half-life period of less than one day, a more precise statement of reference time should be given.)

1.3 Phenomenon of radioactive decay and the radiations

The radioactive decay or transformation, as described earlier, involves transformation of the unstable radioactive nucleus to attain a more stable configuration. As the nucleus contains protons and neutrons, such transformations involve reactions of these sub-atomic particles. In a simplified manner, it could be stated that the stability of the nucleus predominantly depends on the total number of nucleons (protons and neutrons) as well the ratio of the protons (p) to the neutrons (n). While nearly all the isotopes beyond element Bismuth (atomic number 83) are radioactive as the total number of nucleons become too large for stability, the lower atomic number elements have stable as well as radioactive isotopes, depending on the p/n ratio and certain other properties of the nuclide. Generally, a proton rich (or neutron deficient) nuclide would transform to reduce the proton content; while a neutron rich nuclide would transform vice versa. A very heavy radionuclide may attain stability by shedding some nucleons. Such transformations may involve the emission of charged particles, capture of electron from the extra-nuclear orbits by the nucleus, also known as electron capture (EC) or isomeric transition (IT). The charged particles emitted from the nucleus may be alpha (α) particles (helium nucleus of mass number 4) or beta (β) particles. Beta particles may be either, negatively charged β−, also known as negatrons, generally equivalent to electrons or positively charged β+, and also known as positrons. The emission of charged particles from the nucleus may be accompanied by the emission of gamma (γ) rays, which are energetic photons of electromagnetic radiation and do not have any charge or mass. Gamma rays are also emitted in a process called isomeric transition (IT), where an excited state of a radionuclide decays to the de-excited state by gamma-ray emission, with no changes in atomic, mass or neutron number. The emissions of gamma rays may be partly replaced by the ejection of electrons known as internal conversion (IC) electrons, due to the interaction of the gamma ray with the extranuclear orbital electrons. This phenomenon, like the process of electron capture, causes a secondary emission of X-rays (due to the vacancies created in the electronic orbits which are then filled by reorganization of the electrons from the outer orbits in the atom). This secondary emission of X-rays may itself be partly replaced by the ejection of outer electrons known as Auger electrons, due to the interaction of the X-rays with the outer electrons.

The decay of a radionuclide is governed by the laws of probability with a characteristic decay constant (λ) and follows an exponential law. The time in which a given quantity of a radionuclide decays to half its initial value is termed the half-life (T_{1/2}).

Each radionuclide is characterized by an invariable T_{1/2}, expressed in units of time and by the nature and energy of its radiation or radiations. The energy is expressed in electron volts (eV), kilo-electron volts (keV) or mega-electron volts (MeV).

The penetrating power of each radiation varies considerably according to its nature and its energy. Alpha particles, which are the heaviest among the radiations, have the minimum penetration, followed by the beta particles and gamma rays have the most penetrating power. Alpha particles can be stopped within a thickness of a few micrometers to few tens of micrometers of matter, while beta particles require several millimeters to several centimeters of matter for complete attenuation. Gamma rays, on the other hand, are the most penetrating and are attenuated in an exponential manner in matter. High density materials such as lead are used to stop the gamma rays and a ten-fold reduction of energetic gamma rays may require several centimeters of lead. The denser the material used, the higher the attenuation of radiations.
Modes of radioactive decay

**Alpha decay (α).** Radioactive nuclei having too many nucleons (n and p) often undergo alpha decay, in order to achieve nuclear stability. Alpha particle has a mass of 4 units and a charge of +2 units, and is therefore, equivalent to helium+2 ion. Alpha particles from radionuclides have energy ranging from 1.8 to 11.7 MeV. But, artificially, rays (He ions) can be accelerated to energies reaching several GeV.

**Negatron decay (β–).** Radioactive nuclei having neutrons in excess than what is needed for a stable configuration, mostly undergo negatron or β– decay, in order to achieve nuclear stability. Negatrons have the same mass and electrical charge of orbital electrons, but they originate from nucleus at the very instant of decay, when a neutron transforms to a proton. Such a transformation results in increase in atomic number by 1, while the mass does not change significantly. The β- decay phenomenon could be expressed as the following nuclear reaction:

\[ n \rightarrow p + \beta^- + \nu^* \]

\(\nu^*\) represents “anti-neutrino” a sub-atomic entity which does not have any mass or charge, but which can possess energy. The \(\beta^-\) decay equation has to be balanced with respect to mass, charge, energy, momentum as well as spin. The \(\nu^*\) is important for accounting for the conservation of momentum, spin and energy. Thus, unlike particles which are emitted with a single energy from a nuclide, \(\beta^-\) particles from a certain radionuclide could have varied energies, accompanied by the \(\nu^*\) carrying complementary amount of energy, with the total energy being same. \(\beta^-\) particles have energies in the range from a few KeV to 14 MeV. For a given transition, negatrons have a continuum spectrum of energies.

An example of beta decay is:

\[^{32}\text{P} \rightarrow ^{32}\text{S} + \beta^- + \nu^*\]

**Positron decay (β+).** Radioactive nuclei having neutrons lesser than what is needed for a stable configuration undergo positron \(\beta^+\) decay in order to achieve stability, if adequate energy is available from the nucleus for transformation of a proton to a neutron. Such a transformation results in decrease in atomic number by 1, while the mass does not change significantly. The \(\beta^+\) decay phenomenon could be expressed as the following nuclear reaction:

\[ p \rightarrow n + \beta^+ + \nu \]

As in the case of \(\beta^-\) decay, in order to conserve momentum, spin and energy, a sub-atomic entity which does not have any mass or charge known as “neutrino” represented by \(\nu\) is also emitted, which carries some energy with it. Thus, like \(\beta^-\) particles, \(\beta^+\) particles also have varying energies. However, unlike \(\beta^-\) particles, in the case of \(\beta^+\) particle emission, the proton which is lighter is transformed to the heavier particle neutron, along with a positron, resulting in the generation of mass equivalent to 2 electrons (1 positron and another the difference between a neutron and a proton). This cannot be possible, unless energy is available for conversion into the mass equivalent to 2 electrons, which is 1.02 MeV. Hence, unlike \(\beta^-\) decay, \(\beta^+\) decay can occur only when at least 1.02 MeV of energy is available. During transmutation, due to the changes in nuclear energy levels, certain nuclides have energy > 1.03 MeV, in which case, \(\beta^+\) decay can occur. The energy in excess of 1.02 MeV is shared by the \(\beta^+\) and \(\nu\).

An example of \(\beta^+\) decay is:

\[^{18}\text{F} \rightarrow ^{18}\text{O} + \beta^+ + \nu\]

While the \(\beta^-\) particles or negatrons, which are equivalent to electrons are found all around in matter as these are constituents of atoms, \(\beta^+\) particles or positrons are not naturally present in matter. These are “anti-matter” particles, which when meet with the corresponding “matter”
will annihilate each other, resulting in conversion of matter into energy as per Einstein’s mass-energy equation \( E=mc^2 \). In the case of \( \beta^+ \) particles, once they come in contact with the electrons, they will be annihilated. When a positron is emitted, initially it spends all its energy as it travels through matter, comes across an electron, and both undergo annihilation, resulting in two photons of 511 KeV each travelling in opposite directions. It is noteworthy that for \( \beta^+ \) emission energy of 1.02 MeV (2 times 511 keV) is necessary, which later appears as 2 photons of 511 keV each. In order to have conservation of mass, energy and momentum, the 2 photons are emitted in exactly opposite directions.

It may be noted that “positron emission tomography”, a nuclear medicine imaging technique employing radiopharmaceuticals labelled with positron-emitting radionuclide(s), is a highly sensitive imaging technique based on the coincidence counting of the 2 photons emitted at 180°.

**Electron capture (EC).** Radioactive nuclei having neutrons lesser than what is needed for a stable configuration and which do not have adequate energy available to undergo positron \( \beta^+ \) decay, decay by another route named “electron capture”, in order to achieve stability. In this mode of decay an orbital electron is captured and taken into the nucleus, thus facilitating conversion of a proton to a neutron, resulting in a nuclide with decrease in atomic number by 1. An electron capture reaction can be written as:

\[
p + e^- \rightarrow n + \nu
\]

Since there are several orbital electrons (except in the case of elements with very low Z), EC process is a statistical phenomenon, where varied probabilities for EC arise for the K-shell (inner most shell) electrons, L-shell electrons and so on. EC phenomenon results in the depletion of electron in one of the inner shells of the atom, which in turn is a vacancy that is filled by one of the outer shell electrons accompanied by emission of characteristic X-rays. Often, EC mode of decay is accompanied by \( \gamma \) rays and characteristic X-rays as well as Auger electrons that arise due to the interaction of the \( \gamma \) rays and X-rays with the outer orbit electrons.

An example of EC is:

\[
^{125}\text{I} \rightarrow ^{125}\text{Te} + 35 \text{ keV } \gamma \text{ ray (7\%)} + 27-32 \text{ KeV Te X-rays (136 \%)} + \sim 19 \text{ Auger electrons}
\]

While positron emission can occur only if at least 1.02 MeV of energy is available from the decay reaction, EC does not need such energy and both modes of decay result in nuclides with an atomic number lower by one. However, when energy is available for \( \beta^+ \) emission, EC may also occur in some cases, while vice versa is not possible. One example is of \(^{64}\text{Cu}\), which decays by \( \beta^- \) emission, \( \beta^+ \) emission as well as EC. It is noteworthy that several factors that influence nuclear stability are responsible in determining the modes of decay and their probabilities.

**Gamma decay (\( \gamma \)).** Gamma rays are electromagnetic rays coming out of a nucleus as a result of the difference in nuclear energy levels of the excited and the ground states of the daughter nuclide when a nuclear transmutation takes place. Most radioactive decays are accompanied by \( \gamma \) rays, although this is not essential. Since \( \gamma \) rays carry the energy arising out of the difference in nuclear energy levels, these are often highly energetic, with energy greater than those of X-rays.

**Isomeric transition (IT).** When an excited nucleus de-excites by emission of a delayed gamma ray, the daughter nucleus is a nuclear isomer of the parent and the process is called isomeric transition.

As mentioned earlier, gamma rays are emitted owing to the energy difference in the nuclear states of the excited and the ground states of the daughter nuclide after a transmutation or
Such γ-ray emissions are very quick and happen within nanoseconds. However, if the de-excitation of the daughter nuclide from the higher state to ground state does not occur easily (due to rules that govern such transitions – nuclear physics), then such transitions become slow and the excited state of the nuclide is referred to as “metastable” state, indicated by the symbol “m” after the atomic number (e.g. 99mTc). Nuclear isomers have the same number of protons and the same number of neutrons, only they are arranged in a more stable configuration in the daughter nucleus.

1.4 Radiation exposure and the units of radiation dose

Exposure
The sum of all electrical charges of one sign produced by photons in a given mass of air. The unit is the Roentgen (R) which is equal to $2.58 \times 10^{-4}$ coulomb of electric charge produced in 1 kg of dry air at standard temperature and pressure (STP). This definition applies to X-rays and γ rays under 3 MeV of energy. The intensity of gamma radiation field is measured in terms of exposure rate at some distance from the source and is expressed as Roentgen/hour (R/h).

a) Acute exposure: a high dose of radiation is delivered within a short time. This type of exposure results in nonstochastic effects, which means that the severity of the effect increases with the dose given.

b) Chronic exposure: a low dose of radiation is delivered over a long time. Chronic exposure results in stochastic effects, which means that the probability of observing the effect increases with the dose given. Background radiation and occupational exposure of radiation workers are examples of chronic exposure. To prevent unnecessary low-level exposures of radiation workers, the principle of ALARA must be practiced at all times.

Roentgen (R), a unit of exposure of X- or γ-radiation equal to $2.58 \times 10^{-4}$ coulomb/kg in air, is superseded by the SI unit of exposure, the coulomb/kg (C kg$^{-1}$). 1 C kg$^{-1}$ = 3.876 x 10$^3$ R.

Absorbed dose
Energy transferred to and absorbed by a unit mass of a material. The special unit is the radiation absorbed dose (rad), which is equal to 0.01 joule (J) of energy absorbed per kg (10$^{-2}$ J/kg) of any material. In the MKS system, 1 J = force of one newton (N) acting over a distance of 1 m, and 1 N = force which gives a mass of 1 kg an acceleration of 1 m/s each second. The SI unit of absorbed dose is gray (Gy) defined as 1 J/kg and supersedes the rad as a unit of absorbed dose. 1 Gy = 100 rad.

The Roentgen and the rad in soft tissue are approximately equivalent in magnitude for the moderate energies.

Critical organ. The organ that is functionally essential for the body and receives the highest radiation dose after administration of radiopharmaceutical.

Quality factor (QF). The relative effectiveness of the radiation in producing biological response.

Dose equivalent (DE)
Absorbed dose multiplied by quality factor (QF). QF are values, based on linear energy transfer that permit estimates of radiation energy caused by various types of radiation. They are based on degree of ionization produced in water. Radiation that produces 100 ion pairs in 1 micron of water, spends 3.5 KeV of energy per micron receives a QF = 1. Those that produce 100–200 ion pairs gets QF = 2 and so on.
The unit of DE is Roentgen-equivalent-man (rem). A rem is numerically equal to the absorbed dose in rad multiplied by the appropriate QF defining the biological effect and by any other modifying factors. The SI unit of DE is sievert (Sv) and supersedes rem as the unit of dose equivalent. The units for sievert are joule/kg (J Kg\(^{-1}\)) equal to 100 rem.

Sievert (Sv) is numerically equal to the absorbed dose in Gray multiplied by the appropriate QF defining the biological effect and by any other modifying factors expressed in J/kg.

**Annual limit of intake (ALI)**

In order to simplify the comparison of the committed effective doses from intakes with equivalent dose limits, it is convenient to define the secondary dose limit called the ALI. It normally corresponds to a committed effective dose from an intake of a given radionuclide equal to the appropriate equivalent dose limits for workers. Restrictions of intake in each year to less than ALI therefore ensures that the maximum annual equivalent dose from that radionuclide will always be less than the equivalent dose even if intake occurred every year for 50 years.

### 1.5 Production of radionuclides

A radiopharmaceutical preparation monograph describes as precisely as possible the method of production of the radionuclide. A radiopharmaceutical preparation contains its radionuclide as an element in atomic or molecular form, e.g. \([^{133}\text{Xe}]\), \([^{18}\text{O}]\)\(_2\)\(_\text{O}\); as an ion, e.g. \([^{131}\text{I}]\)iodide, \([^{99m}\text{Tc}]\)pertechnetate; included in or attached to organic molecules by chelation, e.g. \([^{111}\text{In}]\)oxine or by covalent bonding, e.g. \(2-[^{18}\text{F}]\)fluoro-2-deoxy-D-glucose.

The practical ways of producing radionuclides for use in, or as radiopharmaceutical preparations are by (a) neutron bombardment of target materials (generally in nuclear reactors); (b) charged particles bombardment of target materials (in accelerators such as cyclotrons); (c) nuclear fission of heavy nuclides of target materials (generally after neutron or particle bombardment); and (d) from a radionuclide generator.

**Neutron or charged particle bombardment**

The nuclear reaction and the probability of its occurrence in unit time are dependent on the nature and physical properties of the target material and the nature, energy and quantity of the incident particles.

The nuclear transformation occurring through particle bombardment may be written in the form:

\[\text{target nucleus (bombarding particle, emitted particle or radiation) produced nucleus}\]

Examples: \(^{58}\text{Fe (n,}\gamma^{59}\text{Fe)}\); \(^{18}\text{O(p,n)}^{18}\text{F}\)

In addition to the desired nuclear reaction, adventitious transformations may occur. These will be influenced by the energy of the incident particle and the purity of the target material. Such adventitious transformations may give rise to radionuclidic impurities.

**Nuclear fission**

A small number of nuclides with a high atomic number are fissionable and the most frequently used reaction is the fission of uranium-235 by neutrons in a nuclear reactor. Iodine-131, molybdenum-99 and xenon-133 may be produced by nuclear fission of uranium-235. Their extraction of the desired radioisotope from a mixture of more than 200 other radionuclides must be carefully controlled in order to minimize the radionuclide impurities, which have to be within permissible levels.
Radionuclide generators
Radionuclide generator systems use a relatively long-lived parent radionuclide which decays to a daughter radionuclide, usually with a shorter half-life. The parent radionuclide and the daughter radionuclide exist in transient or secular equilibria depending on the ratio of the $T_{1/2}$ of parent and daughter radionuclides. The daughter radionuclide is separated from the parent radionuclide using a chemical or physical process. It is possible to use the daughter at a considerable distance from the production site of the generators despite its short half-life. The duration for which the generator can be used will depend on the $T_{1/2}$ of the parent radionuclide.

Target materials
The isotopic composition and purity of the target material determines the relative percentages of the principal radionuclide and radionuclidic impurities. The use of isotopically enriched target material, in which the abundance of the required target nuclide has been artificially increased, can improve the production yield and the purity of the desired radionuclide.

The chemical form, the purity, the physical state and the chemical additives, as well as the bombardment conditions and the direct physical and chemical environment, will determine the chemical state and chemical purity of the radionuclides which are produced.

In the production of radionuclides and particularly of short-lived radionuclides, it may not be possible to determine any of these quality criteria before further processing and manufacture of radiopharmaceutical preparations. Therefore each batch of target material must be tested in test production runs before its use in routine radionuclide production and manufacture of the radiopharmaceutical preparations, to ensure that under specified conditions, the target yields the radionuclide in the desired quantity and quality specified.

The target material is contained in a holder in gaseous, liquid or solid state, in order to be irradiated by a beam of particles. For neutron bombardment, the target material is commonly contained in quartz ampoules or high purity aluminum or titanium containers. It is necessary to ascertain that no interaction can occur between the container and its contents under the irradiation conditions (temperature, pressure, time).

For charged particle bombardment, the holder for target material is usually built of aluminum or another appropriate metal, with a low cross section for the irradiating particles and also having a good thermal conductivity to remove the heat generated. The target will have inlet and outlet ports, a surrounding cooling system and usually a thin metal foil target window. The nature and thickness of the target window have a particular influence on the yield of the nuclear reaction and may also affect the radionuclidic purity.

The production procedure shall clearly describe the target material; construction of the holder for target material; loading of target material into the irradiation system; method of irradiation (bombardment); separation of the desired radionuclide, and evaluates all effects on the efficiency of the production in terms of quality and quantity of the produced radionuclide.

The chemical state of the isolated radionuclide may play a major role in all further processing.

Precursors for synthesis
Generally these precursors are not produced on a large scale. Some precursors are synthesized by the radiopharmaceutical production laboratory; others are supplied by specialized producers or laboratories.

Tests for identity, for chemical purity and assay must be performed by validated procedures.

When batches of precursors are accepted based on the data from the certificates of analysis, suitable evidence has to be established to demonstrate the consistent reliability of the
analyses by suppliers and at least one identity test must be conducted. It is recommended to test precursor materials in production runs before their use for the manufacture of radiopharmaceutical preparations, to ensure that under specified production conditions, the precursor yields the radiopharmaceutical preparation in the desired quantity and quality specified.

**Performance of the production system**

All operations, from the preparation of the target to the dispensing of the final radiopharmaceutical preparation, must be clearly documented including their impact on the purity of the final product and the efficiency of the procedure. Where possible, in-process controls are performed and the results recorded at each production step to identify at which level a possible discrepancy from the normal production procedure may have occurred.

a) The production of radiopharmaceutical preparations may make use of mechanical and automated processes that are used in the pharmaceutical industry, subject to adapting these for use with radioactive material and to the requirements of radioprotection.

b) For radiopharmaceutical preparations containing short-lived radionuclides, such as certain positron emitters, remotely controlled production and automated radiosynthesis are generally used. For radionuclides with a very short half-life (less than 20 min), the control of the performance of the production system is an important measure to assure the quality of the radiopharmaceutical preparation before its release.

c) Any production procedure must be validated in test/trial production runs before its use in routine manufacture of radiopharmaceutical preparations, to ensure that under specified production conditions, the production system yields the radiopharmaceutical preparation in the desired quantity and specified quality.

d) The preparation of the dosage form of the final radiopharmaceutical preparation in the practice of nuclear medicine generally involves limited radioactivity starting from ready-to-use radiopharmaceutical preparations, generators, kits and radioactive precursors. All conditions which may affect the quality of the product (e.g. radiochemical purity, sterility, etc.) must be clearly defined and must include appropriate measures for radiation protection.

### 1.6 Identification

**Radioactive decay**

Radioactivity decays at an exponential rate with a particular decay constant and is a characteristic of each radionuclide.

The exponential decay (decay curve) is described by the equation:

\[ A_t = A_0 e^{-\lambda t} \]

- \( A_t \) = the radioactivity at time \( t \),
- \( A_0 \) = the radioactivity at time \( t = 0 \),
- \( \lambda \) = the decay constant characteristic of each radionuclide, and
- \( e \) = the base of Napierian logarithms.

The half-life \( T_{1/2} \) is related to the decay constant \( (\lambda) \) by the equation:

\[ T1/2 = 0.693/ \lambda \]

The radionuclide is generally identified by its half-life or by the nature and energy of its radiation or radiations emitted or by both, as prescribed in the monograph.
Measurement of $T_{1/2}$

The $T_{1/2}$ is measured with a suitable radiation detector such as an ionization chamber, a Geiger-Müller counter, a scintillation counter (solid crystal or liquid) or a semiconductor detector. The radiopharmaceutical preparation to be tested is used as such or diluted or dried in a capsule after appropriate dilution. The radioactivity chosen, having regard to experimental conditions, must be of a sufficiently high level to allow detection during several estimated $T_{1/2}$, but not too high to minimize count rate losses, for example due to dead time.

The radioactive source is prepared in a manner that will avoid loss of material during handling. If it is a liquid (solution), it is contained in bottles or sealed tubes. If it is a solid (residue from drying in a capsule), it is protected by a cover consisting of a sheet of adhesive cellulose acetate or of some other material.

The same source is measured in the same geometry and at intervals usually corresponding to half of the estimated half-life throughout a time equal to about three half-lives. The performance of the apparatus is checked using a source of long $T_{1/2}$ and, if necessary, corrections for any changes in the count rate have to be applied (see Measurement of radioactivity).

A graph can be drawn with time as the abscissa and the logarithm of the relative instrument reading (e.g. count rate) as the ordinate. The calculated $T_{1/2}$ should not differ by more than 5% from the expected $T_{1/2}$, unless otherwise stated in the pharmacopoeia.

Determination of the nature and energy of the radiation

The nature and energy of the radiation emitted may be determined by several procedures including the construction of an attenuation curve and the use of spectrometry. The attenuation curve can be used for analysis of $\beta$ radiation. Spectrometry is mostly used for identification of $\gamma$ rays and detectable X-rays.

The attenuation curve is drawn for pure electron emitters when no spectrometer for beta rays is available or for beta/gamma emitters when no spectrometer for gamma rays is available. This method of estimating the maximum energy of beta radiation gives only an approximate value. The source, suitably mounted to at fixed geometry, is placed in front of the thin window of a Geiger-Müller counter or a proportional counter. The source is protected as described above. The count rate of the source is then measured. Between the source and the counter are placed, in succession, at least six aluminum screens of increasing mass per unit area. Within such limits that with a pure beta emitter this count rate is not affected by the addition of further screens. The screens are inserted in such a manner that constant geometrical conditions are maintained. A graph is drawn showing the mass per unit area of the screen expressed in milligrams per square centimeter as the abscissa and, the logarithm of the count rate as the ordinate for each screen examined. A graph is drawn in the same manner for a standardized preparation. The mass attenuation coefficients are calculated from the median parts of the curves, which are practically rectilinear.

The mass attenuation coefficient $\mu_m$, expressed in square centimeters per milligram, depends on the energy spectrum of the beta radiation and on the nature and the physical properties of the screen. It therefore allows beta emitters to be identified. It is calculated using the equation:

$$\mu_m = \frac{(2.303(\log A_1 - \log A_2))/(m_1 + m_2)}{m_1}$$

$m_1$ = mass per unit area of the lightest screen,
$m_2$ = mass per unit area of the heaviest screen, $m_1$ and $m_2$ being within the rectilinear part of the curve,
$A_1$ = count rate for mass per unit area $m_1$,
$A2$ = count rate for mass per unit area $m2$. 

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The mass attenuation coefficient $\mu_m$ thus calculated, does not differ by more than 10% from the coefficient obtained under identical conditions using a standardized preparation of the same radionuclide.

The range of $\beta^-$ particles is an additional parameter which can be used for the determination of the $\beta^-$ energy. It is obtained from the graph described above as the mass per unit area corresponding to the intersection of the extrapolations of the descending rectilinear part of the attenuation curve and the horizontal line of background radioactivity.

Liquid scintillation counting may be used to obtain spectra of $\alpha$ and $\beta^-$ emitters (see measurement of radioactivity).

Gamma spectrometry is used to identify radionuclides by the energy and intensity of their $\gamma$ rays and X-rays.

The preferred detector for $\gamma$ and X-ray spectrometry is a germanium semiconductor detector. A thallium-activated sodium iodide scintillation detector is also used but this has a much lower energy resolution.

The gamma detector has to be calibrated using standard sources because the detection efficiency is a function of the energy of the $\gamma$ and X-rays as well as the form of the source and the source-to-detector distance. The detection efficiency may be measured using a calibrated source of the radionuclide to be measured or, for more general work, a graph of efficiency against $\gamma$ and X-ray energy may be constructed from a series of calibrated sources of various radionuclides.

The $\gamma$ and X-ray spectrum of a radionuclide which emits $\gamma$ and X-rays is unique to that nuclide and is characterized by the energies and the number of photons of particular energies emitted per transformation from one energy level to another energy level. This property contributes to the identification of radionuclides present in a source and to their quantification. It allows the estimation of the degree of radionuclidic impurity by detecting peaks other than those expected.

It is possible to establish the rate of the decay of radioactivity using $\gamma$-spectrometry since the peaks diminish in amplitude as a function of the $T_{1/2}$. If, in such a source, a radioactive impurity with a different $T_{1/2}$ is present, it is possible to detect the latter by identification of the characteristic peak or peaks whose amplitudes decrease at a different rate from that expected for the particular radionuclide. A determination of the $T_{1/2}$ of the additional peaks by repeated measurements of the sample will help to identify the impurity.

The table of physical characteristics of radionuclides summarizes the most commonly accepted physical characteristics of radionuclides used in radiopharmaceutical preparations. The table also states the physical characteristics of the main potential impurities of the radionuclides.

By “transition probability” is meant the probability of the transformation of a nucleus in a given energy state, via the transition concerned. Instead of “probability” the terms “intensity” and “abundance” are frequently used.

By “emission probability” is meant the probability of an atom of a radionuclide giving rise to the emission of the particles or radiation concerned.

Irrespective of whether the one or the other meaning is intended, probability is usually measured in terms of 100 disintegrations.

**Measurement of radioactivity**

The radioactivity of a radiopharmaceutical preparation is stated at a given date and, if necessary, time. The absolute measurement of the radioactivity of a given sample may
be carried out if the decay scheme of the radionuclide is known, but in practice, many corrections are required to obtain accurate results. For this reason, it is common to carry out the measurement with the aid of a primary standard source. Primary standards may not be available for short-lived radionuclides, e.g. $\beta^+$ emitters. Measuring instruments are calibrated using suitable standards for the particular radionuclides. Standards are available from the laboratories recognized by the competent authority. Ionization chambers and Geiger-Müller counters may be used to measure $\beta^-$ and $\beta^+ / \gamma$ emitters; scintillation or semiconductor counters or ionization chambers may be used for measuring gamma emitters; low-energy $\beta^+$ emitters require a liquid-scintillation counter. For the detection and measurement of $\alpha$ emitters, specialized equipment and techniques are required. For an accurate comparison of radioactive sources, it is essential for samples and standards to be measured under similar conditions. Low-energy $\beta^-$ emitters may be measured by liquid-scintillation counting. The sample is dissolved in a solution containing one or more often two organic fluorescent substances (primary and secondary scintillators), which convert part of the energy of disintegration into photons of light, which are detected by a photomultiplier and converted into electrical impulses. When using a liquid-scintillation counter, comparative measurements are corrected for light-quenching effects. Direct measurements are made, wherever possible, under similar conditions, (e.g. volumes and type of solutions) for the source to be examined and for the standard source.

All measurements of radioactivity must be corrected by subtracting the background due to radioactivity in the environment and due to spurious signals generated in the equipment itself. With some equipment, when measurements are made at high levels of radioactivity, it may be necessary to correct for the loss by coincidence due to the finite resolving time of the detector and its associated electronic equipment. For a counting system with a fixed dead time $\tau$ following each count, the correction is:

\[
N = \frac{N_{\text{obs}}}{1 - N_{\text{obs}} \times \tau}
\]

$N$ = the true count rate per second, $N_{\text{obs}}$ = the observed count rate per second, and $\tau$ = the dead time, in seconds.

With some equipment this correction is made automatically. Corrections for loss by coincidence must be made before the correction for background radiation.

If the time of an individual measurement, $t_m$, is not negligible short compared with the half-life, $t_{1/2}$, the decay during this measurement time must be taken into account. After having corrected the instrument reading (count rate, ionization current, etc.) for background and, if necessary, for losses due to electronic effects, the decay correction during measurement time is:

\[
R_{\text{corr}} = \frac{R \left( \frac{t_m}{t_{1/2}} \ln 2 \right)}{1 - \exp \left(-\frac{t_m}{t_{1/2}} \ln 2 \right)}
\]

$R_{\text{corr}}$ = instrument reading corrected to the beginning of the individual measurement, $R$ = instrument reading before decay correction, but already corrected for background, etc.

The results of radioactivity determination show variation, which mainly are derived from the random nature of nuclear transformation. A sufficient number of counts must be registered in order to compensate for variations in the number of transformations per unit of time. The standard deviation is the square root of the counts, so at least 10 000 counts are necessary to obtain a relative standard deviation of not more than 1% (confidence interval: 1 sigma).

All statements of radioactive content should be accompanied by a statement of the date and, if necessary, the time at which the measurement was made. This statement of the radioactive
content must be made with reference to a time zone (GMT, CET). The radioactivity at other times can be calculated from the exponential equation or from tables.

The radioactivity of a solution is expressed per unit volume to indicate the radioactive concentration.

**Radionuclidic purity**

In most of the cases, to state the radionuclidic purity of a radiopharmaceutical preparation, the identity of every radionuclide present and their radioactivity must be known. The most generally useful method for the examination of radionuclidic purity is by gamma spectrometry. It is not a completely reliable method because alpha- and beta-emitting impurities are not usually easily detectable and, when sodium iodide detectors are employed, the peaks due to gamma emitting impurities are often obscured by the gamma spectrum of the principal radionuclide.

The individual monographs prescribe the radionuclidic purity required (for example, the $\gamma$-ray spectrum does not significantly differ from that of a standardized preparation) and may set limits for specific radionuclidic impurities (for example, cobalt-60 in cobalt-57). While these requirements are necessary, they are not in themselves sufficient to ensure that the radionuclidic purity of a preparation is sufficient for human use. The manufacturer must examine the product in detail and especially, must examine preparations of radionuclides of short half-life for impurities of long half-life after a suitable period of decay. In this way, information on the suitability of the manufacturing processes and the adequacy of the testing procedures may be obtained. In cases where two or more $\beta^+$ emitting radionuclides need to be identified and/or differentiated, as e.g. $^{18}$F-impurities in $^{13}$N-preparations, half-life determinations need to be carried out in addition to gamma spectrometry.

Due to differences in the half-lives of the different radionuclides present in a radiopharmaceutical preparation, the radionuclidic purity changes with time. The requirement of the radionuclidic purity must be fulfilled throughout the period of validity. It is sometimes difficult to carry out these tests before authorizing the release for use of the batch when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.

**Radiochemical purity**

The determination of radiochemical purity requires separation of the different chemical substances containing the radionuclide and estimating the percentage of radioactivity associated with the declared chemical substance. Radiochemical impurities may originate from radionuclide production; subsequent chemical processing; incomplete preparative separation and chemical changes during storage.

The requirement of the radiochemical purity must be fulfilled throughout the period of validity. In principle, any method of analytical separation may be used in the determination of radiochemical purity. For example, the monographs for radiopharmaceutical products may include paper chromatography (2.4.15), thin-layer chromatography (2.4.17), instant thin-layer chromatography (ITLC), electrophoresis (2.4.12), size-exclusion chromatography (2.4.16), gas chromatography (2.4.13) and liquid chromatography (2.4.14). The technical description of these analytical methods is set out in the monographs. Moreover, certain precautions special to radioactivity must also be taken for radiation protection.

ITLC is a rapid, miniaturized thin layer assay method developed to determine the labeling efficiency of radiopharmaceuticals. The assay uses specific cellulose backed silica gel chromatography strips as solid phase. An ILTC method offers advantages such as easy to use, rapid and can be incorporated easily in a routine quality control programme.
In a hospital environment, thin-layer and paper chromatography are mostly used. In paper and thin-layer chromatography, a volume equal to that described in the monograph is deposited on the starting-line as prescribed in the general methods for chromatography. It is preferable not to dilute the preparation to be examined, but it is important to avoid depositing such a quantity of radioactivity that counting losses by coincidence occur during measurement of the radioactivity. On account of the very small quantities of the radioactive material applied, a carrier may be added when specified in a particular monograph. After development of the chromatogram, the support is dried and the positions of the radioactive areas are detected by autoradiography or by measurement of radioactivity over the length of the chromatogram using suitable collimated counters or by cutting the strips and counting each portion. The positions of the spots or areas permit chemical identification by comparison with solutions of the same chemical substances (non-radioactive) using a suitable detection method.

Radioactivity may be measured by integration using an automatic-plotting instrument or a digital counter. The ratios of the areas under the peaks give the ratios of the radioactive concentration of the chemical substances. When the strips are cut into portions, the ratios of the quantities of radioactivity measured give the ratio of concentrations of the radioactive chemical species.

**Specific radioactivity**

Specific radioactivity is usually calculated taking into account the radioactive concentration (radioactivity per unit volume) and the concentration of the chemical substance being studied, after verification that the radioactivity is attributable only to the radionuclide (radionuclidic purity) and the chemical species (radiochemical purity) concerned.

Specific radioactivity changes with time. The statement of the specific radioactivity therefore includes reference to a date and if necessary, time. The requirement of the specific radioactivity must be fulfilled throughout the period of validity.

**Chemical purity**

The determination of chemical purity requires quantification of the individual chemical impurities specified in the monograph.

**Enantiomeric purity**

Where appropriate, the stereoisomeric purity has to be verified.

**Physiological distribution**

A physiological distribution test is prescribed, if necessary, for certain radiopharmaceutical preparations. The distribution pattern of radioactivity observed in specified organs, tissues or other body compartments of an appropriate animal species (usually rats or mice) can be a reliable indication of the expected distribution in humans and thus of the suitability for the intended purpose.

The individual monograph prescribes the details concerning the performance of the test and the physiological distribution requirements which must be met for the radiopharmaceutical preparation. A physiological distribution conforming to the requirements will assure appropriate distribution of the radioactive compounds to the intended biological target in humans and limits its distribution to non-target areas.

In general, the test is performed as follows.

A minimum of three animals are used per test and each animal is injected intravenously with the preparation to be tested. If relevant, the species, sex, strain and weight and/or age of the animals are specified in the monograph. The test injection is the radiopharmaceutical preparation as it is intended for human use. Where applicable, products are reconstituted.
according to the manufacturer’s instructions. In some cases, dilution immediately before injection may be necessary.

The administration will normally be made via the intravenous route for which purpose the caudal vein is used. Other veins such as saphenous, femoral, jugular or penile veins may be used in special cases. Animals showing evidence of extravasation of the injection (observed at the time of injection or revealed by subsequent assay of tissue radioactivity) are rejected from the test.

Immediately after injection each animal is placed in a separate cage which will allow collection of excreta and prevent contamination of the body surface of the animal. At the specified time after injection, the animals are euthanized by an appropriate method and dissected. Selected organs and tissues are assayed for their radioactivity using a suitable instrument as described elsewhere in this monograph. The physiological distribution is then calculated and expressed in terms of percentage of the radioactivity which is found in each of the selected organs or tissues. For this purpose the radioactivity in an organ may be related to the injected radioactivity calculated from the radioactive content of the syringe measured before and after injection. For some radiopharmaceutical preparations, it may be appropriate to determine the ratio of the radioactivity in weighed samples of selected tissues (radioactivity/mass).

For a preparation to meet the requirements of the test the distribution of radioactivity in at least two of the three animals must comply with all the specified criteria.

Sterility
Radiopharmaceutical preparations for parenteral administration must be prepared using precautions designed to exclude microbial contamination and to ensure sterility. The test for sterility is carried out as described in the general method for sterility (2.2.11). Special difficulties arise with radiopharmaceutical preparations because of the short half-life of some radionuclides, small size batches and the radiation hazards. It is not always possible to wait for the results of the test for sterility before authorization of the release of the radiopharmaceutical product for patients’ use. Parametric release of the product manufactured by a fully validated process is the method of choice in such cases. When aseptic manufacturing is used, the test for sterility has to be executed as a control of the quality of production.

When the size of a batch of the radiopharmaceutical preparation is limited to one or a few samples (e.g. therapeutic or very short-lived radiopharmaceutical preparation), sampling the batch for sterility testing may not be applicable. If the radiopharmaceutical preparation is sterilized by filtration and/or aseptically processed, process validation is critical.

When the half-life of the radionuclide is very short (e.g. less than 20 min), the administration of the radiopharmaceutical preparation to the patient is generally on-line with a validated production system.

For safety reasons (high level of radioactivity), it is not possible to use the quantity of the radiopharmaceutical preparations as required in the test for sterility (2.2.11). The method by membrane filtration is to be preferred to limit radiation exposure to personnel.

Notwithstanding the requirements concerning the use of antimicrobial preservatives in parenteral preparations, their addition to radiopharmaceutical preparations in multidose containers is not obligatory, unless prescribed in the monograph.

Bacterial endotoxins - pyrogens
For certain radiopharmaceutical preparations a test for bacterial endotoxins is prescribed. The test is carried out as described in the general method (2.2.3), taking the necessary precautions to limit radiation exposure to the personnel carrying out the test. For radiopharmaceuticals made with short-lived radioisotopes, endotoxin testing after product release is permitted.
However, with the introduction of the kinetic (photometric) LAL test, which can be completed in 20 minutes, it is possible to complete the test for bacterial endotoxins before releasing the radiopharmaceuticals with $T_{1/2}$ of $> 30$ min.

The limit for bacterial endotoxins is indicated in the individual monograph.

When the nature of the radiopharmaceutical preparation results in an interference by inhibition or activation and it is not possible to eliminate the interfering factor(s), the test for pyrogens (2.2.8) may be specifically prescribed. This happens with many of the $^{99m}$Tc-radiopharmaceuticals since their formulation uses reducing agents and metal chelating agents, which will give false negative or false positive results with the LAL test.

It is sometimes difficult to carry out these tests before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.

**pH**

The pH of PET-radiopharmaceuticals like all pharmaceutical preparations is important and is determined as a part of quality control (QC) testing. However, due to the small volumes involved and the radioactivity present, the conventional use of a glass pH electrode is not practical or necessary. The sample available for all the QC testing (excluding sterility) is very small and the pH range permitted is sufficiently large. Hence, the use of narrow range pH strips is adequate and is preferred as the pH can be tested with a few microlitres of the sample. Further, as they are radioactive after use, they can be easily and safely disposed. pH electrodes, even miniature electrodes, require much cleaning after use and generate radioactive washings that have to be stored and disposed.

**1.7 Storage**

Store in an airtight container in a place that is sufficiently shielded to protect personnel from exposure to primary or secondary emissions and that complies with national and international regulations concerning the storage of radioactive substances. During storage containers may darken due to irradiation. Such darkening does not necessarily involve deterioration of the preparations.

Radiopharmaceutical preparations are intended for use within a short time and the end of the period of validity must be clearly stated.

Radiopharmaceuticals intended for parenteral use should be stored in such a manner so that pharmaceutical purity of the product is maintained.

**1.8 Labelling**

The labelling of radiopharmaceutical preparations complies with the relevant national legislation and complies with the labelling requirements as per good manufacturing practices (GMP).

Apart from the general labelling requirements, the label on the direct container should state (1) notification that the product is radioactive in nature, (2) the name of the preparation and/or its reference, (3) the name of the manufacturer, (4) an identification number, (5) for liquid and gaseous preparations: the total radioactivity in the container, or the radioactive concentration per milliliter at a stated date and stated time, and the volume of liquid in the container, (6) for solid preparations (such as freeze-dried preparations): the total radioactivity at a stated date and stated time. After reconstitution with the appropriate solution, the preparation is considered
as a liquid preparation, (7) for capsules: the radioactivity per capsule at a stated date and time and the number of capsules in the container, and (8) route of administration.

The labelling can be adapted in certain cases (e.g. radiopharmaceutical preparations containing short-lived radionuclides).

The label on the outer package states, in addition to those on the direct container: (1) the route of administration, (2) the period of validity or the expiry date, (3) the name and concentration of any added antimicrobial preservative, and (4) where applicable, any special storage conditions.

**Techno-legal regime in the use of radiopharmaceuticals in the Indian scenario**

Widespread utilization of ionizing radiation and radioactive substances and radioactive substances for multifarious applications in medicine, industry, agriculture, research, etc., has brought in its wake the need for exercising regulatory controls to ensure safety of users, members of the public and the environment. The Atomic Energy Regulatory Board (AERB), constituted under the Atomic Energy Act, 1962 by the Government of India, is entrusted with the responsibility of developing and implementing appropriate regulatory measures aimed at ensuring radiation safety in all applications involving ionizing radiation and radioactive substances. One of the ways to meet these responsibilities is to develop and enforce specific safety codes and standards dealing with radiation safety aspects of various applications of ionizing radiation and radioactive substances to cover the entire spectrum of operations, starting from design of radiation equipment, their installation and use, to ultimate decommissioning and safe disposal.

Specific mandatory requirements are published as AERB Codes & Guides for a nuclear medicine facility, covering the entire spectrum of operations ranging from the site approval, laboratory design and setting up of a facility to its ultimate decommissioning, including procedures to be followed during an emergency situation. The Code also stipulates requirements of qualified personnel's and their responsibilities.


There is also an AERB code that elaborates on regulatory requirements and control of use, possession, transport of radioactive substances and radiation sources.

Annex 1. The dose limits for exposures from ionizing radiations for workers and the members of the public, from AERB SAFETY CODE NO. AERB/RF-MED/SC-2 (Rev. 2)

AERB Directive No. 01/2011


Ref. No. CH/AERB/ITSD/125/2011/1507 dated 27 April 2011

Subject: The dose limits for exposures from ionising radiations for workers and the members of the public

In exercise of Rule 15 of the Atomic Energy (Radiation Protection) Rules, 2004, the Chairman, Atomic Energy Regulatory Board, being the Competent Authority under the said rules, hereby issues an order prescribing the dose limits for exposures from ionizing radiations for workers and the members of the public, which shall be adhered to.

Dose limits

General

i. The limits on effective dose apply to the sum of effective doses from external as well as internal sources. The limits exclude the exposures due to natural background radiation and medical exposures.

ii. Calendar year shall be used for all prescribed dose limits.

1.0 Occupational dose limits

1.1 Occupational workers

The occupational exposures of any worker shall be so controlled that the following limits are not exceeded:

a. an effective dose of 20 mSv/yr averaged over five consecutive years (calculated on a sliding scale of five years);

b. an effective dose of 30 mSv in any year;

c. an equivalent dose to the lens of the eye of 150 mSv in a year;

d. an equivalent dose to the extremities (hands and feet) of 500 mSv in a year;

e. an equivalent dose to the skin of 500 mSv in a year;

f. limits given above apply to female workers also. However, once pregnancy is declared the equivalent dose limit to embryo/fetus shall be 1 mSv for the remainder of the pregnancy.

1.2 Apprentices and trainees

The occupational exposure of apprentices and trainees between 16 and 18 years of age shall be so controlled that the following limits are not exceeded:

a. an effective dose of 6 mSv in a year;

b. an equivalent dose to the lens of the eye of 50 mSv in a year;

c. an equivalent dose to the extremities (hands and feet) of 150 mSv in a year;

d. an equivalent dose to the skin of 150 mSv in a year.

2.0 Dose limits for members of the public

The estimated average doses to the relevant members of the public shall not exceed the following limits:

a. an effective dose of 1 mSv in a year;

b. an equivalent dose to the lens of the eye of 15 mSv in a year;

c. an equivalent dose to the skin of 50 mSv in a year.

Table: Annual limit for intake (ALI) of important radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>ALI (ingestion) (Ci)</th>
<th>ALI (inhalation) (Ci)</th>
<th>Derived air conc. (DAC) (inhalation) (Ci/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m</td>
<td>8 x 10^4</td>
<td>2 x 10^5</td>
<td>1 x 10^-4</td>
</tr>
<tr>
<td>F-18</td>
<td>5 x 10^4</td>
<td>7 x 10^4</td>
<td>3 x 10^-5</td>
</tr>
<tr>
<td>I-125</td>
<td>4 x 10^4</td>
<td>6 x 10^4</td>
<td>3 x 10^-6</td>
</tr>
<tr>
<td>P-32</td>
<td>6 x 10^3</td>
<td>3 x 10^4</td>
<td>1 x 10^-6</td>
</tr>
<tr>
<td>I-131</td>
<td>9 x 10^3</td>
<td>5 x 10^4</td>
<td>2 x 10^-8</td>
</tr>
</tbody>
</table>
Annex 2. Safety considerations

Radiopharmaceuticals, owing to their detrimental effects on cellular structures, need to be monitored for their harmful effects on the personnel involved in handling them. Critical operations include manufacture, storage, transport, compounding, testing, dispensing and administration to the patients.

Complying as per the ALARA principle, in order to minimize the harmful effects of radiopharmaceuticals, there should be specialized techniques for controlling risk. A major consideration of the ALARA principle includes exposure time, distance and radiation shielding. These factors should be carefully considered while designing the safety protocols for radiopharmaceuticals.

Radiation sign

- Restricted area: < 2 mR/h and < 100 mR/year
- Caution, Radiation Area: may exceed 5 mR/h at 30 cm from source
- Caution, High Radioactive Area: may exceed 100 mR/h at 30 cm from source
- Danger, Very High Radiation Area: may reach 500 R/h at 1 m from source (not in NM)

Caution Radioactive Material
- 100 Ci for Cs-137 and Sr-89
- 1 mCi for Mo-99, I-123 and Co-57
- 10 mCi for Tc-99m, Ga-67 and Xe-133.

Radiation safety instruments

- GM survey meters: Laboratory survey
- Portable ion chambers (cutie pies): High level exposure rate monitoring (In RPD)
- Pocket dosimeter: Personnel exposure monitoring
- Wipe test counters: GM counters to detect low level activity
- Film badges: To detect and measure personnel exposure
- Thermoluminescent dosimeters: More sensitive than film badges

Scintillation detectors

- Portable scintillation survey detectors for gamma survey of lab surfaces
- Well type single channel analyzers for measurement of wipe tests
- Multiwell gamma ray spectrometer to identify and quantify gamma contamination
Annex 3. Physical characteristics of radionuclides

The values are obtained from the database of the National Nuclear Data Center (NNDC) at Brookhaven National Laboratory, Upton, N.Y., USA, directly accessible via Internet at http://www.nndc.bnl.gov/nndc/nudat/radform.html.

In case another source of information is preferred (more recent values) this source is explicitly mentioned.

Other data sources:

* DAMRI (Département des Applications et de la Métrologie des Rayonnements Ionisants, CEA Gif-sur-Yvette, France),

** PTB (Physikalisch-Technische Bundesanstalt, Braunschweig, Germany),

*** NPL (National Physical Laboratory, Teddington, Middlesex, UK).

The uncertainty of the half-lives is given in parentheses. In principle the digits in parentheses are the standard uncertainty of the corresponding last digits of the indicated numerical value (Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization (ISO), 1993, ISBN 92-67-10188-9).

The following abbreviations are used:

\( e_A \) = Auger electrons,
\( ce = \) conversion electrons,
\( \beta^- = \) electrons,
\( \beta^+ = \) positrons,
\( \gamma = \) gamma rays,
\( X = \) X-rays.

\(^a\) Mean energy of the \( \beta \) spectrum.

\(^b\) Maximum emission probability corresponding to a total annihilation in the source per 100 disintegrations.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Electronic emission</th>
<th>Photon emission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Type</td>
<td>Energy (MeV)</td>
</tr>
<tr>
<td>Tritium ((^3)H)</td>
<td>12.33 (6) years</td>
<td>( \beta^- )</td>
<td>0.006(^{\text{I}}) (max: 0.019)</td>
</tr>
<tr>
<td>Carbon-11 ((^11)C)</td>
<td>20.385 (20) min</td>
<td>( \beta^+ )</td>
<td>0.386(^{\text{II}}) (max: 0.960)</td>
</tr>
<tr>
<td>Nitrogen-13 ((^13)N)</td>
<td>9.965 (4) min</td>
<td>( \beta^+ )</td>
<td>0.492(^{\text{II}}) (max: 1.198)</td>
</tr>
<tr>
<td>Oxygen-15 ((^15)O)</td>
<td>122.24 (16) s</td>
<td>( \beta^+ )</td>
<td>0.735(^{\text{II}}) (max: 1.732)</td>
</tr>
<tr>
<td>Fluorine-18 ((^18)F)</td>
<td>109.77 (5) min</td>
<td>( \beta^+ )</td>
<td>0.250(^{\text{II}}) (max: 0.633)</td>
</tr>
<tr>
<td>Phosphorus-32 ((^32)P)</td>
<td>14.26 (4) days</td>
<td>( \beta^- )</td>
<td>0.695(^{\text{I}}) (max: 1.71)</td>
</tr>
<tr>
<td>Phosphorus-33 ((^33)P)</td>
<td>25.34 (12) days</td>
<td>( \beta^- )</td>
<td>0.076(^{\text{I}}) (max: 0.249)</td>
</tr>
<tr>
<td>Sulphur-35 ((^35)S)</td>
<td>87.51 (12) days</td>
<td>( \beta^- )</td>
<td>0.049(^{\text{I}}) (max: 0.167)</td>
</tr>
<tr>
<td>Chromium-51 ((^51)Cr)</td>
<td>27.7025 (24) days</td>
<td>( e_A )</td>
<td>0.004</td>
</tr>
</tbody>
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Continued
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Continued (Abbreviations: see page 182)
### Radionuclides and their Properties

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### Table of Properties

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*Continued (Abbreviations: see page 182)*
### Radionuclide Decay Properties

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Electronic emission</th>
<th>Photon emission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Type</td>
<td>*Energy (MeV)</td>
</tr>
<tr>
<td>Iodine-125 (¹²⁵I)</td>
<td>59.402 (14) days</td>
<td>eₐ₋e⁰</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ce</td>
<td>0.023-0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β₋</td>
<td>0.109(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.290(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.459(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine-126 (¹²⁶I)</td>
<td>13.11 (5) days</td>
<td>eₐ</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ce</td>
<td>0.354</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.634</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β₋</td>
<td>0.109(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.290(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.459(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine-131 (¹³¹I)</td>
<td>8.02070 (11) days</td>
<td>ce</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.330</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β₋</td>
<td>0.069(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.097(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.192(5)</td>
</tr>
</tbody>
</table>

*Abbreviations: see page 182*
### Radionuclide Half-life | Electronic emission | Photon emission
--- | --- | ---
| **Type** | *Energy (MeV)* | *Emission probability (per 100 disintegrations)* | **Type** | *Energy (MeV)* | *Emission probability (per 100 disintegrations)*

**Xenon-131m (131mXe)**  
11.84 (7) days

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_-$</td>
<td>0.025</td>
<td>6.8</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.129</td>
<td>61</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.159</td>
<td>28.5</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.163</td>
<td>8.3</td>
</tr>
</tbody>
</table>

**Iodine-133 (133I) (decays to radioactive Xenon-133)**  
20.8 (1) hours

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta^-$</td>
<td>0.140$^{(i)}$</td>
<td>3.8</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.162$^{(i)}$</td>
<td>3.2</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.299$^{(i)}$</td>
<td>4.2</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.441$^{(i)}$</td>
<td>83</td>
</tr>
</tbody>
</table>

**Xenon-133 (133Xe)**  
5.243 (1) days

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_-$</td>
<td>0.026</td>
<td>5.8</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.045</td>
<td>55.1</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.075-0.080</td>
<td>9.9</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.101$^{(i)}$</td>
<td>99.0</td>
</tr>
</tbody>
</table>

**Xenon-133m (133mXe) (decays to radioactive Xenon-133)**  
2.19 (1) days

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_-$</td>
<td>0.025</td>
<td>7</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.199</td>
<td>64.0</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.228</td>
<td>20.7</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.232</td>
<td>4.6</td>
</tr>
</tbody>
</table>

**Iodine-135 (135I) (decays to radioactive Xenon-135)**  
6.57 (2) hours

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta^-$</td>
<td>0.140$^{(i)}$</td>
<td>7.4</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.237$^{(i)}$</td>
<td>8</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.307$^{(i)}$</td>
<td>8.8</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.352$^{(i)}$</td>
<td>21.9</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.399$^{(i)}$</td>
<td>8</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.444$^{(i)}$</td>
<td>7.5</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.529$^{(i)}$</td>
<td>23.8</td>
</tr>
</tbody>
</table>

**Xenon-135 (135Xe)**  
9.14 (2) hours

<table>
<thead>
<tr>
<th>Type</th>
<th><em>Energy (MeV)</em></th>
<th><em>Emission probability (per 100 disintegrations)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>0.214</td>
<td>5.5</td>
</tr>
<tr>
<td>$\beta^-$</td>
<td>0.171</td>
<td>3.1</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.308</td>
<td>96.0</td>
</tr>
</tbody>
</table>

*Abbreviations: see page 182*
### Radionuclide Half-life Electronic emission Photon emission

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Electronic emission</th>
<th>Photon emission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Type</td>
<td>Energy (MeV)</td>
</tr>
<tr>
<td>Caesium-137 ((^{137}\text{Cs})) in equilibrium with Barium-137m ((^{137m}\text{Ba}))</td>
<td>30.04 (3) years</td>
<td>e(_A)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha)</td>
<td>0.624</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta^-)</td>
<td>0.656</td>
</tr>
<tr>
<td>Thallium-200 ((^{200}\text{Tl}))</td>
<td>26.1 (1) hours</td>
<td>(\alpha)</td>
<td>0.285</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.353</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\beta^+)</td>
<td>0.495(^{59})</td>
</tr>
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</tr>
<tr>
<td>Lead-201 ((^{201}\text{Pb})) (decays to radioactive Thallium-201)</td>
<td>9.33 (3) hours</td>
<td>e(_A)</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha)</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.276</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.316</td>
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<td></td>
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</tr>
</tbody>
</table>
### Radionuclide and Emission Properties

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th><strong>Electronic emission</strong></th>
<th><strong>Photon emission</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type</td>
<td><em>Energy (MeV)</em></td>
<td><em>Emission probability (per 100 disintegrations)</em></td>
</tr>
<tr>
<td>Thallium-201 (201Tl)</td>
<td>72.912 (17) hours</td>
<td>ce</td>
<td>0.016-0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.027-0.029</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.153</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium-202 (202Tl)</td>
<td>12.23 (2) days</td>
<td>ea</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ce</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead-203 (203Pb)</td>
<td>51.873 (9) hours</td>
<td>ea</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ce</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** cf, X; ce, γ

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*Continued (Abbreviations: see page 182)*


**Natrii iodidi (\(^{131}\)I) capsulae**

Sodium iodide (\(^{131}\)I) capsules

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/14.577, March 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

**Latin.** Natrii iodidi (\(^{131}\)I) capsulae

**English.** Sodium \([^{131}\text{I}]\)iodide capsules

**Structural formula**

\[
Na^{[^{131}\text{I}]}^{-}
\]

**Relative molecular mass.** 153.895

**Chemical name.** Sodium \([^{131}\text{I}]\)iodide

**Description.** White or coloured gelatin capsules. Iodine-131 has a half-life of 8.02 days.

**Category.** Diagnostic or therapeutic.

**Storage.** Sodium iodide (\(^{131}\)I) capsules should be preserved in well-closed containers in a fume hood or well ventilated room.

**Labelling.** The label complies with the General monograph, monograph of Radiopharmaceuticals.

**Manufacture**

Iodine-131 may be obtained by neutron irradiation of tellurium as carrier free sodium iodide or by extraction from uranium fission products.

**Requirements**

Complies with the monograph for Capsules and with that for Radiopharmaceuticals.

**Definition**

Sodium iodide (\(^{131}\)I) capsules contain radioactive iodine-131 as sodium iodide adsorbed onto a solid matrix, such as anhydrous sodium thiosulfate or anhydrous disodium hydrogen phosphate, which is contained in hard gelatine capsules. Sodium iodide (\(^{131}\)I) capsules are suitable for oral administration. The capsules contain not less than 90% and not more than 110% of the content of iodine-131 stated on the label at the reference date and time. Not less than 99.9% of the total radioactivity is due to iodine-131. Not less than 95% of the total iodine-131 radioactivity is present as iodide. The specific activity for therapeutic or diagnostic use should not less than 185 MBq per microgram of iodine at the reference date and time stated on the label. Iodide should not more than 20 µg per capsule.

**Identity tests**

A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of iodine-131 in that it exhibits a major peak of 365 keV. Iodine-133...
has a half-life of 20.8 hours and main peaks of 530 keV and 875 keV. Iodine-135 has a half-life of 6.55 hours and main peaks of 527 keV, 1132 keV and 1260 keV.

Standardized iodine-131, iodine-133 and iodine-135 solutions are available from laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 7.61 and 8.42 days.

Radionuclidic purity. A solution or suspension of one or more capsules in water should comply with the tests of radionuclidic purity as described under the monograph of Natrii iodidi (\textsuperscript{131}I) solutio – Sodium iodide (\textsuperscript{131}I) solution. Not less than 99.9\% of the total radioactivity is due to iodine-131.

Chemical purity

Iodide. Dissolve the capsule to be examined in 10 mL of water R. Filter through a 0.2 µm filter. Carry out the test of iodide as described under the specific monograph of Natrii iodidi (\textsuperscript{131}I) solutio – Sodium iodide (\textsuperscript{131}I) solution. The area of the peak due to iodide should not be larger than the area of the corresponding peak in the chromatogram obtained with reference solution (c).

Radiochemical purity

• Either test A or test B may be applied

  A. Homogenize the contents of a capsule in 5 mL of water R, add 5 mL of methanol R and centrifuge. The supernatant should meet the requirements of the test (1.14.2 Paper chromatography) as described under the specific monograph of Natrii iodidi (\textsuperscript{131}I) solutio – Sodium iodide (\textsuperscript{131}I) solution. Not less than 95\% of the total radioactivity is due to [\textsuperscript{131}I] iodide.

  B. Prepare the capsule for testing as described under the test of iodide. Carry out the test (1.14.4 High-performance liquid chromatography) as described under the specific monograph of Natrii iodidi (\textsuperscript{131}I) solutio – Sodium iodide (\textsuperscript{131}I) solution. Not less than 95\% of the total radioactivity is due to [\textsuperscript{131}I] iodide.

Disintegration. In a water-bath at 37°C, warm 10 ml of a potassium iodide (2 g/l) TS solution. Add a capsule to be examined and stir with a magnetic stirrer at a rotation speed of 20 revolutions per minute. The shell and its contents dissolve completely within 15 minutes.

Uniformity of content. Determine the radioactivity of 10 capsules individually and determine the average radioactivity per capsule. The radioactivity of none of the capsules differs by more than 10\% from the average radioactivity per capsule. The relative standard deviation is not greater than 3.5\%.

Radioactivity

Measure the radioactivity using a suitable instrument as described under R.1.1 Detection and measurement of radioactivity.

Impurities

A. [\textsuperscript{131}I]iodate ion,
B. iodine-130,
C. iodine-133,
D. iodine-135.

***
Iobenguani (\(^{131}\text{I}\)) injectio
Iobenguane (\(^{131}\text{I}\)) injection

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.578, March 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

Latin. Iobenguani (\(^{131}\text{I}\)) injection

English. Iobenguane (\(^{131}\text{I}\)) injection

Structural formula

![Structural formula image]

\(\text{C}_8\text{H}_{10}^{131}\text{IN}_3\)

Relative molecular mass. 279.19

Chemical name. 1-((3-[\(^{131}\text{I}\)]iodophenyl)methyl)guanidine

Other names. m-Iodobenzylguanidine (\(^{131}\text{I}\)) injection; (\(^{131}\text{I}\))-MIBG injection.

Description. Iobenguane (\(^{131}\text{I}\)) injection is a clear, colourless or slightly yellow aqueous solution.

Iodine-131 has a half-life of 8.02 days.

Category. Diagnostic and therapy.

Storage. Iobenguane (\(^{131}\text{I}\)) injection should be kept protected from light and during transportation, at a temperature below -10°C.

Labelling. The label complies with the General monograph, monograph of Radiopharmaceuticals. The label should include the specific activity of iodine-131 in Becquerel per gram. The label states the date of withdrawal of the first dose for multidose containers.

Manufacture

Iodine-131 may be obtained by neutron irradiation of tellurium or by extraction from uranium fission products. Iobenguane (\(^{131}\text{I}\)) is generally prepared by isotope exchange reaction (the formulations contain large amounts of unlabelled MIBG molecules). The injection may contain fillers, antimicrobial preservatives, buffers and stabilizing agents.

Additional information

Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.
Requirements

Complies with the monograph for Parenteral Preparations and with that for Radiopharmaceuticals.

Definition. Iobenguane (\(^{131}\text{I}\)) injection is a sterile, bacterial endotoxin-free aqueous solution of iodine-131 in the form of 1-((3-\([^{131}\text{I}]\)iodophenyl)methyl)guanidine or its salts, suitable for intravenous administration. The injection contains sufficient sodium chloride to make the solution isotonic with blood. The injection contains not less than 90% and not more than 110% of the content of iodine-131 stated on the label at the reference date and time. Not less than 99.9% of the total radioactivity is due to iodine-131. Not less than 94% of the total iodine-131 radioactivity should present as iobenguane when it is used for diagnosis. Not less than 92% of the total iodine-131 radioactivity should present as iobenguane when it is used for therapy. The radiolabelled \(^{131}\text{I}\)-MIBG for diagnosis or therapy should be with high specific activity as the cold MIBG molecules are competitively inhibitor of the uptake of radiolabelled \(^{131}\text{I}\)-MIBG by adrenergic and neuroendocrine cells expressing norepinephrine transporter. The specific activity for diagnosis should not be less than 20 GBq of iodine-131 per gram of iobenguane base at the reference date and time stated on the label. For therapy, specific activity should not be less than 400 GBq of iodine-131 per gram of iobenguane base at the reference date and time stated on the label.

Identity tests

- Either tests A and C or tests B and C may be applied.
  - A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131 suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of iodine-131 in that it exhibits a major peak of 365 keV.
  
    Iodine-133 has a half-life of 20.83 hours and main peaks of 530 keV and 875 keV.

  Iodine-135 has a half-life of 6.58 hours and main peaks of 527 keV, 1132 keV and 1260 keV. Standardized iodine-131, iodine-133 and iodine-135 solutions are available from laboratories recognized by the relevant national or regional authority.
  
  B. The half-life determined using a suitable detector system is between 7.61 and 8.42 days.
  
  C. Examine the radiochromatogram obtained in the test for radiochemical purity (see the high-performance liquid chromatography under the test of Radiochemical purity):

For \(^{131}\text{I}\)Iobenguane injection for diagnostic use: Not less than 94% of the total radioactivity should be in the peak corresponding to iobenguane.

For \(^{131}\text{I}\)Iobenguane injection for therapeutic use: Not less than 92% of the total radioactivity should be in the peak corresponding to iobenguane.

pH value

Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for Radiopharmaceuticals, pH of the injection should be between 3.5 and 8.0.

Sterility

The injection complies with 3.2 Test for sterility, modified as described in the monograph for Radiopharmaceuticals. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.
Bacterial endotoxins
Carry out the test as described under 3.4 Test for bacterial endotoxins, modified as described in the monograph for Radiopharmaceuticals. The injection contains not more than 175/U I.U of endotoxins per millilitre.

Radionuclidic purity
Record the gamma-ray and X-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of iodine-131, iodine-133, iodine-135 and other radionuclidic impurities that may be present. Not less than 99.9% of the total radioactivity is due to iodine-131.

Radiochemical purity
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.0 mm) packed with silica gel for chromatography R (5µm). As the mobile phase, use a mixture of 80 g/l solution of ammonium nitrate R, ammonia (~ 35 g/l) TS and methanol R (1:2:27 V/V/V). Operate with a flow rate of 1.0 ml/min. As a detector, use detectors suitable for radioactivity and a spectrophotometer set at a wavelength of 254 nm. Prepare the following solutions: Solution (1), use the injection to be examined. Solution (2), prepare 0.1% (w/v) solution of sodium iodide R in the mobile phase. Solution (3), prepare 0.02% (w/v) solution of iobenguane sulfate R, in 50 ml of the mobile phase and dilute to 100 ml with the mobile phase. Inject separately 10 µl of solutions (1), (2) and (3). Examine the obtained radiochromatogram as follows:

\[ ^{[131I]} \text{Iobenguane injection (diagnostic use)} \]: In the chromatogram obtained with solution (1), not less than 94% of the total radioactivity should be in the peak corresponding to iobenguane. Not more than 5% of the total radioactivity corresponding to \([^{131}I]\)iodide and not more than 1% of the total radioactivity is found in other peaks.

\[ ^{[131I]} \text{Iobenguane injection for therapeutic use} \]: In the chromatogram obtained with solution (1), not less than 92% of the total radioactivity should be in the peak corresponding to iobenguane. Not more than 7% of the total radioactivity corresponding to \([^{125}I]\)iodide and not more than 1% of the total radioactivity is found in other peaks.

Radioactivity
Measure the radioactivity as described under R.1.1 Detection and measurement of radioactivity.

Impurities
A. \([^{131}I]\)iodide,
B. Iodine-133,
C. Iodine-135.

***
Fluconazoli capsulae  
Fluconazole capsules

This is a draft proposal for The International Pharmacopoeia (Working document QAS/12.470/Rev.2, May 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Category. Antifungal.

Storage. Fluconazole capsules should be kept in a tightly closed container.

Additional information. Strengths in the current WHO Model list of essential medicines: 50 mg. Strength in the current WHO Model list of essential medicines for children: 50 mg.

Requirements
Comply with the monograph for Capsules.

Definition. Fluconazole capsules contain fluconazole. They contain not less than 90.0% and not more than 110.0% of the amount of fluconazole (C_{13}H_{12}F_{2}N_{6}O) stated on the label.

Identity tests
• Either tests A and C or tests B and C may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in methanol R. For solution (A) shake a quantity of the mixed contents of the capsules, equivalent to about 100 mg of Fluconazole, with 10 ml of methanol R, filter and use the clear filtrate. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a mixture of 2 mg of fluconazole RS and 1 mg of ketoconazole RS per ml. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. To a quantity of the capsule content, containing 2 mg of fluconazole, add 10 ml of ethanol R, shake and filter. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.
Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under “Assay”, Method B. Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 10 mg of fluconazole per ml and filter the solution. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.1 mg of fluconazole impurity C RS per ml. For solution (4) transfer 1.0 ml of solution (3) to a 10 ml volumetric flask, add 1.0 ml of solution (1) and make up to volume.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid, unless in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and to fluconazole is at least 3.0

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- the area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);
- the area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Dissolution test

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of pH 6.8 dissolution buffer TS, rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of about 10 ml of the medium through a suitable 0.45 μm filter. Measure the absorbance (1.6) of a 1 cm layer of the filtered solution, suitably diluted if necessary, at the maximum at about 261 nm. At the same time measure the absorbance (1.6) at the maximum at 261 nm of a solution containing 0.1 mg of fluconazole RS per ml in the dissolution medium, using the same solution as the blank.

For each of the capsules tested calculate the total amount of fluconazole (C_{13}H_{12}F_{2}N_{6}O) in the medium from the absorbances obtained, using the declared content of C_{13}H_{12}F_{2}N_{6}O in fluconazole RS. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms. Acceptance criteria to evaluate the results. The amount in solution is not less than 85% (Q) of the amount declared on the label.
Assay

• Either test A or B may be applied.

A. Mix the contents of 20 capsules and transfer a quantity containing about 50 mg of fluconazole, accurately weighed, to a 100 ml volumetric flask and dilute to volume with hydrochloric acid (~4 g/l) TS. Shake to dissolve, filter a portion of this solution and dilute 10 ml of the filtered solution to 25 ml with the same solution. Measure the absorbance of a 1 cm layer at the maximum at about 261 nm.

At the same time measure the absorbance of a solution of 0.2 mg of fluconazole RS per ml of hydrochloric acid (~4 g/l) TS, prepared and examined in the same manner, and calculate the percentage content of fluconazole \( \text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_6\text{O} \) in the capsules, using the declared content of \( \text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_6\text{O} \) in fluconazole RS.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).\(^1\) As the mobile phase use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 0.5 mg of fluconazole per ml and filter the solution. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole \( \text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_6\text{O} \) in the capsules, using the declared content of \( \text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_6\text{O} \) in fluconazole RS.

Reagent to be defined:

Ammonium formate R

\( \text{CH}_5\text{NO}_2 \). Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

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\( ^{1} \) Capcell Pak\textsuperscript{®} C18 MGII (4.6×250 mm, 5 μm) has been found suitable.
**Fluconazoli injectio**

**Fluconazole injection**

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/12.471/Rev.2, May 2014).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

**Description.** A clear, colourless solution.

**Category.** Antifungal.

**Storage.** Fluconazole injection should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines: 2 mg/ml in vial.

**Requirements**

Complies with the monograph for *Parenteral preparations*.

**Definition.** Fluconazole injection is a sterile solution of fluconazole in water for injections.

The solution is sterilized by a suitable method (see [5.8 Methods of sterilization](#)). Fluconazole injection contains not less than 90.0% and not more than 110.0% of the amount of fluconazole ($C_{13}H_{12}F_2N_6O$) stated on the label.

**Identity tests**

- Either test A and C or test B and C may be applied.
  
  A. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R6 as the coating substance and a mixture of 80 volumes of dichloromethane R, 20 volumes of methanol R and 1 volume of ammonia (~260 g/l) TS solution as the mobile phase. Apply separately to the plate 20 μl of each of the following three solutions. For solution (A) use the injection to be examined. For solution (B) use 2 mg of fluconazole RS per ml in methanol R. For solution (C) use a mixture of 2 mg of fluconazole RS per ml and 1 mg of ketoconazole RS per ml in methanol R. After application allow the spots to dry in a current of air. Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

    The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

  B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

  C. Dilute a volume of the injection containing 2 mg of fluconazole to 10 ml with water R. The absorption spectrum ([1.6](#)) of the resulting solution, when observed between 230
nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

**pH value** (1.3). pH of the injection, 4.0–6.0.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under “Assay”. Prepare the solutions in the mobile phase. For solution (1) use the injection to be examined. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.02 mg of fluconazole impurity C RS per ml. For solution (4) mix 1 volume of solution (3) with 1 volume of solution (1).

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks due to impurity C and to fluconazole is at least 3.0

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5, is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- the area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);
- the area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

- Either test A or B may be applied.

  A. Dilute an accurately measured volume of the injection equivalent to about 2 mg with hydrochloric acid (~4 g/l) TS to 10 ml and mix. Measure the absorbance of a 1 cm layer at the maximum at about 261 nm. At the same time measure the absorbance of a solution of 0.2 mg of fluconazole RS per ml of hydrochloric acid (~4 g/l) TS, prepared and examined in the same manner, and calculate the percentage content of fluconazole (C_{13}H_{12}F_{2}N_{6}O) in the injection, using the declared content of C_{13}H_{12}F_{2}N_{6}O in fluconazole RS.
B. Carry out the test as described under \textit{1.14.4 High-performance liquid chromatography}, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).\(^1\)

As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) dilute 5.0 ml of the injection to be examined to 20.0 ml. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of fluconazole (C\textsubscript{13}H\textsubscript{12}F\textsubscript{2}N\textsubscript{6}O) in the injection using the declared content of C\textsubscript{13}H\textsubscript{12}F\textsubscript{2}N\textsubscript{6}O in fluconazole RS.

\textbf{Bacterial endotoxins.} Carry out the test as described under \textit{3.4 Test for bacterial endotoxins}; contains not more than 0.416 IU of endotoxin RS per mg of fluconazole.

\textbf{Reagent to be defined:}

\textbf{Ammonium formate R}

CH\textsubscript{5}NO\textsubscript{2}. Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

\textbf{Reagent to be defined:}

\textbf{Ammonium formate R}

CH\textsubscript{5}NO\textsubscript{2}. Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

\textbf{Reagent to be defined:}

\textbf{Ammonium formate R}

CH\textsubscript{5}NO\textsubscript{2}. Deliquescent crystals or granules, very soluble in water R, soluble in dehydrated ethanol R. Melting range: 119°C to 121°C. Storage in an airtight container.

\footnote{Capcell Pak\textsuperscript{®} C18 MGII (4.6×250 mm, 5 μm) has been found suitable.}
Levamisoli hydrochloridum  
Levamisole hydrochloride

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.584, May 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

\[
\text{C}_{11}\text{H}_{12}\text{N}_{2}\text{S},\text{HCl}
\]

**Relative molecular mass.** 240.8

**Chemical name.** (-)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-b]thiazole monohydrochloride; (S)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole monohydrochloride; CAS Reg. No. 16595-80-5.

**Description.** A white or almost white, crystalline powder.

**Solubility.** Freely soluble in water; soluble in ethanol (~750 g/l) TS; slightly soluble in dichloromethane R.

**Category.** Anthelminthic drug.

**Storage.** Levamisole hydrochloride should be kept in a well-closed container, protected from light.

**Requirements**

Levamisole hydrochloride contains not less than 98.5% and not more than 101.0% of \( \text{C}_{11}\text{H}_{12}\text{N}_{2}\text{S},\text{HCl} \), calculated with reference to the dried substance.

**Identity tests**

- Either tests A and D or tests B, C and D may be applied.
  
  **A.** Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from levamisole hydrochloride RS or with the reference spectrum of levamisole hydrochloride.

  **B.** Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of toluene R, 40 volumes of acetone R and 1 volume of ammonia (~260g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following two solutions in methanol R. For solution (A) use 2 mg of the test substance per ml. For solution (B) use 2 mg of levamisole hydrochloride RS per ml. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).
C. Dissolve about 0.06 g of the test substance in 20 ml of water, add 2 ml of sodium hydroxide (~80 g/l) TS, boil for 10 minutes and cool. Add a few drops of sodium nitroprusside (45 g/l) TS; a red colour is produced which fades on standing.

D. A 0.05 g/ml solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

**Specific optical rotation.** Use a 0.050 g/ml solution in carbon-dioxide-free water R and calculate with reference to the dried substance; \([\alpha]^{20}_D = -121.5^\circ \text{ to } -128^\circ\).

**Clarity and colour of solution.** A solution of 0.50 g in 10 ml of carbon-dioxide-free water R is clear and not more intensely coloured than standard colour Yw1 when compared as described under 1.11 Colour of liquids.

**Sulfated ash.** Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant mass at 105 °C; it loses not more than 5.0 mg/g.

**pH value.** pH of a 0.05 g/ml solution, 3.5–5.0.

**Related substances.** Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm x 4.6 mm) packed with particles of base-deactivated silica gel, the surface of which has been modified by chemically-bonded octadecylsilyl groups (3 µm).

Use the following conditions for gradient elution:

Mobile phase A: dissolve 0.5 g of ammonium dihydrogen phosphate R in 90 mL of water R, adjust to pH 6.5 with a 40 g/l solution of sodium hydroxide R and dilute to 100 ml with water R.

Mobile phase B: acetonitrile R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–8</td>
<td>90–30</td>
<td>10–70</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>8–10</td>
<td>30</td>
<td>70</td>
<td>Isocratic</td>
</tr>
<tr>
<td>10–11</td>
<td>30–90</td>
<td>70–10</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>11–15</td>
<td>90</td>
<td>10</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 215 nm.

As a dissolution solvent prepare a mixture of 90 volumes of methanol R and 10 volumes of ammonia (~260 g/l) TS. Prepare the following solutions: For solution (1) transfer 100 mg of the test substance to a 10 ml volumetric flask and dilute to volume with the dissolution solvent. For solution (2) dilute 10.0 ml of solution (1) to 100.0 ml with methanol R. For solution (3) dissolve 20 mg of the test substance in 5 ml of a 0.1 mol/l solution of sodium hydroxide R in a test tube. Close and heat the test tube in a water-bath at 100 °C for 5 hours. Allow to cool and dilute 1 ml of the resulting solution to 25 ml with methanol R. For solution (4) transfer 5.0 ml of solution (2) to a 50 ml volumetric flask and dilute to volume with methanol.

Inject 10 µl of solution (3). The test is not valid unless the resolution between the peak due to levamisole (retention time about 3.5 minutes) and the peak due to impurity C (relative retention of about 1.5) is at least 15.

Inject separately 10 µl each of solutions (1) and (4).
The following peaks are eluted at the following relative retention with reference to levamisole (retention time about 3.5 minutes): impurity A about 0.9; impurity B about 1.4; impurity C about 1.5; impurity D about 1.6; impurity E about 2.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.0, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.7, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 2.9, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.3, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 0.2 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.2 %);
- the area of any other peak, other than the principal peak, is not greater than 0.1 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.1 %);
- the sum of the corrected areas of any peak corresponding to impurity A, B, C, D and E and the areas of all other peaks, other than the principal peak, is not greater than 0.3 times the area of the peak due to levamisole in the chromatogram obtained with solution (4) (0.3 %). Disregard any peak with an area less than 0.05 times the area of the peak due to levamisole the chromatogram obtained with solution (4) (0.05 %).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, use procedure 1 or procedure 3 for the preparation of the test solution; determine the heavy metals content according to Method A; not more than 20 μg/g.

Assay

Dissolve about 0.2 g, accurately weighed, in 30 ml of ethanol (~750 g/l) TS and add 5 ml of hydrochloric acid (0.01 mol/l) VS. Titrate with sodium hydroxide (0.1 mol/l) VS, determining the two inflection points potentiometrically. Record the volume, in ml, of sodium hydroxide (0.1 mol/l) VS consumed between the two inflection points.

Each ml of sodium hydroxide (0.1mol/l) VS is equivalent to 24.08 mg of C_{11}H_{12}N_{2}S.HCl.

Impurities

![Chemical structure](image)

A. 3-[(2RS)-2-amino-2-phenylethyl]thiazolidin-2-one,
B. 3-[(E)-2-phenylethenyl]thiazolidin-2-imine,

C. (4RS)-4-phenyl-1-(2-sulfanylethyl)imidazolidin-2-one,

D. 6-phenyl-2,3-dihydroimidazo[2,1-b]thiazole,

E. 1,1′-[(disulfane-1,2-diyl)bis(ethylene)]bis[(4RS)-4-phenylimidazolidin-2-one].

Reference substances to be established
levamisole hydrochloride RS

***
Dextromethorphan hydrobromide

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.585, May 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Note from the Secretariat. Following consumption of dextromethorphan cough syrups contaminated with levomethorphan approximately 50 persons died in Pakistan in January 2013. A further suspected drug intoxication involving 11 patients was reported several months later, in September 2013, in Paraguay. Investigations revealed that the medicines administered were manufactured using adulterated dextromethorphan hydrobromide, which contained levomethorphan at levels varying between 9.5% to 22.6%. Following these incidents the World Health Organization issued Drug Alerts Nos 126 and 129 and called on all Member States to increase vigilance against adulterated Dextromethorphan/ Dextromethorphan hydrobromide API.

It is proposed to revise the monograph on Dextromethorphan hydrobromide in The International Pharmacopoeia with a view to add a statement under the section “Manufacture” requiring that the production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide. This limit was deemed appropriate following a scientific assessment on behalf of the WHO Prequalification Team.

A chiral method, selective for levomethorphan, is currently under development and shall be included in the “Supplementary Information Section” of The International Pharmacopoeia once elaborated.

Changes from the current monograph are indicated in the text by insert or delete.

Molecular formula. \( \text{C}_{18}\text{H}_{25}\text{NO},\text{HBr},\text{H}_{2}\text{O} \)

Relative molecular mass. 370.3

Graphic formula.

Chemical name.
(+)-3-Methoxy-17-methyl-9α,13α-14α-morphinan hydrobromide monohydrate; (+)-cis-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2\(\text{H}\)-10,4a-iminoethanophenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

Description. A white or almost white, crystalline powder; odourless or almost odourless.

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antitussive drug.

Storage. Dextromethorphan hydrobromide should be kept in a well-closed container.

Requirements

Definition. Dextromethorphan hydrobromide contains not less than 98.0% and not more than 101.0% of \( \text{C}_{18}\text{H}_{25}\text{NO},\text{HBr} \), calculated with reference to the anhydrous substance.
Manufacture. The production method is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide using a suitable chiral method.

Identity tests
- Either tests A and E or tests B, C, D and E may be applied.
  - Dry a small quantity of the test substance for 4 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R and carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from dextromethorphan hydrobromide RS similarly prepared or with the reference spectrum of dextromethorphan hydrobromide.
  - The absorption spectrum of a 0.10 mg/ml solution in sodium hydroxide (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a maximum at 280 nm; the absorbance of a 1 cm layer at this wavelength is about 0.59.
  - Dissolve 0.05 g in 2 ml of sulfuric acid (~100 g/l) TS. Add 1 ml of mercury/nitric acid TS drop by drop while shaking; a white, crystalline precipitate in the form of platelets is produced and the solution does not immediately turn red. Heat on a water-bath for about 10 minutes; a yellow to red colour develops.
  - Melting temperature, about 125°C with decomposition.
  - To a 5 mg/ml solution add 0.25 ml of nitric acid (~130 g/l) TS; this test yields reaction B described under 2.1 General identification tests as characteristic of bromides.

Specific optical rotation. Use a 20 mg/ml solution in hydrochloric acid (0.1 mol/l) VS and calculated with reference to the anhydrous substance; \( \alpha_D^{20\circ} = +28.0^\circ \) to +30.0°.

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.2 g of the substance; the water content is not less than 35 mg/g and not more than 55 mg/g.

pH value. Dissolve 0.4 g in carbon-dioxide-free water R using gentle heat, dilute to 20 ml with the same solvent and measure the pH at 20°C; the value lies between 5.2 and 6.5.

Dimethylaniline. Dissolve 0.5 g in 15 ml of water using gentle heat, cool and add 4 ml of acetic acid (~60 g/l) TS, 1 ml of sodium nitrite (10 g/l) TS and sufficient water to produce 25 ml. Prepare similarly a reference solution containing 5 μg of N,N-dimethylaniline R in 25 ml. The colour produced in the test solution is not more intense than that produced in the reference solution when compared as described under 1.11 Colour of liquids; the dimethylaniline content is not more than 10 μg/g.

Phenolic substances. To 5 mg add 1 drop of hydrochloric acid (~70 g/l) TS, 1 ml of water and 0.2 ml of ferric chloride (50 g/l) TS. Mix, add 0.2 ml of potassium ferricyanide (50 g/l) TS, dilute to 5 ml with water, shake well and allow to stand for 15 minutes; the solution is yellowish brown and shows no greenish or blue colour.

Assay
Dissolve about 0.5 g, accurately weighed, in 40 ml of glacial acetic acid R1 and add 10 ml of mercuric acetate/acetic acid TS, warming slightly if necessary to effect solution. Titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 35.23 mg of \( \text{C}_{18}\text{H}_{25}\text{NO}_{3}\text{HBr} \).