Technical Guide

for the elaboration of monographs on radiopharmaceutical preparations

European Pharmacopoeia

European Directorate for the Quality of Medicines & HealthCare

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INTRODUCTION

This Technical guide for the elaboration of monographs on radiopharmaceutical preparations supplements the Style guide for the elaboration of monographs. The general principles described herein do not differ from those applied to monographs on pharmaceutical substances. For this reason, in this guide attention is only given to those subjects, which are particular to radiopharmaceutical preparations. Unless specifically exempted, the requirements of the general monographs on *Substances for pharmaceutical use (2034)* and *Radiopharmaceutical preparations (0125)*, as well as other general texts, for example, on dosage forms apply to the individual monographs on radiopharmaceutical preparations. To avoid any doubt this may in some cases be explicitly stated.

MONOGRAPH TITLE

For a radiopharmaceutical preparation the title is given according to the INN nomenclature, provided this is available. The radionuclide symbol follows the name of the entity that is or contains the element.

Examples:

TECHNETIUM (^{99m}Tc) EXAMETAZIME INJECTION

FLUDEOXYGLUCOSE (^{18}F) INJECTION

If an INN is not available, the title is unambiguous and well known by the users. The radionuclide involved is stated as well as the position of the radionuclide in the molecule, if there is more than one possibility.

Example:

L-METHIONINE ([^{11}C]METHYL) INJECTION, instead of L-METHIONINE (^{11}C) INJECTION

In the case of a radioactive precursor, the name of the substance is completed by “FOR RADIOLABELLING”.

Example:

FLUORIDE (^{18}F) SOLUTION FOR RADIOLABELLING

For a non-radioactive precursor the wording "FOR RADIOPHARMACEUTICAL PREPARATIONS" is added to the name of the substance. This allows the publication of precursor monographs in the section for radiopharmaceutical preparations and distinguishes between qualities that are suitable for radiopharmaceutical preparations and those that are not.

Example:

IOBENGUANE FOR RADIOPHARMACEUTICAL PREPARATIONS

This Guide will however deal no further with non-radioactive precursors because these are more appropriately covered by the more general Style guide.

DEFINITION

Formulae and names

Within the definition section, the name of the principal chemical compound is given (with the radionuclide symbol) according to IUPAC conventions. If an abbreviated version or INN is subsequently used in the rest of the text, it is shown in parentheses after the IUPAC name in the definition.

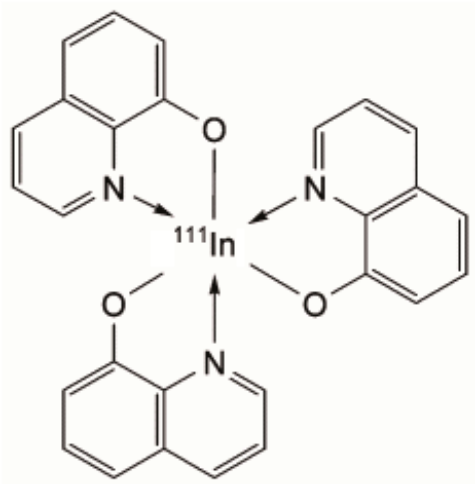
Examples:

Sterile solution containing 2-[^{18}F]fluoro-2-deoxy-D-glucopyranose (2-[^{18}F]fluoro-2-deoxy-D-glucose) prepared by nucleophilic substitution.

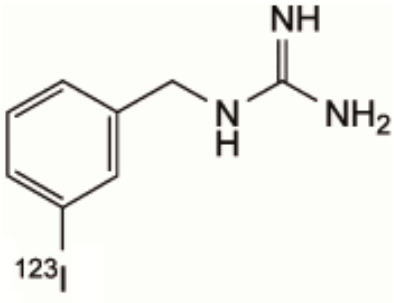
It is prepared by dissolving [[[(3-bromo-2,4,6-trimethylphenyl)carbamoyl] methyl]imino]diacetic acid (mebrofenin) in the presence of…

For well-defined radiolabelled substances, a graphic formula is given.

Example:



[^{111}In]Indium oxine



1-(3-[^{123}I]iodobenzyl)guanidine or [^{123}I]iobenguane

The molecular formula is given according to the IUPAC conventions for isotopically modified compounds (labelled) and the relative molecular mass is stated for the completely labelled compound. As noted however in the general monograph *Radiopharmaceutical preparations (0125)*, the actual relative molecular mass will vary according to the specific radioactivity.

Example:

$C_{27}H_{18}[^{111}In]N_3O_3$	M_r 543.5
$C_8H_{10}[^{123}I]N_3$	M_r 271.2

The content section only includes statements that are essential to the substance or the preparation.

Example:

fluorine-18: 90 per cent to 110 per cent of the declared fluorine-18 radioactivity at the date and time stated on the label.

If necessary, the maximum content of the non-radioactive molecule in the raiopharmaceutical preparation is stated in order to give a lower limit for the specific radioactivity.

Example:

2-fluoro-2-deoxy-D-glucose: maximum 0.5 mg per maximum recommended dose in millilitres.

For preparations comprising a radionuclide and a complexing ligand, the maximum content of complexing ligand may be stated in cases, for example, where it may be pharmacologically active.

Example:

Edotreotide: maximum 50 µg per maximum recommended dose in millilitres.

Content specifications are only given if the monograph allows their verification.

Content specifications are not given for substances which are considered as impurities.

If additives may be used these are stated, generally in a non-explicit manner.

Examples:

It may contain stabilisers and inert additives.

The preparation may contain stabilisers such as ascorbic acid and edetic acid.

If applicable, the definition states that the monograph applies to the substance obtained by a certain route of production. This information is not included in the title of the monograph.

Examples:

This monograph applies to an injection containing 6-[^{18}F]fluorolevodopa produced by electrophilic substitution.

Sterile solution containing 2-[^{18}F]fluoro-2-deoxy-D-glucopyranose (2-[^{18}F]fluoro-2-deoxy-D-glucose) prepared by nucleophilic substitution.

Sterile solution of a complex of technetium-99m with sodium hydroxymethylenediphosphonate. It is prepared using *Sodium pertechnetate (^{99m}Tc) injection (fission) (0124)* or *Sodium pertechnetate (^{99m}Tc) injection (non-fission) (0283)*.

PRODUCTION

According to the *General notices (1.)*, the statements in this section constitute mandatory requirements, unless otherwise stated. These requirements are related to source materials, the manufacturing process itself and its validation and control, or to testing that is to be carried out by the manufacturer on the finished product, either on selected batches or on each batch prior to release. These statements may not necessarily be verified on a sample of the finished product.

Example:

No carrier iodide is added.

There is no need to give details of the production procedure if various possibilities exist. For information purposes, these will be given in the Knowledge database. The use of phrases such as "may be produced by various reactions..." and "the most frequently used method" are to be avoided. Such statements are included within the Definition or, if not directly relevant to the interpretation and use of the monograph, in the introductory note in Pharmeuropa.

CHARACTERS

The statements under the heading Characters are not to be interpreted in a strict sense and are not analytical requirements. The appearance of the preparation is given for information.

Examples:

Appearance: clear, colourless or slightly yellow solution.

Appearance: white or almost white suspension which may separate on standing.

Appearance: colourless gas.

Reference is also made to half-life and nature of the radiation of the radionuclide involved in the preparation.

Example:

Half-life and nature of radiation of fluorine-18: see general chapter *5.7. Table of physical characteristics of radionuclides*.

IDENTIFICATION

This section should provide assurance that the correct radionuclide is present (gamma-ray and X-ray spectrometry, half-life determination) and that the substance is present in the correct chemical form (for example, by a separation technique or a specific chemical reaction). For short-lived radionuclides, the determination of half-life can also be done approximately.

Examples:

A. Test A for radionuclidic purity (see Tests).

A. Gamma-ray spectrometry.
Result: the principal photons have an energy of 0.511 MeV and, depending on the measurement geometry, a sum peak of 1.022 MeV may be observed.

A. Gamma-ray spectrometry.
Result: the most prominent gamma photon of technetium-99m has an energy of 0.141 MeV.

B. Determine the approximate half-life by no fewer than 3 measurements of the activity of a sample in the same geometrical conditions within a suitable period of time (for example, 30 min).

Result: 105 min to 115 min.

C. Examine the chromatograms obtained in test A for radiochemical purity (see Tests).

Result: the principal peak in the radiochromatogram obtained with the test solution is similar in retention time / retardation factor to the principal peak in the chromatogram obtained with reference solution (a).

C. Examine the chromatograms obtained in test A for radiochemical purity (see Tests).

Result: the retardation factor of the principal peak in the radiochromatogram obtained with the test solution is 0.0 to 0.1.

TESTS

If relevant for the monograph, tests for sterility, bacterial endotoxins and residual solvents must be stated explicitly, as long as these tests are not covered by the general monograph *Radiopharmaceutical preparations* (*0125*). The order of the tests follows that in the style guide.

pH

The test is to be performed on the undiluted preparation, unless otherwise stated. The pH value may be determined by the use of potentiometry (*2.2.3*) or by the use of an appropriate reagent indicator solution (*2.2.4*) or strip, or by determination of acidity or alkalinity (*2.2.4*).

Examples:

pH (*2.2.3*): 4.5 to 8.5.

Acidity (*2.2.4*): the solution is strongly acidic.

Alkalinity (*2.2.4*): the solution is strongly alkaline.

pH: 5.0 to 9.0, using a *pH indicator strip R.*

Non-radioactive substances and impurities (former Chemical purity section)

This section consists of tests for specific non-radioactive substances and known or potential non-radioactive impurities. If the definition mentions limits for the specific radioactivity or for the non-radioactive substance of the preparation, then a test must be given to determine the content of the non-radioactive substance of the preparation. Within the text of a monograph, impurities (chemical and radiochemical) are referred to as "Impurity A", "Impurity B" etc. These are defined in the transparency statement at the end of the monograph applying the terminology of the glossary of chapter *5.10. Control of impurities in substances for pharmaceutical use*. In the text, the titles of tests for impurities will refer to "Impurity A", "Impurity B" etc., however the first time an impurity is mentioned (for example in the preparation of reference solutions), the name of the reagent is used, followed by the impurity's identification in parentheses.

Example:

Dissolve 1.0 mg of *2-chloro-2-deoxy-* D-*glucose R* (impurity A) in *water R*.

The limits are set based on toxicology data and on observed results.

The following example also serves as a guide to the standard style for the description of such a test.

Example:

2-Fluoro-2-deoxy-D-glucose and impurity A. Liquid chromatography (*2.2.29*).
Test solution. The preparation to be examined.
Reference solution (a). Dissolve 1.0 mg of *2-fluoro-2-deoxy-D-glucose R* in *water R* and dilute to 2.0 ml with the same solvent. Dilute 1.0 ml of the solution to *V* with *water R*, *V* being the maximum recommended dose in millilitres.
Reference solution (b). Dissolve 1.0 mg of *2-chloro-2-deoxy-D-glucose R* (impurity A) in *water R* and dilute to 2.0 ml with the same solvent. Dilute 1.0 ml of the solution to *V* with *water R*, *V* being the maximum recommended dose in millilitres.
Reference solution (c). Dissolve 1.0 mg of *2-fluoro-2-deoxy-D-mannose R* in *water R* and dilute to 2.0 ml with the same solvent. Mix 0.5 ml of this solution with 0.5 ml of reference solution (a).
Column:
- *size*: *l* = 0.25 m, Ø = 4.0 mm;
- *stationary phase*: *strongly basic anion exchange resin for chromatography R* (10 µm).
Mobile phase: 4 g/l solution of *sodium hydroxide R* in *carbon dioxide-free water R* protected from atmospheric carbon dioxide.

Flow rate: 1 ml/min.

Detection: suitable detector for carbohydrates in the required concentration range, such as pulse amperometric detector and radioactivity detector connected in series.

Injection: 20 µl.

Run time: twice the retention time of 2-fluoro-2-deoxy-D-glucose.

Relative retention with reference to 2-fluoro-2-deoxy-D-glucose (retention time = about 12 min): 2-fluoro-2-deoxy-D-mannose = about 0.9; impurity A = about 1.1.

System suitability: reference solution (c) using the carbohydrate detector:

- *resolution*: minimum 1.5 between the peaks due to 2-fluoro-2-deoxy-D-mannose and 2-fluoro-2-deoxy-D-glucose;
- s*ignal-to-noise ratio*: minimum 10 for the peak due to 2-fluoro-2-deoxy-D-glucose.

Limits: in the chromatogram obtained with the carbohydrate detector:

- *2-fluoro-2-deoxy-D-glucose*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 mg/*V*);
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 mg/*V*).

The column temperature is mentioned only if absolutely necessary or if it is outwith room temperature (15 °C to 25 °C). Unless otherwise stated, it is assumed that the column temperature is to be constant.

Residual solvents

These are usually limited according to general chapter *5.4. Resisual solvents*. For short-lived radionuclides, the statement "The preparation may be released for use before completion of the test" may be added.

Example:

Residual solvents: limited according to the principles defined in general chapter *5.4. Resisual solvents.* The preparation may be released for use before completion of the test.

Physiological distribution

Tests involving animals should be avoided. Some radiopharmaceutical preparations may comprise a mixture of radiolabelled components of varying composition not readily determined by other analytical methods. Where the physico-chemical test(s) for radiochemical purity are not adequate to completely define and control the radiochemical species in a radiopharmaceutical preparation, a physiological distribution test may be required. General guidance on the performance of the test is given in the general monograph *Radiopharmaceutical Preparations (0125)* but the wording of the test and limits will depend on the precise nature of the test, although harmonisation with similar texts is desirable.

Sterility

If considered necessary, on a case-by-case basis, the statement "The preparation may be released for use before completion of the test" may be added.

Examples:

> **Sterility**. It complies with the test for sterility prescribed in the monograph *Radiopharmaceutical preparations (0125)*.

> **Sterility**. It complies with the test for sterility prescribed in the monograph *Radiopharmaceutical preparations (0125)*. The preparation may be released for use before completion of the test.

Bacterial endotoxins

Because of possible confusion over which parts of the text *Parenteral Preparations (0520)* apply to radiopharmaceutical injections, all such monographs will now contain a standard limit for bacterial endotoxins of 175/*V* IU/ml unless a lower limit is required (for example, for products intended for intrathecal administration).

Examples:

> **Bacterial endotoxins** (*2.6.14*): less than 175/*V* IU/ml, *V* being the maximum recommended dose in millilitres.

> **Bacterial endotoxins** (*2.6.14*): less than 175/*V* IU/ml, *V* being the maximum recommended dose in millilitres. The preparation may be released for use before completion of the test.

For radioactive starting materials, such as solutions for radiolabelling, a lower value is specified for the bacterial endotoxins limit and provision can be made for release for use before completion of the test.

Example:

> **Bacterial endotoxins** *(2.6.14):* less than 20 IU/ml, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins. The preparation may be released for use before completion of the test.

RADIONUCLIDIC PURITY

This section ensures a maximum limit for the content of radionuclidic impurities and a minimum content of the radionuclide in question.

Example *(for an iodine-123 labelled preparation):*

RADIONUCLIDIC PURITY
The preparation may be released for use before completion of the test.
Iodine-123: minimum 99.7 per cent of the total radioactivity.
Gamma-ray spectrometry.
Determine the relative amounts of iodine-123, iodine-125, tellurium-121 and other radionuclidic impurities present. For the detection of tellurium-121 and iodine-125, retain the preparation to be examined for a sufficient time to allow iodine-123 to decay to a level which permits the detection of radionuclidic impurities. No radionuclides with a half-life longer than that of iodine-125 are detected.

Radionuclidic impurities with a half-life longer than that of the radionuclide in the preparation are determined after a suitable period of decay. In this case, indications are given on how long a sample is to be retained before starting the measurement of the remaining longer-lived impurities and it is stated that the preparation may be released for use before completion of this part of the test.

Example *(for a fluorine-18 labelled preparation)*:

RADIONUCLIDIC PURITY
The preparation may be released for use before completion of test B.
Fluorine-18: minimum 99.9 per cent of the total radioactivity.
A. Gamma-ray spectrometry. Preliminary test.
Limit: peaks in the gamma spectrum corresponding to photons with an energy different from 0.511 MeV or 1.022 MeV represent not more than 0.1 per cent of the total radioactivity.
B. Gamma-ray spectrometry.
Determine the amount of fluorine-18 and radionuclidic impurities with a half-life longer than 2 h. For the detection and quantification of impurities, retain the preparation to be examined for at least 24 h to allow the fluorine-18 to decay to a level that permits the detection of impurities.
Result: the total radioactivity due to radionuclidic impurities is not more than 0.1 per cent.

For radiopharmaceutical preparations labelled with technetium-99m a radionuclidic purity test is not described because these are prepared with *Sodium pertechnetate (^{99m}Tc) injection (fission) (0124)* or *Sodium pertechnetate (^{99m}Tc) injection (non-fission) (0283)* for which radionuclidic requirements are already defined.

RADIOCHEMICAL PURITY

This section is one of the most important and specific tests for a radiopharmaceutical preparation and the most difficult for which to provide a standard text. It ensures that the radionuclide in question is present in the desired chemical form. The impurity(ies) tested for is(are) used as the title of the test whenever possible. Limits are expressed as a minimum percentage of the total radioactivity of the radionuclide concerned. In

some circumstances limits may also be given for the maximum percentage of individual or combined radiochemical impurities.

Example *(for a fluorine-18 labelled preparation)*:

> *RADIOCHEMICAL PURITY*
>
> - *6-[^{18}F]fluorolevodopa*: minimum 95 per cent of the total radioactivity due to fluorine-18.
>
> Liquid chromatography (*2.2.29*) as described in the test for 6-fluorolevodopa, dopa, impurity A and impurity B.
>
> Examine the chromatogram recorded using the radioactivity detector and locate the peak due to 6-[^{18}F]fluorolevodopa by comparison with the chromatogram obtained with reference solution (a) and the spectrophotometer.

Example *(for a technetium-99m labelled preparation using only paper or thin-layer chromatography)*:

> *RADIOCHEMICAL PURITY*
>
> **Impurities A, B, C, D, E, F**. Thin-layer chromatography (*2.2.27*).
>
> *Test solution*. The preparation to be examined.
>
> *Reference solution (a)*. To vial B of *bicisate labelling kit CRS* in lead shielding add 2 ml of sodium pertechnetate (^{99m}Tc) injection (fission or non-fission) containing 400-800 MBq. Dissolve the contents of vial A of *bicisate labelling kit CRS* in 3 ml of a 9 g/l solution of *sodium chloride R*. Immediately transfer 1.0 ml of the solution contained in vial A to vial B. Mix and allow to stand for 30 min at room temperature.
>
> *Reference solution (b)*. Sodium pertechnetate (^{99m}Tc) injection (fission or non fission).
>
> *Plate*: *TLC silica gel plate R.*
>
> *Mobile phase*: *ethyl acetate R.*
>
> *Application*: 5 µl, allow the spots to dry for 5-10 min.
>
> *Development*: over 4/5 of the plate.
>
> *Drying*: in air.
>
> *Detection*: suitable detector to determine the distribution of radioactivity.
>
> *Retardation factors*: [^{99m}Tc]technetium bicisate = more than 0.4; impurities A, B, C, D, E and F = less than 0.2.
>
> *System suitability*: the retardation factor of the principal peak in the chromatogram obtained with reference solution (a) is clearly different from the retardation factor of the peak in the chromatogram obtained with reference solution (b).
>
> *Limit*:
>
> *-sum of impurities A, B, C, D, E and F*: not more than 6 per cent of the total radioactivity due to technetium-99m.

Where there is a need for a reference solution for "[^{99m}Tc]technetium in colloidal form" this may be prepared immediately before use.

Example:

Reference solution (a). To 1 ml of a 1 g/l solution of *stannous chloride R* in a 51.5 g/l solution of *hydrochloric acid R* in a closed vial, add 2 ml of sodium pertechnetate (^{99m}Tc) injection (fission or non-fission). Use within 30 min after preparation.

For determination of radiochemical purity using liquid chromatography the potential for retention of radioactivity on the column must be considered. This is reflected in a formula for the calculation of the limits.

Example:

Calculate the percentage of radioactivity due to [^{99m}Tc]technetium mebrofenin using the following expression:
$$(100 - A) \times T$$
A = percentage of radioactivity due to impurity A determined in the test for impurity A under radiochemical purity;
T = proportion of the radioactivity in the peak due to [^{99m}Tc]technetium mebrofenin relative to the total eluted radioactivity in the chromatogram obtained with the test solution.

RADIOACTIVITY

This section corresponds to the assay section in monographs of chemical substances.

Example:

RADIOACTIVITY
Determine the radioactivity using a calibrated instrument.

STORAGE

Information regarding storage is included in the general monograph on *Radiopharmaceutical Preparations* (*0125*). If additional information is necessary for the interpretation of the requirements this is specified in the individual monograph.

Examples:

STORAGE
In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.

STORAGE
Protected from light, at 25 °C or below.

LABELLING

Information regarding labelling is included in the general monograph *Radiopharmaceutical Preparations* (*0125*). If additional information is necessary for the interpretation of the requirements this is specified in the individual monograph.

Examples:

LABELLING

The label states:

— that the solution is not for direct administration to humans;

— where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

LABELLING

The label states the maximum recommended dose in millilitres.

LABELLING

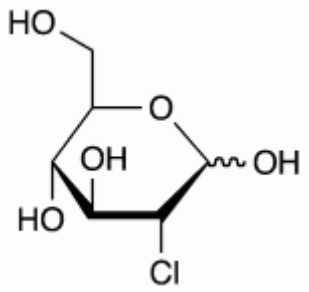
The label states the specific radioactivity expressed in GBq of iodine-123 per gram of iobenguane base.

IMPURITIES (see general chapter *5.10. Control of impurities in substances for pharmaceutical use*)

Where there are potential chemical, radiochemical or radionuclidic impurities limited by the prescribed tests these are listed with a graphical formula where possible:

Examples:

Specified impurities: A, B, C, D, E.



A. 2-chloro-2-deoxy-D-glucopyranose (2-chloro-2-deoxy-D-glucose),

•

•

•

E. [^{18}F]fluoride.

A. [^{99m}Tc]technetium in colloidal form,

B. [^{99m}Tc]pertechnetate ion

C. [^{123}I]iodate ion.

A. iodine-125,
B. tellurium-121,

Non-radioactive inorganic impurities (e.g. metals) are not listed in the impurities section.