

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

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

11 MONOGRAPH TITLE

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

15 Examples:

16

TECHNETIUM (^{99m} Tc) EXAMETAZIME INJECTION

17

18

FLUDEOXYGLUCOSE (¹⁸ F) INJECTION
--

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

22 Example:

23

L-METHIONINE ([¹¹ C]METHYL) INJECTION, instead of L-METHIONINE 24 (¹¹ C) INJECTION

25

26 In the case of a radioactive precursor, the name of the substance is completed by
27 "FOR RADIOLABELLING".

28 Example:

29

FLUORIDE (¹⁸ F) SOLUTION FOR RADIOLABELLING

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

35 Example:

36

IOBENGUANE FOR RADIOPHARMACEUTICAL PREPARATIONS

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

39

40 **DEFINITION**

41 **Formulae and names**

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

46 Examples:

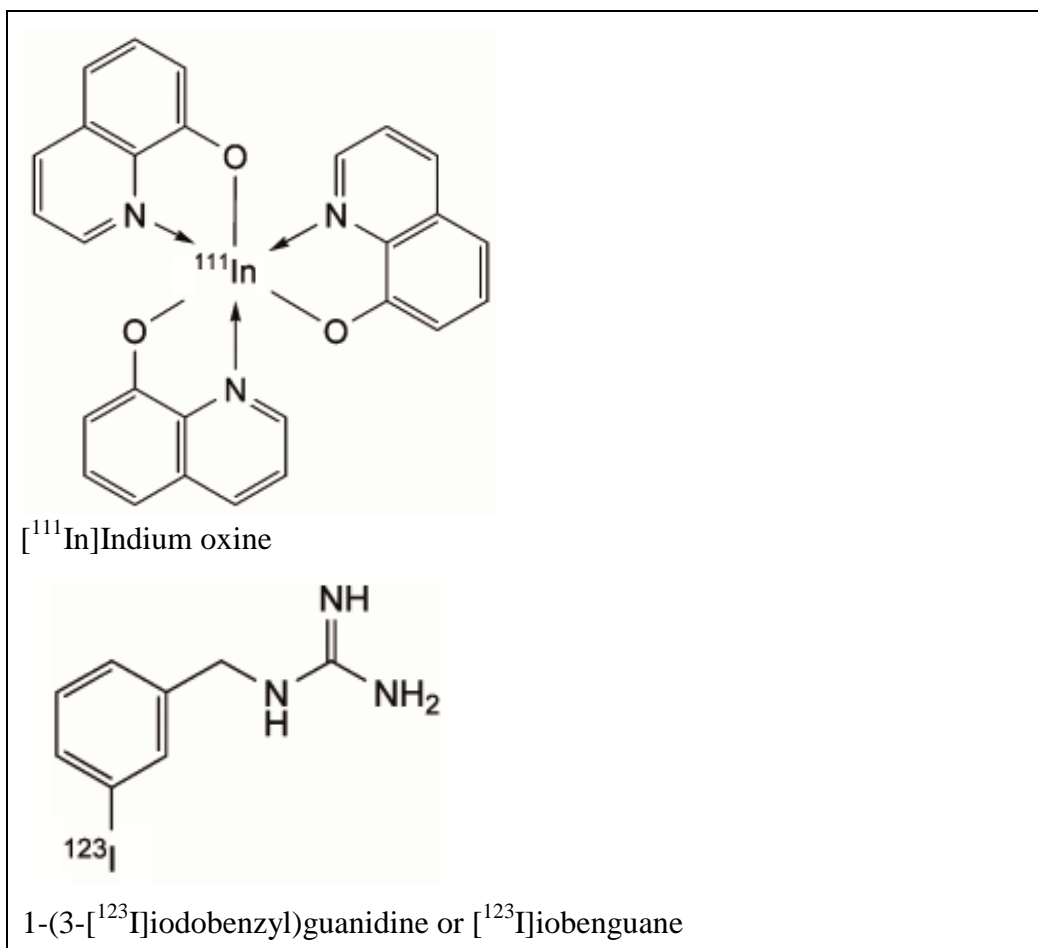
47 Sterile solution containing 2-^[18F]fluoro-2-deoxy-D-glucopyranose
48 (2-^[18F]fluoro-2-deoxy-D-glucose) prepared by nucleophilic substitution.

49

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

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

53 Example:



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

59

60 Example:

61	$C_{27}H_{18}[^{111}In]N_3O_3$	M_r 543.5
62	$C_8H_{10}[^{123}I]N_3$	M_r 271.2

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

65 Example:

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

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

71 Example:

72 *2-fluoro-2-deoxy-D-glucose*: maximum 0.5 mg per maximum recommended
73 dose in millilitres.

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

77 Example:

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

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

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

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

82 Examples:

83 It may contain stabilisers and inert additives.

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

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

88 Examples:

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

92 Sterile solution containing 2- $[^{18}F]$ fluoro-2-deoxy-D-glucopyranose
93 (2- $[^{18}F]$ fluoro-2-deoxy-D-glucose) prepared by nucleophilic substitution.

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

99 **PRODUCTION**

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

106 Example:

107

No carrier iodide is added.

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

114 **CHARACTERS**

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

118 Examples:

119

<i>Appearance</i> : clear, colourless or slightly yellow solution.
--

120
121

<i>Appearance</i> : white or almost white suspension which may separate on 122 standing.

123
124

<i>Appearance</i> : colourless gas.

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

127 Example:

128

<i>Half-life and nature of radiation of fluorine-18</i> : see general chapter 5.7. <i>Table</i> 129 <i>of physical characteristics of radionuclides</i> .
--

130 **IDENTIFICATION**

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

136 Examples:

137

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

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

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

144 B. Determine the approximate half-life by no fewer than 3 measurements of
145 the activity of a sample in the same geometrical conditions within a suitable
146 period of time (for example, 30 min).
147 *Result:* 105 min to 115 min.

148 C. Examine the chromatograms obtained in test A for radiochemical purity
149 (see Tests).
150 *Result:* the principal peak in the radiochromatogram obtained with the test
151 solution is similar in retention time / retardation factor to the principal peak in
152 the chromatogram obtained with reference solution (a).

153 C. Examine the chromatograms obtained in test A for radiochemical purity
154 (see Tests).
155 *Result:* the retardation factor of the principal peak in the radiochromatogram
156 obtained with the test solution is 0.0 to 0.1.

157 TESTS

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

162 pH

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

167 Examples:

168 **pH** (2.2.3): 4.5 to 8.5.

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

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

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

172

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

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

186 Example:

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

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

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

191 Example:

192 **2-Fluoro-2-deoxy-D-glucose and impurity A.** Liquid chromatography
193 (2.2.29).

194 *Test solution.* The preparation to be examined.

195 *Reference solution (a).* Dissolve 1.0 mg of 2-fluoro-2-deoxy-D-glucose R in
196 water R and dilute to 2.0 ml with the same solvent. Dilute 1.0 ml of the
197 solution to V with water R, V being the maximum recommended dose in
198 millilitres.

199 *Reference solution (b).* Dissolve 1.0 mg of 2-chloro-2-deoxy-D-glucose R
200 (impurity A) in water R and dilute to 2.0 ml with the same solvent. Dilute
201 1.0 ml of the solution to V with water R, V being the maximum recommended
202 dose in millilitres.

203 *Reference solution (c).* Dissolve 1.0 mg of 2-fluoro-2-deoxy-D-mannose R in
204 water R and dilute to 2.0 ml with the same solvent. Mix 0.5 ml of this solution
205 with 0.5 ml of reference solution (a).

206 *Column:*

207 - size: $l = 0.25$ m, $\varnothing = 4.0$ mm;

208 - stationary phase: strongly basic anion exchange resin for
209 chromatography R (10 μ m).

210 *Mobile phase:* 4 g/l solution of sodium hydroxide R in carbon dioxide-free
211 water R protected from atmospheric carbon dioxide.

212 *Flow rate:* 1 ml/min.

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

216 *Injection:* 20 µl.

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

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

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

222 - *resolution:* minimum 1.5 between the peaks due to 2-fluoro-2-deoxy-D-
 223 mannose and 2-fluoro-2-deoxy-D-glucose;

224 - *signal-to-noise ratio:* minimum 10 for the peak due to 2-fluoro-2-deoxy-D-
 225 glucose.

226 *Limits:* in the chromatogram obtained with the carbohydrate detector:

227 - *2-fluoro-2-deoxy-D-glucose:* not more than the area of the corresponding
 228 peak in the chromatogram obtained with reference solution (a) (0.5 mg/V);

229 - *impurity A:* not more than the area of the corresponding peak in the
 230 chromatogram obtained with reference solution (b) (0.5 mg/V).

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

234 **Residual solvents**

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

238 Example:

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

242 **Physiological distribution**

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

252 **Sterility**

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

255 Examples:

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

258

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

262 **Bacterial endotoxins**

263 Because of possible confusion over which parts of the text *Parenteral Preparations*
264 *(0520)* apply to radiopharmaceutical injections, all such monographs will now contain
265 a standard limit for bacterial endotoxins of $175/V$ IU/ml unless a lower limit is
266 required (for example, for products intended for intrathecal administration).

267 Examples:

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

270

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

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

277 Example:

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

282

283 ***RADIONUCLIDIC PURITY***

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

286

287

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

289

RADIONUCLIDIC PURITY

290

The preparation may be released for use before completion of the test.

291

Iodine-123: minimum 99.7 per cent of the total radioactivity.

292

Gamma-ray spectrometry.

293

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.

294

295

296

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298

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

304

Example (for a fluorine-18 labelled preparation):

305

RADIONUCLIDIC PURITY

306

The preparation may be released for use before completion of test B.

307

Fluorine-18: minimum 99.9 per cent of the total radioactivity.

308

A. Gamma-ray spectrometry. Preliminary test.

309

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.

310

311

312

B. Gamma-ray spectrometry.

313

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.

314

315

316

317

Result: the total radioactivity due to radionuclidic impurities is not more than 0.1 per cent.

318

319 For radiopharmaceutical preparations labelled with technetium-99m a radionuclidic
320 purity test is not described because these are prepared with *Sodium pertechnetate*
321 (*^{99m}Tc*) injection (fission) (0124) or *Sodium pertechnetate* (*^{99m}Tc*) injection (non-
322 fission) (0283) for which radionuclidic requirements are already defined.

323

RADIOCHEMICAL PURITY

324

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

325

326

327

328

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

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

332 **RADIOCHEMICAL PURITY**
333 - 6-[¹⁸F]fluorolevodopa: minimum 95 per cent of the total radioactivity due to
334 fluorine-18.
335 Liquid chromatography (2.2.29) as described in the test for 6-fluorolevodopa,
336 dopa, impurity A and impurity B.
337 Examine the chromatogram recorded using the radioactivity detector and
338 locate the peak due to 6-[¹⁸F]fluorolevodopa by comparison with the
339 chromatogram obtained with reference solution (a) and the spectrophotometer.

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

342 **RADIOCHEMICAL PURITY**
343 **Impurities A, B, C, D, E, F.** Thin-layer chromatography (2.2.27).
344 *Test solution.* The preparation to be examined.
345 *Reference solution (a).* To vial B of *bicisate labelling kit CRS* in lead shielding
346 add 2 ml of sodium pertechnetate (^{99m}Tc) injection (fission or non-fission)
347 containing 400-800 MBq. Dissolve the contents of vial A of *bicisate labelling*
348 *kit CRS* in 3 ml of a 9 g/l solution of *sodium chloride R*. Immediately transfer
349 1.0 ml of the solution contained in vial A to vial B. Mix and allow to stand for
350 30 min at room temperature.
351 *Reference solution (b).* Sodium pertechnetate (^{99m}Tc) injection (fission or non
352 fission).
353 *Plate:* *TLC silica gel plate R*.
354 *Mobile phase:* *ethyl acetate R*.
355 *Application:* 5 µl, allow the spots to dry for 5-10 min.
356 *Development:* over 4/5 of the plate.
357 *Drying:* in air.
358 *Detection:* suitable detector to determine the distribution of radioactivity.
359 *Retardation factors:* [^{99m}Tc]technetium bicisate = more than 0.4; impurities A,
360 B, C, D, E and F = less than 0.2.
361 *System suitability:* the retardation factor of the principal peak in the
362 chromatogram obtained with reference solution (a) is clearly different from the
363 retardation factor of the peak in the chromatogram obtained with reference
364 solution (b).
365 *Limit:*
366 -sum of impurities A, B, C, D, E and F: not more than 6 per cent of the total
367 radioactivity due to technetium-99m.

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

370 Example:

371 *Reference solution (a)*. To 1 ml of a 1 g/l solution of *stannous chloride R* in a
372 51.5 g/l solution of *hydrochloric acid R* in a closed vial, add 2 ml of sodium
373 pertechnetate (^{99m}Tc) injection (fission or non-fission). Use within 30 min
374 after preparation.

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

378 Example:

379 Calculate the percentage of radioactivity due to [^{99m}Tc]technetium mebrofenin
380 using the following expression:

381
$$(100 - A) \times T$$

382 A = percentage of radioactivity due to impurity A determined in the
383 test for impurity A under radiochemical purity;
384 T = proportion of the radioactivity in the peak due to
385 [^{99m}Tc]technetium mebrofenin relative to the total eluted
386 radioactivity in the chromatogram obtained with the test
387 solution.

388 RADIOACTIVITY

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

390 Example:

391 RADIOACTIVITY

392 Determine the radioactivity using a calibrated instrument.

393 STORAGE

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

397 Examples:

398 STORAGE

399 In an airtight container, protected from light, at a temperature of 2 °C to 8 °C.
400

401 STORAGE

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

403 LABELLING

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

407

408

409 Examples:

410 LABELLING

411 The label states:

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

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

415

416 LABELLING

417 The label states the maximum recommended dose in millilitres.

418

419 LABELLING

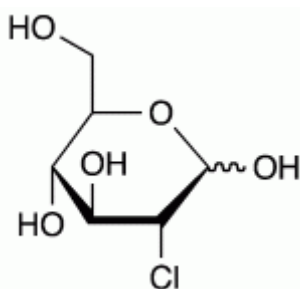
420 The label states the specific radioactivity expressed in GBq of iodine-123 per
421 gram of iobenguane base.

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

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

426 Examples:

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



428

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

430 •

431 •

432 •

433 E. [¹⁸F]fluoride.

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

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

436 C. [¹²³I]iodate ion.

437

438

A. iodine-125,

439

B. tellurium-121,

440

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

441

section.