



1 15 November 2018
2 EMA/CHMP/SWP/686140/2018
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on the non-clinical requirements for**
5 **radiopharmaceuticals**
6 **Draft**

Draft agreed by Safety Working Party	October 2018
Adopted by CHMP for release for consultation	15 November 2018
Start of public consultation	22 November 2018
End of consultation (deadline for comments)	30 June 2019

7
8 This guideline replaces the non-clinical part of the Note for Guidance on Radiopharmaceuticals/
9 Eudralex 3AQ20a and 3Q21a. For quality aspects, 3AQ20a has been replaced by the 'Guideline on
10 Radiopharmaceuticals' (EMA/CHMP/QWP/306970/2007).

11
12 Comments should be provided using this [template](#). The completed comments form should be sent to
SWP-H@ema.europa.eu

13

Keywords	<i>radiopharmaceuticals, radiodiagnostics, radiotherapeutics, non-clinical safety assessment</i>
-----------------	---



14 **Guideline on the non-clinical requirements for**
15 **radiopharmaceuticals**

16 **Table of contents**

17 **Executive summary 3**

18 **1. Introduction (background) 3**

19 **2. Scope..... 3**

20 **3. General principles..... 3**

21 **4. Legal basis 4**

22 **5. "Targeted" non-clinical evaluation of radiopharmaceuticals 4**

23 5.1. Basic considerations 4

24 5.2. Non-clinical safety programme for a known or minimally changed non-radioactive part of

25 a new radiopharmaceutical..... 6

26 5.2.1. Pharmacology 6

27 5.2.2. Pharmacokinetics..... 6

28 5.2.3. Toxicology 6

29 5.3. Non-clinical safety programme of a new radiopharmaceutical using microdose..... 7

30 5.3.1. Recommendations for Radiodiagnostics 7

31 5.3.2. Recommendations for Radiotherapeutics 8

32 5.4. Non-clinical safety programme of a new radiopharmaceutical using single sub-

33 pharmacological or pharmacologically active doses 8

34 5.4.1. Recommendations for Radiodiagnostics 8

35 5.4.2. Recommendations for Radiotherapeutics 9

36 5.5. Non-clinical safety programme for radiopharmaceuticals using multiple dosing 9

37 5.5.1. Pharmacology 9

38 5.5.2. Pharmacokinetics..... 9

39 5.5.3. Toxicology 9

40 5.5.4. Genotoxicity 10

41 5.5.5. Reproductive toxicity and Carcinogenicity 10

42 **6. GLP..... 10**

43 **7. Definitions 10**

44

45 **Executive summary**

46 This guideline describes the non-clinical data that need to be submitted in relation to the non-
47 radioactive part of radiopharmaceuticals, in the context of applications for marketing authorisations or
48 clinical trials.

49 **1. Introduction (background)**

50 The need for a guidance paper focusing specifically on the non-clinical testing requirements for
51 radiopharmaceuticals has emerged since currently there is no detailed guidance available. Therefore, in
52 addition to the general non-clinical requirements described in e.g. ICH M3(R2), ICH S9 and ICH S6(R1),
53 the principles for non-clinical data generation in support of the specific clinical uses of
54 radiopharmaceuticals are laid down in this guideline.

55 **2. Scope**

56 This guideline covers radiodiagnostics as well as radiotherapeutics, and provides guidance for a targeted
57 approach to assess pharmacology and safety of the non-radioactive part of a radiopharmaceutical. The
58 principles explained in this document address the non-clinical evaluation as prerequisite for a clinical
59 trial authorisation as well as for a marketing authorisation application. According to the categorisation of
60 the "Guideline on radiopharmaceuticals" (EMA/CHMP/QWP/306970/2007) "ready to use"
61 radiopharmaceuticals will be covered. However, some of the principles outlined in this guideline might
62 also apply to the non-radioactive component of so called "kits" and non-radioactive chemical precursors.
63 The toxicity induced by the radiation of the radionuclide (which for radiotherapeutics is the wanted
64 property) is not addressed in this guideline, since radiation induced clinical toxicity is covered by
65 Directives of EURATOM (Directive 2013/59/Euratom).

66 **3. General principles**

67 Scientific innovation and the ability to generate highly-targeted ligands led to the development of many
68 different types of radiopharmaceuticals which show a large variety of clinical uses. They may be used as
69 radiodiagnostics for scintigraphy imaging, for measurement of biodistribution or as radiotherapeutics
70 administered to humans only once or with a low frequency of repeated administrations at doses lacking
71 a measurable pharmacological effect. One common feature is that many of these radiopharmaceuticals
72 are prepared in small-scale quantities for the use in exploratory trials and will not undergo a full
73 development programme aiming to marketing authorisation. However, like for other medicinal products,
74 the same principles of safety evaluation should apply prior to the use of radiopharmaceuticals in humans
75 in clinical trials as well as for marketing authorisation purposes. Therefore, a non-clinical risk
76 assessment in line with the respective legislation is needed prior to the first in human (FIH)
77 administration of a radiopharmaceutical and subsequent clinical development. The risk assessment will
78 in general be covered in the non-clinical programme and will influence the risk mitigation plan included
79 in the clinical study protocol.

80 In the case of radiopharmaceuticals it has to be considered that they represent a special class of
81 pharmaceuticals due to their conjugated design and radiolabel. They are composed of a non-radioactive,
82 "cold", part with a radionuclide attached. The radionuclide may be linked to the non-radioactive ligand
83 by a linker and/or chelators also called "carrier". In the following, all possible forms of the non-
84 radioactive moiety will be named "non-radioactive part" throughout the paper.

85 General guidance, especially for the timing and duration of nonclinical safety studies, can be received
86 from ICH M3(R2) EMA/CPMP/ICH/286/1995. However, in many cases knowledge of the non-clinical
87 characteristics and a clinical experience already exists for the non-radioactive part. In common with any
88 other submission the presence of published or clinical data may obviate the need to conduct the
89 complete non-clinical programme in line with ICH M3(R2). This would also contribute to a reduction of
90 animal use in line with the principles of 3Rs. Factors that are important to consider are the level of
91 evidence on the pharmacological properties and toxicological characteristics of the non-radioactive part,
92 the anticipated mass dose of the radiopharmaceutical in the clinical trial or for marketing authorisation
93 and the duration of treatment.

94 The need for physiological distribution studies for the sole purpose of ensuring quality of the
95 investigational radiopharmaceutical should be avoided by any means. Instead, appropriate
96 characterisation of the relevant product parameters is expected by state-of-the art methods.

97 **4. Legal basis**

98 This guideline has to be read in conjunction with:

- 99 • Directives of the European Atomic Energy Community (EURATOM) (Directive 2013/59/Euratom).
- 100 • Directive 2001/83/EC, as amended in particular Directive 2001/83/EC Art 10(4) and Part II of the
101 Annex I of Directive 2001/83/EC, as amended.
- 102 • Directive 2010/63/EU on the protection of animals used for scientific purposes.
- 103 • Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions
104 relating to the application of the principles of good laboratory practice and the verification of their
105 applications for tests on chemical substances.
- 106 • CHMP/SWP/28367/07 (July 2017): "Guideline on strategies to identify and mitigate risks for first in
107 human and early clinical trials with investigational medicinal products".
- 108 • EMEA/CHMP/QWP/306970/2007: "Guideline on Radiopharmaceuticals".
- 109 • ICH S6(R1) (December 2011): "Preclinical safety evaluation of biotechnology-derived
110 pharmaceuticals".
- 111 • ICH S9 (Oct 29, 2009): "Nonclinical evaluation for anticancer pharmaceuticals".
- 112 • ICH M3(R2) (Dec. 2009): "Non-clinical safety studies for the conduct of human clinical trials and
113 marketing authorisation for pharmaceuticals".
- 114 • ICH S7A (June 2001): "Note for guidance on safety pharmacology studies for human
115 pharmaceuticals".

116 **5. "Targeted" non-clinical evaluation of radiopharmaceuticals**

117 **5.1. Basic considerations**

118 Toxicity of radiopharmaceuticals may be driven by the non-radioactive as well as the radioactive
119 components of the radiopharmaceutical. The radiation emitted by the radionuclide is a wanted property
120 of radiotherapeutics. In the case of radiodiagnostics, however, radionuclides with much lower emission
121 of radiation and with usually a very short physical half-life are used.

122 For characterisation of a new radiopharmaceutical, a biodistribution study in animals is usually
123 conducted with the radiolabelled compound allowing to measure tissue distribution and elimination. In
124 addition, calculation of dosimetry in order to predict the radioactive exposure in humans and to mitigate
125 radiation induced toxicity, is performed. However, as mentioned in the scope, recommendations for the
126 non-clinical development of the non-radioactive part are the focus of this guideline.

127 For different scenarios as outlined below, where evidence needs to be only partly generated, a targeted
128 (in the sense of a reduced) non-clinical programme for the non-radioactive part of the
129 radiopharmaceutical can be considered:

130 a) Radionuclide changed in a known radiopharmaceutical: only the radionuclide is changed and the
131 non-radioactive part was already used in numerous clinical trials or even authorised with other
132 radionuclides. In this case, evidence should be provided by the applicant on the availability and
133 results of the non-clinical testing already performed for the non-radioactive unchanged part of the
134 formerly used radiopharmaceutical(s). Reference in the dossier to previous applications with the
135 investigational radiopharmaceutical may be possible in cases the applicant is the same or has
136 obtained permission to use non-clinical data of other applications. The use of literature or other
137 publicly available data is possible but should be of good scientific quality and justified by the
138 applicant.

139 In these cases a flexible, but targeted approach is required to identify possible remaining gaps in
140 the safety information for the new investigational radiopharmaceutical especially with focus on
141 pharmacology.

142 b) Radionuclide added to a known non-radioactive pharmaceutical: information is needed that the
143 radiolabelling does not significantly alter the pharmacology of the whole molecule when the
144 radionuclide is replacing an existing non-radioactive atom.

145 c) Minimal change of the non-radioactive part of a radiopharmaceutical: this could be a small change in
146 the amino acid sequence of a peptide or another small change in the molecular structure of the non-
147 radioactive part of a known radiopharmaceutical, intended for example to improve stability. For this
148 new but structurally closely related entity, the applicant should bridge from existing non-clinical data
149 of the known radiopharmaceutical and address possible changes in its pharmacology and safety in
150 order to allow for a possible reduced non-clinical programme.

151 The microdose approach described in ICH M3(R2) is reflecting single as well as multiple administrations
152 up to five including a wash out period and implies a reduced non-clinical testing in which safety
153 assessment in a single (rodent) species can suffice.

154 Due to possible peculiarities as outlined above a reduced non-clinical testing could be anticipated for
155 additional scenarios. For example at dosages outside microdose toxicities related to the non-radioactive
156 part are usually still minor compared to radiation-induced toxicities of a radiotherapeutic in oncology
157 treatment. The amount of non-clinical data needed for the non-radioactive part is therefore dependent
158 on risk–benefit considerations and exposure levels to the non-radioactive part. Hence, also in these
159 cases a study in one species could be considered to be sufficient.

160 The aspects outlined above give rise to specific considerations regarding the extent and type of the non-
161 clinical data package to support clinical trial and marketing authorisation of radiopharmaceuticals.
162 Specific approaches will avoid the unnecessary use of animals, allowing an optimal use of resources and,
163 ultimately, facilitate the progression of these medicinal products into clinical use. In this regard, such a
164 targeted non-clinical programme represents an opportunity for limiting animal testing in accordance
165 with the 3Rs principles and is strongly encouraged.

166 However, the spectrum of possible combinations of molecules to construct a radiopharmaceutical in
167 addition to the possible therapeutic targets of radiopharmaceuticals is very broad. Therefore, a flexible
168 approach on a case by case basis might still be needed despite this guideline.

169 **5.2. Non-clinical safety programme for a known or minimally changed non-** 170 **radioactive part of a new radiopharmaceutical**

171 In case no reference is possible to previous applications or other public data using the identical non-
172 radioactive part of the investigational radiopharmaceutical, the reduced non-clinical programme outlined
173 below for a known or minimally changed non-radioactive part should be considered.

174 **5.2.1. Pharmacology**

175 The appropriate characterisation of pharmacology of the non-radioactive part alone is also expected in
176 the case where the non-radioactive part of an already known radiopharmaceutical is claimed to be
177 minimally changed. Emphasis should be laid on in vitro target/ receptor profiling. The selectivity and
178 specificity of the non-radioactive part as well as secondary pharmacodynamics, defined as effects on
179 other than the desired therapeutic targets, should be critically evaluated and documented. Measureable
180 pharmacodynamic effects are normally not expected to be seen from the non-radioactive part of most
181 radiopharmaceuticals for diagnostic or therapeutic purposes. However, evidence for the absence of
182 pharmacodynamic effects is expected, and should be supported by appropriate data.

183 If no data are provided, the applicant has to justify the absence of in vitro/in vivo pharmacology data
184 even in the case of a minimal change to the molecule.

185 **5.2.2. Pharmacokinetics**

186 For such minimally changed radiopharmaceuticals information on in vivo stability should be available. In
187 addition, the biodistribution study performed in healthy animals of a relevant species including
188 dosimetry should be thoroughly evaluated to detect any change in biodistribution and target organs
189 related to the non-radioactive part compared to the former, known molecule. For radiotherapeutics, the
190 study may be performed in an animal model of disease, if appropriate, to support that the targeted area
191 / organ will still be reached adequately.

192 **5.2.3. Toxicology**

193 Main focus should be laid on the evaluation of the target organs of biodistribution and possible
194 persistence of the modified non-radioactive part possibly leading to so far unknown toxic effects even if
195 the change is claimed to be minimal. A biodistribution study in one species with single application and
196 integrated measurement of toxicity endpoints can be generally considered sufficient. If off target binding
197 is likely to be minimal from the results of the dosimetry study, histopathological examination may be
198 limited to target organs.

199 In the case of an exploratory trial with intended clinical dose of the radiopharmaceutical being a
200 microdose according to approach 1 or approach 2 as outlined in ICH M3(R2) (see also 5.3) and if, in
201 addition, the absence of pharmacological activity of the non-radioactive part could be demonstrated,
202 such a biodistribution study could be waived.

203 **5.3. Non-clinical safety programme of a new radiopharmaceutical using**
204 **microdose**

205 The majority of clinical trials performed with radiopharmaceuticals falls under the scope of exploratory
206 trials. Therefore, the microdose approach as outlined in ICH M3(R2) can be applied. According to the
207 definition given there, a microdose is a total dose $\leq 100 \mu\text{g}$ (no inter-dose interval limitations) and total
208 dose $\leq 1/100^{\text{th}}$ NOAEL and $\leq 1/100^{\text{th}}$ pharmacologically active dose (approach 1), or a total cumulative
209 dose $\leq 500 \mu\text{g}$, maximum of 5 administrations with a washout between doses (6 or more actual or
210 predicted half-lives) and each dose $\leq 100 \mu\text{g}$ and each dose $\leq 1/100^{\text{th}}$ of the NOAEL and $\leq 1/100^{\text{th}}$ of
211 the pharmacologically active dose (approach 2). Due to differences in molecular weights between
212 biologicals and chemicals, and due to the fact that pharmacological and toxicological effects are usually
213 driven by the molar amount and not by the mass, a maximum dose above $100 \mu\text{g}$ based on molar
214 amount can be accepted for high molecular weight molecules taking into account the potency of the
215 molecule (approach 1 for biologicals). Approach 2 may be less relevant for biologicals with a long
216 elimination half-life.

217 Accordingly, the minimal requirements for the non-clinical development of a radiopharmaceutical
218 carrying a new non-radioactive part using the microdose approach are outlined below. This non-clinical
219 package is usually also considered sufficient for marketing authorisation applications using the same
220 dosing regimen.

221 **5.3.1. Recommendations for Radiodiagnostics**

222 In most cases microdose approach 1 of ICH M3(R2) will be used for radiodiagnostics since no
223 pharmacological effect is intended and only a very small mass dose is administered after single
224 administration.

225 **5.3.1.1. Pharmacology**

226 Radiodiagnostics are not intended to exert pharmacological activity, but evidence for the absence of
227 pharmacological activity of the non-radioactive part should be provided. In this context, in vitro target/
228 receptor profiling is usually sufficient.

229 **5.3.1.2. Pharmacokinetics**

230 A biodistribution study including dosimetry should be performed with a single dose of the
231 radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow
232 estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for
233 distribution and persistence of the radiodiagnostic. If relevant, information should be provided on
234 absorption and biotransformation.

235 **5.3.1.3. Toxicology**

236 According to microdose approach 1 outlined in ICH M3(R2), the results of an extended single dose
237 toxicity study using the intended route of administration (usually i.v. route for radiodiagnostics), with
238 toxicokinetic data should be available for the non-radioactive part.

239 When using the microdose approach 2, a repeat dose study for at least 7 days would be expected. A
240 study of shorter duration may be considered on a case by case basis.

241 For both approaches a study in one species, usually rodent, can be generally considered sufficient.

242 In the extended single dose, as well as in repeat dose studies, haematology, clinical chemistry, necropsy
243 data and histopathology will be fully evaluated.

244 Investigation of local tolerance, where applicable, should be done as an integral part of the extended
245 single dose study.

246 **5.3.1.4. Genotoxicity**

247 Genotoxicity studies are not recommended. However, if e.g. data on structure-activity relationship
248 (SAR) assessment are available they should be submitted.

249 **5.3.2. Recommendations for Radiotherapeutics**

250 The same testing strategy as outlined above for radiodiagnostics will also apply for new
251 radiotherapeutics when using the microdose approach. The only additional aspect to consider in these
252 cases is that the dosimetry study might be performed in an animal model of disease, if appropriate, to
253 support that the targeted area will be reached adequately.

254 **5.4. Non-clinical safety programme of a new radiopharmaceutical using 255 single sub-pharmacological or pharmacologically active doses**

256 The minimal requirements for the non-clinical development of a radiopharmaceutical carrying a new
257 non-radioactive part using single sub-pharmacological (but above microdose) or pharmacologically
258 active doses are outlined below. This non-clinical package is usually also considered sufficient for
259 marketing authorisation applications using the same dosing regimen.

260 **5.4.1. Recommendations for Radiodiagnostics**

261 **5.4.1.1. Pharmacology**

262 Radiodiagnostics may exert pharmacological activity at doses above a microdose. The pharmacological
263 activity of the non-radioactive part or its absence has to be shown by the applicant. In this context, in
264 vitro target/ receptor profiling is usually sufficient.

265 **5.4.1.2. Pharmacokinetics**

266 A biodistribution study including dosimetry should be performed with a single dose of the
267 radiodiagnostic. Information on in vivo stability, distribution and elimination should be available to allow
268 estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for
269 distribution and persistence of the radiodiagnostic. If relevant, information should be provided on
270 absorption and biotransformation.

271 **5.4.1.3. Toxicology**

272 Generally, extended single dose toxicity studies in both a rodent and non-rodent should be available
273 using the intended clinical route of administration with toxicokinetics, haematology, clinical chemistry,
274 necropsy data and histopathology as evaluated endpoints.

275 If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity at the
276 intended clinical dose only one relevant species, usually rodent, is sufficient.

277 Investigation of local tolerance, where applicable, should be done as integral part of the extended single
278 dose study.

279 In addition, the standard core battery for safety pharmacology may be included as integral part of the
280 extended single dose toxicity study.

281 **5.4.1.4. Genotoxicity**

282 For the genotoxicity testing of the non-radioactive part of the radiodiagnostic, if not a biotechnology
283 derived product, e.g. an Ames test, would be expected.

284 **5.4.2. Recommendations for Radiotherapeutics**

285 The same testing strategy as outlined above for radiodiagnostics will apply for new radiotherapeutics in
286 the case using single sub-pharmacological or pharmacologically active doses are used. The only
287 additional aspect to consider in these cases is that the dosimetry study might be performed in an animal
288 model of disease, if appropriate, to support that the targeted area will be reached adequately.

289 **5.5. Non-clinical safety programme for radiopharmaceuticals using multiple** 290 **dosing**

291 In absence of complete clearance between administration of multiple doses in the therapeutic range
292 standard ICH M3(R2) requirements should be followed for the non-radioactive part. There are no
293 general differences in this respect between the expected non-clinical data package for radiodiagnostics
294 and radiotherapeutics. In the case of a radiotherapeutic used in oncology, ICH S9 should be considered
295 if applicable.

296 **5.5.1. Pharmacology**

297 Pharmacological activity of the non-radioactive part or its absence has to be shown by the applicant. In
298 this context, in vitro target/ receptor profiling is usually sufficient.

299 **5.5.2. Pharmacokinetics**

300 A biodistribution study including dosimetry after administration of the whole radiodiagnostic should be
301 performed. Information on in vivo stability, distribution and elimination should be available to allow
302 estimation of tissue and whole-body radiation doses in the clinic and to identify target organs for
303 distribution and persistence of the radiodiagnostic.

304 **5.5.3. Toxicology**

305 In the case of complete washout between dosing an extended single dose toxicity study in both a rodent
306 and non-rodent should be available using the intended clinical route of administration with
307 toxicokinetics, haematology, clinical chemistry, necropsy data and histopathology as evaluated
308 endpoints. If the non-radioactive part of the radiopharmaceutical does not show pharmacological activity
309 at the intended clinical dose only one relevant species, usually rodent, is sufficient.

310 Investigation of local tolerance, where applicable, should be done as an integral part of the extended
311 single dose study.

312 In addition, the standard core battery for safety pharmacology may be included as integral part of the
313 extended single dose toxicity study.

314 **5.5.4. Genotoxicity**

315 For the genotoxicity testing of the non-radioactive part of the radiotherapeutic, if not a biotechnology
316 derived product, e.g. an Ames test would be expected. In the case of a radiotherapeutic used in
317 oncology, an Ames assay may not be required for advanced cancers where ICH S9 is applicable.

318 **5.5.5. Reproductive toxicity and Carcinogenicity**

319 For radiopharmaceuticals carrying a radionuclide with a high emission of radiation and a long half-life
320 such as anticancer drugs, carcinogenicity and reproductive toxicity studies could be waived since the
321 radiation emission of these medicinal products is causing well known DNA damage with consequences
322 for carcinogenicity and reproductive toxicity. However, the respective risk should be outlined in the
323 product labelling.

324 Reproductive toxicity and a carcinogenicity studies for the non-radioactive part alone are usually not
325 required unless there is concern due to the duration of the treatment while the radiation emission of the
326 attached radionuclide is low.

327 **6. GLP**

328 It is generally expected that non-clinical safety studies are carried out in conformity with the principles
329 of GLP (Dir 2004/10/EC), but also principles of animal welfare should be applied. However, it is
330 recognized that, due to the specific characteristics of radiopharmaceuticals, it might not be possible to
331 conduct every study in conformity with GLP, in particular when the radiation emission is high.
332 Frequently, such non-GLP results come from biodistribution and dosimetry studies. Therefore, in
333 practice the relevant safety aspects are usually sufficiently addressed by conducting the non-clinical
334 studies with the non-radioactive part of the radiopharmaceutical according to GLP.

335 If a pivotal non-clinical safety study has not been conducted in conformity with the GLP principles, a
336 scientific justification should be submitted. This justification should also address the potential impact of
337 the non-compliance on the reliability of the safety data. In any case the study should run according to
338 the principles of GLP as close as possible. Detailed documentation of the study conduct, results and
339 archiving of data should be ensured. In addition, the study should be performed in accordance with a
340 prospectively designed study protocol.

341 **7. Definitions**

342 DNA - Deoxyribonucleic Acid

343 EURATOM - European atomic energy community

344 FIH – First in human

345 GLP – Good laboratory practice

346 NOAEL – No observed adverse effect level