
Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Haleh Saber or John Leighton at 301-796-7550.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2018
Pharmacology/Toxicology**

Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry

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1 **Oncology Therapeutic Radiopharmaceuticals:**
2 **Nonclinical Studies and Labeling Recommendations**
3 **Guidance for Industry¹**
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8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

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16
17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to provide information to assist sponsors in the design of an
20 appropriate nonclinical program for the development of radiopharmaceuticals to treat cancer —
21 also known as oncology therapeutic radiopharmaceuticals — and to provide recommendations
22 for certain aspects of product labeling. For the purpose of this guidance, a therapeutic
23 radiopharmaceutical is a product that contains a radionuclide and is used in patients with cancer
24 for treatment of the disease or for palliation of tumor-related symptoms (e.g., pain).
25 Recommendations in this guidance are applicable to products that are administered systemically
26 and undergo alpha, beta, and/or gamma decay.
27

28 This guidance is specific to therapeutic radiopharmaceuticals for oncology indications and
29 covers topics that are not addressed in current FDA or International Council for Harmonisation
30 (ICH) guidance, such as nonclinical studies in support of first-in-human (FIH) trials and approval
31 for oncology therapeutic radiopharmaceuticals. This complementary guidance provides
32 additional information that supplements the guidance for industry *Nonclinical Evaluation of Late*
33 *Radiation Toxicity of Therapeutic Radiopharmaceuticals* for the design of late radiation toxicity
34 studies.²
35

¹ This guidance has been prepared by the Division of Hematology, Oncology, Toxicology in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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36 The recommendations in this guidance generally apply to new products with no previous clinical
37 experience. Often, there is clinical experience with the **ligand** (e.g., an antibody previously
38 evaluated for its safety and efficacy in the treatment of cancer).³ When there is experience with
39 the radionuclide or the ligand components of the radiopharmaceutical being developed, the
40 nonclinical program can be abbreviated as needed, and the FIH dose can be based on clinical
41 data, as appropriate.

42

43 This guidance discusses the following concepts:

44

- 45 • Evaluation of toxicities from the ligand
- 46 • Evaluation of radiation toxicities
- 47 • Information for product labeling as related to reproductive toxicity, genotoxicity,
48 carcinogenicity, contraception, and use in lactating women

49

50 This guidance is not applicable to oncology therapeutic radiopharmaceuticals with a local route
51 of administration, such as intratumoral, intrathecal, or inhalation route of administration, because
52 the nonclinical study designs and the approach to FIH dose selection discussed in this guidance
53 may not apply. In addition, this guidance is not applicable to external beam radiation therapy,
54 radiolabeled vaccine products, diagnostic radiopharmaceuticals, or radioactive drugs for research
55 use as described in 21 CFR 361.1.

56

57 Topics related to the product quality, such as impurity level and specification, product stability,
58 or labeling kit (used to produce a radiopharmaceutical before human use) are not discussed in
59 this guidance. However, the entire radioactive decay cascade, also known as daughter decays,
60 should be considered in the biodistribution and **dosimetry** studies for estimation of radiation
61 activities in organs and absorbed radiation doses.

62

63 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
64 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
65 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
66 the word *should* in Agency guidances means that something is suggested or recommended, but
67 not required.

68

69

70 **II. BACKGROUND**

71

72 Radiation therapy may be delivered through an external source or by systemic administration of
73 a radioactive compound. Oncology therapeutic radiopharmaceuticals are generally administered
74 intravenously, and are intended to deliver cytotoxic levels of radiation selectively to tumor sites.
75 Targeted delivery is generally achieved by the use of a targeting moiety, such as a peptide or an
76 antibody. Some radionuclides (known as organ seekers) are naturally directed to a particular
77 organ, reaching a desired organ without a ligand. Examples include radium, which is a bone
78 seeker, and iodine, which is a thyroid seeker.

79

³ Words bolded at first use are described in the Glossary.

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80 FDA supports the principles of the 3Rs, to reduce, refine, and replace animal use in testing when
81 feasible. Sponsors can consult with FDA if they wish to use a nonanimal testing method they
82 believe is suitable, adequate, validated, and feasible. FDA will consider if such an alternative
83 method could be assessed for equivalency to an animal test method.

84
85

86 **III. PHARMACOLOGY**

87
88

A. Primary Pharmacology

89
90

91 Sponsors should conduct proof-of-concept studies before initiation of a FIH study to show
92 uptake by the tumor and antitumor activity. Preliminary characterization of the mechanism of
93 action can be through in vitro (such as target binding and antitumor activity) and animal studies
94 and should include appropriate endpoints. These studies may inform species selection for
95 biodistribution and toxicology studies.

96
97

B. Safety Pharmacology

98
99

100 Stand-alone studies to assess the pharmaceutical's effect on vital organ functions
101 (cardiovascular, respiratory, and central nervous systems) generally are not warranted to initiate
102 a study in patients with cancer or for approval. These safety endpoints can be incorporated into
103 the design of toxicology and/or animal biodistribution studies. Detailed clinical observations
104 following dosing in rodents and nonrodents, and appropriate electrocardiographic measurements
105 in nonrodents, are generally considered sufficient safety assessments. In addition, the results of a
106 biodistribution study can provide further evidence of the potential for adverse effects on these
107 organ systems. For instance, distribution of radioactivity into the central nervous system (CNS)
108 can indicate the potential for anatomic and functional neurological deficits resulting from
109 radiation-induced vascular abnormalities, demyelination, and necrosis in the CNS (Greene-
110 Schloesser et al. 2012).

111
112

113 **IV. ANIMAL BIODISTRIBUTION AND DOSIMETRY**

114
115

116 Sponsors should conduct a single-dose biodistribution and dosimetry study in animals to guide in
117 dose selection for the human biodistribution and dosimetry study (typically a single dose of the
118 radiopharmaceutical or its theranostic pair in patients). A single animal species, that is
119 scientifically justified, is usually sufficient. All relevant information should be considered for
120 selection of the animal species, including pharmacology data and tissue cross reactivity for
121 biological products, as applicable, to compare distribution in animal and human tissues.

122
123

124 Radioactivity in organs over time should be evaluated postadministration, using sufficient
125 duration of sampling (e.g., 5 x **effective half-lives**) to generate the **time-integrated activity**
126 curves, also referred to as **cumulated activity** (Siegel et al. 1999). The sampling interval should
127 be scientifically justified. Sponsors should consider daughter decays and their half-lives when
128 designing the animal biodistribution study. Duration of data collection can be adjusted as needed
129 (e.g., when a long effective half-life could result in a substantial increase in the number of

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126 animals and potential delays in drug development, or a multi-exponential time-integrated activity
127 curve may necessitate many sampling time points). In such cases, alternative approaches and
128 modeling can be considered to integrate the terminal portion of the activity time curve. If
129 alternative approaches and modeling are used, they should be described in the investigational
130 new drug application (IND).

131
132 The design of an animal biodistribution study should incorporate aspects of the planned clinical
133 biodistribution and dosimetry study that might affect distribution of the product. For instance, if
134 the planned clinical study includes patients being pretreated with thyroid-protecting agents to
135 reduce radioiodine uptake by the thyroid, then this same design should be considered in the
136 animal biodistribution study. Additionally, because the amount of radioactive and
137 nonradioactive materials in the dosing mixture can affect the biodistribution, the ratio used in
138 animal studies should be comparable to that proposed in patients or be justified.

139
140 Organs assessed for distribution of time-integrated activity generally include the adrenals, bone
141 and bone marrow, brain, small and large intestine walls, stomach, heart, kidneys, liver, lungs,
142 muscles, ovaries, pancreas, spleen, testes, thymus, thyroid, urinary bladder, uterus, and total
143 body. Additional organs can be included as appropriate based on the potential distribution
144 specific to the particular radiopharmaceutical (e.g., eyes and skin for melanin-binding
145 compounds). Excretion data in urine and feces should be collected. The number of organs
146 assessed can be abbreviated if adequately justified (e.g., when the product is a radiolabeled
147 antibody and tissue cross-reactivity indicates binding to a limited number of organs). The
148 abbreviated organ list should include bone marrow and organs of excretion such as kidneys and
149 liver because these organs are generally affected, regardless of target binding.

150
151 Both male and female animals should be included in the study for uptake of radioactivity by
152 male- and female-specific organs, unless the indication is sex-specific. Dosimetry in large
153 animals (e.g., monkeys) is usually done with imaging techniques, and hence, a small number of
154 animals (e.g., three males and three females) may be sufficient to assess activity levels and
155 distribution over time. For small animals such as mice and rats, there should be a sufficient
156 number of animals per time point when a method requiring animal sacrifice is used (e.g.,
157 autoradiography).

158
159 The activity time curve in organs of animals should be used to estimate the percent administered
160 activity (%ID), residence time, and time-integrated activity in human organs. See the Glossary
161 for examples of methods used for animal-to-human extrapolations; other methods can be used
162 and should be described in the IND. The estimated human values should be used to generate the
163 radiation **absorbed doses** in human organs, through mathematical calculations or by using
164 appropriate software programs. Dosimetry methodology and associated software, including
165 version identification, should be described in the IND.

166
167

168 **V. TOXICOLOGY**

169

170 **A. General Toxicology**

171

172 *1. Toxicology Studies to Support the FIH Therapeutic Phase*

173

174 Sponsors should evaluate both radiation- and ligand-related toxicities. Such evaluations can be
175 through toxicology studies or biodistribution studies, as appropriate. Generally no toxicity
176 studies are warranted before a FIH study when the radiopharmaceutical is a **neat radionuclide**
177 (i.e., contains no ligand). Toxicities of the radiopharmaceutical are from the radionuclide decay,
178 and thus, the results of the animal biodistribution and dosimetry study with added safety
179 endpoints can be used to determine short-term radiation-related toxicities. Below are
180 recommendations for radiation- and ligand-related safety assessment.

181

182 • **Evaluation of radiation-induced toxicity:** A general toxicology study with the
183 radiopharmaceutical usually is not warranted. The animal biodistribution and dosimetry
184 studies, together with the general knowledge of organ-specific radiation-induced
185 toxicities, are usually sufficient to address toxicities from the radiation. Published
186 articles on organ-specific radiation-induced toxicities should be included in the
187 submission. Sponsors should consider the addition of safety endpoints, such as clinical
188 signs, body weight (BW), hematology, and serum chemistry, into the design of the
189 biodistribution study.

190

191 • **Evaluation of ligand-induced toxicity:** To identify any ligand-related toxicities,
192 sponsors should conduct a general toxicology study with the **cold pharmaceutical** in a
193 relevant species before initiation of a FIH study. Ligand-related toxicities have been
194 observed but are usually minor compared with radiation-induced toxicities, and hence, a
195 study in one species is generally considered sufficient. Unless otherwise justified, the
196 species selected for toxicology study should be the same as the species used for animal
197 biodistribution and dosimetry study. Frequency of administration in the toxicology study
198 should follow recommendations in the ICH guidance for industry *S9 Nonclinical*
199 *Evaluation for Anticancer Pharmaceuticals* and should take into account the frequency of
200 administration in the FIH trial (both the human biodistribution and dosimetry and the
201 therapeutic phase that follows it).

202

203 *2. Long-Term Toxicity Assessments to Support Marketing*

204

205 In general, the nonclinical data and the clinical phase 1 data should be sufficient for moving to
206 phase 2. Sponsors should conduct long-term toxicity assessment studies to support marketing,
207 and the results should be submitted with the marketing application. These studies should assess
208 both ligand- and radiation-related toxicities. The dosing period in animals can follow ICH S9.
209 For most pharmaceuticals intended for the treatment of patients with advanced cancer,
210 nonclinical studies of 3 months' duration are considered sufficient to support marketing. Below
211 are recommendations for study design and circumstances when studies may not be needed.

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213 • **Evaluation of ligand-induced toxicity:** Chronic toxicity studies of the cold
214 pharmaceutical may not be needed in several circumstances: when a limited number of
215 doses are administered to patients (e.g., two or three doses), when the ligand is for
216 delivery purposes only and administration will result in a small dose (e.g., in microgram
217 ranges), or when the cold pharmaceutical has a short half-life and dosing frequency is
218 low (e.g., every 4 to 8 weeks). When a chronic study is needed, a study in a single
219 species is generally considered sufficient. This study can be combined with the late
220 radiation toxicity study.

221
222 • **Evaluation of late radiation toxicity:** An assessment of late radiation toxicities is
223 warranted when patients have a long life expectancy that could be affected by late
224 radiation adverse effects. For recommendations on animal study design and endpoints,
225 see the guidance for industry *Nonclinical Evaluation of Late Radiation Toxicity of*
226 *Therapeutic Radiopharmaceuticals*. Identification of a no observed adverse effect level
227 is not needed. The study in a single species is generally considered sufficient. When a
228 limited number of organs is examined by histopathology, the organs selected should be
229 justified. Any organs with gross pathology finding should be examined microscopically.

230 231 **B. Genotoxicity, Reproductive Toxicology, and Carcinogenicity Studies**

232
233 No genetic or reproductive toxicity or carcinogenicity study with the radiopharmaceutical or the
234 cold pharmaceutical is warranted during drug development or for approval. Alpha, beta, and
235 gamma radiation cause deoxyribonucleic acid damage and are inherently genotoxic and
236 carcinogenic, and damage male and female germ cells and a developing conceptus. These risks
237 should be communicated in product labeling (see section VII., Labeling Recommendations).

238 239 240 **VI. FIH DOSE SELECTION**

241
242 FIH dose estimation should be based on two factors: the radioactive **administered dose** (i.e.,
243 administered activity) of the radiopharmaceutical and the **mass dose** of the pharmaceutical.
244 Sponsors should consider the following recommendations.

245 246 **A. Radiation Administered Dose**

247
248 Selection of the activity to be administered (Becquerel (Bq) or curie (Ci) per BW or body surface
249 area) for patient dosimetry should be based on the animal biodistribution and dosimetry data, the
250 estimated absorbed radiation doses in human organs, and tolerance of normal human organs to
251 radiation. As described in the Glossary and section IV., Animal Biodistribution and Dosimetry,
252 activity over time in each **source organ** is extrapolated from animals to humans to obtain the
253 estimated absorbed doses in human organs. The radiation dose administered in patients should
254 be adjusted based on tolerated absorbed radiation doses in human organs (e.g., using threshold
255 from external radiation therapy as a starting point), not to exceed prespecified limits. The
256 cumulative radiation administered dose is generally used to determine the FIH dose when dose
257 fractionation is proposed, unless data are provided to show that for the organ of interest, dose
258 fractionation results in higher tolerance.

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259
260 As described in the guidance for industry *Nonclinical Evaluation of Late Radiation Toxicity of*
261 *Therapeutic Radiopharmaceuticals*, organ tolerance doses for systemically administered
262 radiopharmaceuticals can differ from the tolerance doses for external radiation beam. However,
263 because there currently are no accepted criteria for determination of organ tolerance for internal
264 radiation from radiopharmaceuticals, sponsors should use published literature on external
265 radiation therapy as a starting point for radiopharmaceuticals (e.g., American Society for
266 Radiation Oncology 2010; Emami et al. 1991; Emami 2013; Stewart et al. 2012). Further
267 adjustment to a radiation administered dose can be made based on data.

268
269 Because the normal organ tolerance described in the published articles is for external beam (X-
270 ray and gamma radiation), caution should be exercised in extrapolating the data to acceptable
271 organ doses for alpha decay. For estimating the **equivalent dose** of alpha-emitting therapeutic
272 radiopharmaceuticals, the absorbed dose with an appropriate value (e.g., 5; Sgouros 2015) of
273 relative biological effectiveness (RBE) can be used. An RBE of 5 means that there is a five-fold
274 higher toxicity associated with alpha irradiation than there would be for X-ray or gamma
275 irradiation delivering the same absorbed dose (gray (Gy)). An RBE of 5 is recommended when
276 using organ tolerance data generated with external beam radiation. Results of dosimetry in
277 patients can then guide in selection of a reasonably safe therapeutic radiation administered dose.

278
279 **B. Mass Dose**

280
281 The total dose of the cold pharmaceutical should be considered for the FIH dose selection unless
282 the dose of the cold pharmaceutical is low (e.g., microgram doses). Results from general
283 toxicology studies or other nonclinical studies conducted with the cold pharmaceutical can be
284 used to define the appropriate FIH mass dose, according to principles described in ICH S9 and
285 the ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived*
286 *Pharmaceuticals*.

287
288
289 **VII. LABELING RECOMMENDATIONS**

290
291 **A. Genotoxicity, Reproductive Toxicology, and Carcinogenicity**

292
293 Product labeling must describe the potential for adverse reproductive toxicity, genotoxicity, and
294 carcinogenicity.⁴ Nonclinical studies specifically designed to evaluate these effects are not
295 warranted for radiopharmaceuticals (see section V.B., Genotoxicity, Reproductive Toxicology,
296 and Carcinogenicity Studies). However, any available animal data or anticipated effects that
297 suggest carcinogenicity, genotoxicity, or impairment of fertility should be discussed in the
298 *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection,⁵ while animal data or

⁴ See 21 CFR 201.57.

⁵ See 21 CFR 201.57(c)(14)(i).

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299 anticipated effects that suggest adverse developmental effects should be discussed in the
300 *Pregnancy* subsection.⁶

301
302 Radiopharmaceuticals are genotoxic (see section V.B., Genotoxicity, Reproductive Toxicology,
303 and Carcinogenicity Studies), many of which have effective half-lives of a week or longer. The
304 information on contraception use before, during, and after treatment should be communicated in
305 the *Females and Males of Reproductive Potential* subsection.⁷

- 306
- 307 • Female patients should be advised to use contraception during treatment and then for at
308 least a period of time that equals five effective half-lives and an additional 6 months after
309 the last dose of the radiopharmaceutical. The half-life of daughter decays also should be
310 considered. The five effective half-lives allow elimination of approximately 97 percent
311 of the radioactivity and the additional 6 months is to ensure that damaged follicles and
312 oocytes are released before fertilization.
 - 313
 - 314 • Male patients with female partners of reproductive potential should be advised to use
315 contraception during treatment and then for at least a period of time that equals five
316 effective half-lives and an additional 3 months after the last dose of the
317 radiopharmaceutical. The half-life of daughter decays also should be considered. The
318 five effective half-lives allow elimination of approximately 97 percent of the
319 radioactivity and the additional 3 months takes into account the duration of
320 spermatogenesis and the residence time of unejaculated sperm.

B. Lactation

321
322
323
324 When applicable, methods to minimize drug exposure to the breastfed child should be included
325 in the *Lactation* subsection.⁸ Because of high sensitivity of infants to radiation and risk of
326 toxicities, the following concepts are provided to calculate a period when breastfeeding is not
327 recommended to avoid or minimize exposure to radiopharmaceuticals in a nursing child.

328
329 Lactating women should be advised not to breastfeed during treatment with an oncology
330 therapeutic radiopharmaceutical and if applicable for a specific period of time after the last dose.
331 If a decision is made to pump and discard breast milk, a period during which a woman should
332 not breastfeed should be long enough to limit the radiation effective dose to the nursing child to
333 no more than one millisievert (1 mSv; Nuclear Regulatory Commission 2008). An actual
334 duration for advising against breastfeeding post-treatment should be proposed and should be
335 supported by estimation of radioactivity present in the breast milk at the end of this period and an

⁶ See 21 CFR 201.57(c)(9)(i) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*. When final, this guidance will represent the FDA's current thinking on this topic.

⁷ See 21 CFR 201.57(c)(9)(iii) and the draft guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*. When final, this guidance will represent the FDA's current thinking on this topic.

⁸ See 21 CFR 201.57(c)(9)(ii) and the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*.

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336 assumption of complete absorption by the nursing child. Any residual milk should be discarded
337 before nursing resumes.
338

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GLOSSARY

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Activity: Activity of a given amount of radioactive material is the number of transitions or decays per unit of time. The SI unit of activity is Bq, which is one transition per second. The legacy unit of activity is denoted Ci.

$$1 \text{ MBq} = 27 \text{ } \mu\text{Ci}; 1 \text{ mCi} = 37 \text{ MBq}$$

Cold pharmaceutical: The nonradioactive or decayed form of the product. For the purpose of this guidance, this terminology is used when the product contains a ligand.

Dose

Mass Dose: The dose (mass unit) of the cold pharmaceutical administered per BW or per body surface area.

Radiation Dose

Administered dose: The amount of radioactivity administered to animals or to patients and expressed as the unit of activity (e.g., in units of MBq or mCi).

Absorbed dose (D): The ionizing-radiation energy deposited per unit mass of an organ or tissue. The SI unit of absorbed dose is Gy, where 1 Gy = 1 J/kg (International Commission on Radiation Units and Measurements (ICRU) 2011). The legacy unit of absorbed dose is denoted rad.

$$1 \text{ Gy} = 100 \text{ rad}; 1 \text{ cGy} = 1 \text{ rad}$$

Equivalent dose (H): A measure of biological effect of the radioactive dose that takes into account both the absorbed dose and biological effectiveness of the radiation, and hence, the radiation type. The SI unit is Sievert (Sv) and the legacy unit is rem.

$$1 \text{ Sv} = 100 \text{ rem}$$

The equivalent dose is dependent on the RBE. RBE can be defined as the ratio of biological effectiveness of one type of ionizing radiation to another radiation of interest (e.g., gamma rays or beta particles to alpha particles). The RBE of alpha particles is higher compared to beta particles and gamma and X-rays. For oncology pharmaceuticals, an RBE of 5 can be assigned to alpha particles, signifying that there is a five-fold higher toxicity associated with alpha irradiation than there would be for beta particles, gamma, or X-rays delivering the same absorbed dose (Gy). RBE has no unit.

$$H \text{ (Sv)} = \text{RBE} \cdot D \text{ (Gy)}$$

Dosimetry: For the purpose of this guidance, refers to measuring and characterizing the effects of radiation in organs — including activity and/or absorbed radiation dose in an organ and its biological effects — after administration of a radiopharmaceutical.

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385 **Half-life**

386 *Biological half-life:* Half-life of the cold pharmaceutical in the living system.

387
388 *Physical half-life:* Half-life of the radionuclide itself, not affected by surrounding conditions,
389 independent of the living system.

390
391 *Effective half-life:* Half-life of radionuclide in a living system and affected by the conditions
392 (e.g., as a function of elimination due to the elimination of the ligand that carries it).

393
394 The effective half-life can be calculated mathematically (see below) or obtained
395 experimentally. T_p is the **physical half-life**, T_b is the **biological half-life**, and T_e is the
396 effective half-life.

397
398
$$1/T_p + 1/T_b = 1/T_e$$

399
400 **Ligand:** For the purpose of this guidance, refers to any moiety used to chelate the radionuclide
401 or to deliver/target the radionuclide to an organ or tissue.

402
403 **Neat radionuclide:** For the purpose of this guidance, refers to a radionuclide administered
404 without any ligand.

405
406 **Organ**

407 *Source organ:* The organ that takes up the radiopharmaceutical and hence contains
408 significant levels of radioactivity.

409
410 *Target organ:* The organ in which energy is deposited from the source organ; for example,
411 an organ adjacent to the source organ. All source organs are also target organs.

412
413 **Parameters from animal biodistribution and dosimetry and extrapolation to human**

414 *Cumulated activity or time-integrated activity (\tilde{A}):* The activity as a function of time in each
415 organ ($\mu\text{Ci-h}$ or MBq-s). Activity time curves can be obtained by measurements of activity
416 over time and it is a function of the initial activity A_0 (Ci or Bq unit) and the residence time τ
417 (hour).

418
419
$$\tilde{A} = A_0 \cdot \tau$$

420
421 *Estimation of human values of activity and residence time in source organs*
422 Values in humans can be based on data obtained from animals. One method for
423 extrapolating animal data to humans is using animal and human organ/BW ratios, based on
424 Kirshner et al. 1975, as shown below.

425
426
$$\tau(\text{human}) = \tau(\text{animal}) \cdot \frac{\text{Organ weight (human)}}{\text{Organ weight (animal)}} \frac{\text{BW (animal)}}{\text{BW (human)}}$$

427
428
429
$$\%ID(\text{human}) = \%ID(\text{animal}) \cdot \frac{\text{Organ weight (human)}}{\text{Organ weight (animal)}} \frac{\text{BW (animal)}}{\text{BW (human)}}$$

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Or:

$$\frac{\%ID (human)}{g \text{ of organ (human)}} \cdot kg \text{ of BW (human)} = \frac{\%ID (animal)}{g \text{ of organ (animal)}} \cdot kg \text{ of BW (animal)}$$

%ID (human): the fraction of the total administered activity in human organ.

%ID (animal): the fraction of the total administered activity in animal organ.

The values extrapolated from animals to humans can then be used to estimate the radiation absorbed dose in **target organs** of humans and to support a human dosimetry.

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