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# **Guidance for Industry**

## **Developing Medical Imaging Drug and Biological Products**

### **Part 1: Conducting Safety Assessments**

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

**June 2004  
Clinical Medical**

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### Part 1: Conducting Safety Assessments

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3 **Guidance for Industry<sup>1</sup>**  
4 **Developing Medical Imaging Drug and Biological Products**  
5 **Part 1: Conducting Safety Assessments**  
6  
7

8  
9 This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It  
10 does not create or confer any rights for or on any person and does not operate to bind FDA or the public.  
11 You can use an alternative approach if the approach satisfies the requirements of the applicable statutes  
12 and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for  
13 implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate  
14 number listed on the title page of this guidance.  
15

16  
17  
18  
19 **I. INTRODUCTION**  
20

21 This guidance is one of three guidances intended to assist developers of medical imaging drug  
22 and biological products (*medical imaging agents*) in planning and coordinating their clinical  
23 investigations and preparing and submitting investigational new drug applications (INDs), new  
24 drug applications (NDAs), biologics license applications (BLAs), abbreviated NDAs (ANDAs),  
25 and supplements to NDAs or BLAs. The three guidances are: *Part 1: Conducting Safety*  
26 *Assessments*; *Part 2: Clinical Indications*; and *Part 3: Design, Analysis, and Interpretation of*  
27 *Clinical Studies*.  
28

29 Medical imaging agents generally are governed by the same regulations as other drug and  
30 biological products. However, because medical imaging agents are used solely to diagnose and  
31 monitor diseases or conditions as opposed to treat them, development programs for medical  
32 imaging agents can be tailored to reflect these particular uses. Specifically, this guidance  
33 discusses our recommendations on conducting safety assessments of medical imaging agents.  
34

35 FDA's guidance documents, including this guidance, do not establish legally enforceable  
36 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
37 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
38 cited. The use of the word *should* in Agency guidances means that something is suggested or  
39 recommended, but not required.  
40

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<sup>1</sup> This guidance has been prepared by the Division of Medical Imaging and Radiopharmaceutical Drug Products and the Office of Therapeutics Research and Review in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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41 A glossary of common terms used in diagnostic medical imaging is provided at the end of this  
42 document.

43  
44

### 45 **II. SCOPE — TYPES OF MEDICAL IMAGING AGENTS**

46

47 This guidance discusses medical imaging agents that are administered in vivo and are used for  
48 diagnosis or monitoring with a variety of different modalities, such as radiography, computed  
49 tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and radionuclide  
50 imaging. The guidance is not intended to apply to the development of in vitro diagnostic or  
51 therapeutic uses of these agents.<sup>2</sup>

52

53 Medical imaging agents can be classified into at least two general categories, contrast agents and  
54 diagnostic radiopharmaceuticals.

55

#### 56 **A. Contrast Agents**

57

58 As used in this guidance, a *contrast agent* is a medical imaging agent used to improve the  
59 visualization of tissues, organs, and physiologic processes by increasing the relative difference of  
60 imaging signal intensities in adjacent regions of the body. Types of contrast agents include, but  
61 are not limited to, (1) iodinated compounds used in radiography and CT; (2) paramagnetic  
62 metallic ions (such as ions of gadolinium, iron, and manganese) linked to a variety of molecules  
63 and microparticles (such as superparamagnetic iron oxide) used in MRI; and (3) microbubbles,  
64 microaerosomes, and related microparticles used in diagnostic ultrasonography.

65

#### 66 **B. Diagnostic Radiopharmaceuticals**

67

68 As used in this guidance, a *diagnostic radiopharmaceutical* is (1) an article that is intended for  
69 use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans and that  
70 exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or  
71 photons or (2) any nonradioactive reagent kit or nuclide generator that is intended to be used in

---

<sup>2</sup> The guidance is not intended to apply to the development of research drugs that do not provide direct patient benefit with respect to diagnosis, therapy, prevention, or prognosis, or other clinically useful information. These include radioactive drugs for research that are used in accordance with 21 CFR 361.1. Section 361.1(a) states that radioactive drugs (defined in 21 CFR 310.3(n)) are generally recognized as safe and effective when administered under specified conditions to human research subjects in the course of a project intended to obtain basic information about the metabolism of a radioactively labeled drug or about human physiology, pathophysiology, or biochemistry. However, if a radioactive drug is used for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans, or if the radioactive drug has a pharmacological effect in the human body, an IND is required. FDA is developing a guidance on determining when research with radioactive drugs may be conducted under § 361.1.

The Agency recognizes the potential of imaging agents as research tools for aiding the development of therapeutic drugs, and some of the principles of the guidance may be applicable to such research. Sponsors of such imaging research agents are urged to contact the Division of Medical Imaging and Radiopharmaceutical Drug Products for advice on development of the imaging research agent.

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72 the preparation of such an article.<sup>3</sup> As stated in the preamble to FDA's proposed rule on  
73 Regulations for In Vivo Radiopharmaceuticals Used for Diagnosis and Monitoring, the Agency  
74 interprets this definition to include articles that exhibit spontaneous disintegration leading to the  
75 reconstruction of unstable nuclei and the subsequent emission of nuclear particles or photons  
76 (63 FR 28301 at 28303; May 22, 1998).

77  
78 Diagnostic radiopharmaceuticals are generally radioactive drug or biological products that  
79 contain a radionuclide that typically is linked to a ligand or carrier.<sup>4</sup> These products are used in  
80 nuclear medicine procedures, including planar imaging, single photon emission computed  
81 tomography (SPECT), positron emission tomography (PET), or in combination with other  
82 radiation detection probes.

83  
84 Diagnostic radiopharmaceuticals used for imaging typically have two distinct components.

- 85
- 86 • A radionuclide that can be detected in vivo (e.g., technetium-99m, iodine-123, indium-  
87 111).

88  
89 The radionuclide typically is a radioactive atom with a relatively short physical half-life  
90 that emits radioactive decay photons having sufficient energy to penetrate the tissue mass  
91 of the patient. These photons can then be detected with imaging devices or other  
92 detectors

- 93
- 94 • A nonradioactive component to which the radionuclide is bound that delivers the  
95 radionuclide to specific areas within the body.

96  
97 This nonradionuclidic portion of the diagnostic radiopharmaceutical often is an organic  
98 molecule such as a carbohydrate, lipid, nucleic acid, peptide, small protein, or antibody.

99  
100 As technology advances, new products may emerge that do not fit into these traditional  
101 categories (e.g., agents for optical imaging, magnetic resonance spectroscopy, combined contrast  
102 and functional imaging). It is anticipated, however, that the general principles discussed here  
103 could apply to these new diagnostic products. Developers of these products should contact the  
104 appropriate reviewing division for advice on product development.

105  
106  
107 **III. GENERAL CONSIDERATIONS FOR SAFETY ASSESSMENTS OF MEDICAL**  
108 **IMAGING AGENTS**

109  
110 **A. Medical Imaging Agent Characteristics Relevant to Safety**

111

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<sup>3</sup> 21 CFR 315.2 and 601.31.

<sup>4</sup> In this guidance, the terms *ligand* and *carrier* refer to the entire nonradionuclidic portion of the diagnostic radiopharmaceutical.

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112 The following sections discuss the special characteristics of a medical imaging agent that can  
113 lead to a more focused safety evaluation. Characteristics include its radiation absorbed dose,  
114 mass dose, route of administration, frequency of use, biodistribution, and biological, physical,  
115 and effective half-lives in the serum, the whole body, and critical organs.<sup>5</sup>

### *1. Mass Dose*

118  
119 Some medical imaging agents can be administered at low mass doses. For example, the mass  
120 dose of a single administration of a diagnostic radiopharmaceutical can be small because device  
121 technologies can typically detect relatively small amounts of a radionuclide (e.g.,  
122 radiopharmaceuticals for myocardial perfusion imaging). When a medical imaging agent is  
123 administered at a mass dose that is at the low end of the dose-response curve, dose-related  
124 adverse events are less likely to occur.

### *2. Route of Administration*

125  
126  
127 Some medical imaging agents are administered by routes that decrease the likelihood of systemic  
128 adverse events. For example, medical imaging agents that are administered as contrast media for  
129 radiographic examination of the gastrointestinal tract (e.g., barium sulfate) can be administered  
130 orally, through an oral tube, or rectally. In patients with normal gastrointestinal tracts, many of  
131 these products are not absorbed, so systemic adverse events are less likely to occur. In general,  
132 nonradiolabeled contrast agents pose safety issues similar to therapeutic drugs because of the  
133 inherently large amounts needed for administration. Therefore, nonradiolabeled drugs generally  
134 should be treated like therapeutic agents for the purpose of conducting clinical safety  
135 assessments.

### *3. Frequency of Use*

136  
137  
138  
139 Many medical imaging agents, including both contrast agents and diagnostic  
140 radiopharmaceuticals, are administered infrequently or as single doses. Accordingly, adverse  
141 events that are related to long-term use or to accumulation are less likely to occur with these  
142 agents than with agents that are administered repeatedly to the same patient. Therefore, the  
143 nonclinical development programs for such single-use products usually can omit long-term (i.e.,  
144 3 months' duration or longer), repeat-dose safety studies. In clinical settings where it is possible  
145 that the medical imaging agent will be administered to a single patient repeatedly (e.g., to  
146 monitor disease progression), we recommend that repeat-dose studies (of 14 to 28 days'  
147 duration) be performed to assess safety.

148  
149 Biological medical imaging agents are frequently immunogenic, and the development of  
150 antibodies after intermittent, repeated administration can alter the pharmacokinetics,  
151 biodistribution, safety, and/or imaging properties of such agents and, potentially, of  
152 immunologically related agents. We recommend that studies in which repeat dosing of a  
153 biological imaging agent is planned incorporate pharmacokinetic data, human anti-mouse  
154

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<sup>5</sup> See also 21 CFR 315.6 on evaluation of safety. When a medical imaging agent does not possess any of these special characteristics, as described in section III.A.1-4, complete standard safety assessments should be performed.

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155 antibody (HAMA), human anti-humanized antibody (HABA), or human anti-chimeric antibody  
156 (HACA) levels as well as whole body biodistribution imaging to assess for alterations in the  
157 biodistribution of the imaging agent following repeat dosing. Studies of immunogenicity in  
158 animal models are generally of limited value. Therefore, we recommend that human clinical  
159 data assessing the repeat use of a biological imaging agent be obtained prior to application for  
160 licensure of such an agent.

161

### 162 4. *Biological, Physical, and Effective Half-Lives*

163

164 Diagnostic radiopharmaceuticals often use radionuclides with short physical half-lives or that are  
165 excreted rapidly. The biological, physical, and effective half-lives of diagnostic  
166 radiopharmaceuticals are incorporated into radiation dosimetry evaluations<sup>6</sup> that require an  
167 understanding of the kinetics of the distribution and excretion of the radionuclide and its mode of  
168 decay. We recommend that biological, physical, and effective half-lives be considered in  
169 planning appropriate safety and dosimetry evaluations of diagnostic radiopharmaceuticals.

170

### 171 **B. Performance of Nonclinical Safety Assessments**

172

173 We recommend that the nonclinical development strategy for an agent be based on sound  
174 scientific principles, the agent's unique chemistry (including, for example, those of its  
175 components, metabolites, and impurities), and the agent's intended use. Because each product is  
176 unique, we encourage sponsors to consult with us before submitting an IND application and  
177 during product development. The number and types of nonclinical studies recommended would  
178 depend in part on the phase of development, what is known about the agent or its pharmacologic  
179 class, its proposed use, and the indicated patient population. If you determine that nonclinical  
180 pharmacology or toxicology studies are not needed, we are prepared to grant a waiver under  
181 21 CFR 312.10 if you provide adequate justification.

182

183 In the discussion that follows, a distinction is made between drug products and biological  
184 products. Existing specific guidance for biological products is referenced but not repeated here  
185 (see section III.B.2).

186

### 187 1. *Nonclinical Safety Assessments for Nonbiological Drug Products*

188

#### 189 a. *Timing of Nonclinical Studies Submitted to an IND Application*

190

191 We recommend that nonclinical studies be timed so that they help facilitate the  
192 timely conduct of clinical trials (including appropriate safety monitoring based on  
193 findings in nonclinical studies) and to reduce the unnecessary use of animals and

---

<sup>6</sup> *Biological half-life* is the time needed for a human or animal to remove, by biological elimination, half of the amount of a substance that has been administered. *Effective half-life* is the time needed for a radionuclide in a human or animal to decrease its activity by half as a combined result of biological elimination and radioactive decay. *Physical half-life* is the time needed for half of the population of atoms of a particular radioactive substance to disintegrate to another nuclear form.

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194 other resources.<sup>7</sup> The recommended timing of nonclinical studies for medical  
195 imaging drugs is summarized in Table 1.

196  
197 **b. Contrast Agents**

198  
199 Because of the characteristics of contrast drug products (e.g., variable biologic  
200 half-life) and the way they are used, we recommend that nonclinical safety  
201 evaluations of such drug products be made more efficient with the following  
202 modifications:

- 203  
204 • Long-term (i.e., greater than 3 months), repeat-dose toxicity studies in animals  
205 usually can be omitted. (Exceptions are products with long residence time,  
206 e.g., > 90 days.)
- 207  
208 • Long-term rodent carcinogenicity studies usually can be omitted.<sup>8</sup>
- 209  
210 • Reproductive toxicology studies required under § 312.23(a)(8)(ii)(a) often can  
211 be limited to an evaluation of embryonic and fetal toxicities in rats and rabbits  
212 and to evaluations of reproductive organs in other short-term toxicity studies.<sup>9</sup>  
213 If you determine that such reproductive studies are not needed, we are  
214 prepared to grant a waiver under § 312.10 if you provide adequate  
215 justification.

216  
217 We recommend that studies be conducted to address the effects of large mass  
218 dose and volume (especially for iodinated contrast materials administered  
219 intravenously); osmolality effects; potential transmetalation of complexes of  
220 gadolinium, manganese, or iron (generally MRI drugs); potential effects of tissue  
221 or cellular accumulation on organ function (particularly if the drug is intended to  
222 image a diseased organ system); and the chemical, physiological, and physical  
223 effects of ultrasound microbubble drugs (e.g., coalescence, aggregation,  
224 margination, and cavitation).

225

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<sup>7</sup> See the guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*. This and all other guidances cited in this document are available at FDA's Web site at <http://www.fda.gov/cder/guidance/index.htm>.

<sup>8</sup> Circumstances in which carcinogenicity testing may be recommended are summarized in the guidance *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

<sup>9</sup> See the guidance *S5A Detection of Toxicity to Reproduction for Medicinal Products* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

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225 **Table 1: Timing of Nonclinical Studies for Nonbiological Products Submitted to an IND**  
 226

<b>Study Type</b>	<b>Before Phase 1</b>	<b>Before Phase 2</b>	<b>Before Phase 3</b>	<b>Before NDA</b>
Safety pharmacology	Major organs, <sup>(a)</sup> and organ systems the drug is intended to visualize			
Toxicokinetic pharmacokinetic	See ICH guidances			
Expanded single-dose toxicity	Expanded acute single dose <sup>(b)</sup>			
Short-term (2 to 4 weeks) multiple dose toxicity		Repeat-dose toxicity <sup>(c)</sup>		
Special toxicology	Conduct as necessary based on route-irritancy, blood compatibility, protein flocculation, misadministration, extravasation			
Radiation dosimetry	If applicable			
Genotoxicity	In vitro <sup>(d)</sup>	Complete standard battery		
Immunotoxicity			May be needed based on molecular structure, biodistribution pattern, class concern, or clinical or nonclinical signal	
Reproductive and developmental toxicity			Needed or waiver obtained <sup>(d)</sup>	
Drug interaction				As needed
Other based on data results				As needed

227 (a) See the guidances *S7A Safety Pharmacology Studies for Human Pharmaceutical* and *S7B Safety Pharmacology*  
 228 *Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human*  
 229 *Pharmaceuticals* (note that *S7B* allows for phase evaluation of the required studies).

230 (b) See the guidance *Single Dose Acute Testing for Pharmaceuticals*.

231 (c) When repeat-dose toxicity studies have been performed, but single-dose toxicology studies have not, dose  
 232 selection for initial human studies will likely be based on the results of the no-adverse-effect level (NOAEL)  
 233 obtained in the repeat-dose study. The likely result will be a mass dose selection for initial human administration  
 234 that is lower than if the dose selection had been based on the results of acute, single-dose toxicity studies.

235 (d) See radiopharmaceutical discussion in section III.B.1.c of this document.

236  
 237

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### 237 c. Diagnostic Radiopharmaceuticals (Nonbiological Products)

238  
239 Because of the characteristics of diagnostic radiopharmaceuticals and the way  
240 they are used, we recommend that nonclinical safety evaluations of these drugs be  
241 made more efficient by the following modifications:

- 242
- 243 • Long-term, repeat-dose toxicity studies in animals typically can be omitted.
- 244
- 245 • Long-term rodent carcinogenicity studies typically can be omitted.
- 246
- 247 • Reproductive toxicology studies can be waived when adequate scientific  
248 justification is provided.<sup>10</sup>
- 249
- 250 • Genotoxicity studies should be conducted on the nonradioactive component  
251 because the genotoxicity of the nonradioactive component should be  
252 identified separately from that of the radionuclide. Genotoxicity studies can  
253 be waived if adequate scientific justification is provided.<sup>11</sup>
- 254

255 We recommend that special safety considerations for diagnostic  
256 radiopharmaceuticals include verification of the mass dose of the radiolabeled  
257 and unlabeled moiety; assessment of the mass, toxic potency, and receptor  
258 interactions for any unlabeled moiety; assessment of potential pharmacologic  
259 or physiologic effects due to molecules that bind with receptors or enzymes;  
260 and evaluation of all components in the final formulation for toxicity (e.g.,  
261 excipients, reducing drugs, stabilizers, anti-oxidants, chelators, impurities, and  
262 residual solvents). We recommend that the special safety considerations  
263 include an analysis of particle size (for products containing particles) and an  
264 assessment of instability manifested by aggregation or precipitation. We also  
265 recommend that an individual component be tested if specific toxicological  
266 concerns are identified or if toxicological data for that component are lacking.  
267 However, if toxicological studies are performed on the combined components  
268 of a radiopharmaceutical and no significant toxicity is found, toxicological  
269 studies of individual components are seldom required.

### 270

### 271 2. *Nonclinical Safety Assessments for Biological Products*

272  
273 Many biological products raise relatively distinct nonclinical issues such as immunogenicity and  
274 species specificity. We recommend the following Agency documents be reviewed for guidance  
275 on the preclinical evaluation of biological medical imaging agents:

- 276
- 277 • *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

---

<sup>10</sup> See footnote 11.

<sup>11</sup> See guidances *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals*.

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278

- 279           • *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products*  
280           *for Human Use*

281

282 Sponsors are encouraged to consult with the appropriate reviewing division for additional  
283 information when needed.

284

285

### 286 **IV. CLINICAL SAFETY ASSESSMENTS**

287

288 Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(d)),  
289 FDA cannot approve a new drug application (NDA) unless it contains adequate tests  
290 demonstrating whether the proposed drug product is safe for use under the conditions prescribed,  
291 recommended, or suggested in its proposed labeling.<sup>12</sup> All drugs have risks, including risks  
292 related to the intrinsic properties of the drug, the administration process, the reactions of the  
293 patient, and incorrect diagnostic information. Incorrect diagnostic information includes  
294 inaccurate structural, functional, physiological, or biochemical information; false positive or  
295 false negative diagnostic determinations; and information leading to inappropriate decisions in  
296 diagnostic or therapeutic management. Even if risks are found to be small, all drug development  
297 programs must also obtain evidence of drug effectiveness under section 505 of the Act.  
298 Although it has been suggested that a demonstration of effectiveness not be required for *safer*  
299 drugs, this statutory requirement cannot be waived. FDA weighs the benefits and risks of each  
300 proposed drug product when making its decision about whether to approve a marketing  
301 application (e.g., an NDA or BLA).

302

#### 303 **A. Group 1 and 2 Medical Imaging Agents**

304

305 The special characteristics of medical imaging agents may allow for a more efficient clinical  
306 safety program. This guidance describes two general categories for medical imaging agents:  
307 Group 1 and Group 2. The extent of clinical safety monitoring and evaluation that we  
308 recommend differs for these two categories. Generally, a less extensive clinical safety  
309 evaluation is appropriate for Group 1 agents. Conversely, we recommend that Group 2 agents  
310 undergo standard clinical safety evaluations in clinical trials throughout their development.  
311 These different groups have been conceived to help drug sponsors identify and differentiate  
312 those characteristics that are of greatest interest to the Agency in assessing the potential safety of  
313 a medical imaging agent.

314

315 FDA anticipates that it can assess which agents are Group 1 agents based on the safety-margin  
316 criteria from animal studies and initial human trials completed at the end of Phase 1.

317

##### 318 *1. Group 1 Medical Imaging Agents*

319

320 For purposes of this guidance, a Group 1 medical imaging agent generally exhibits the following  
321 three characteristics.

---

<sup>12</sup> For approval of a biological license application, the safety of the proposed product must be demonstrated under section 351 of the Public Health Service Act (42 U.S.C. 262).

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- 322
- 323
- 324
- The medical imaging agent meets *either* the safety-margin considerations *or* the clinical-use considerations described below (see sections B.1 and B.2, respectively).

325

    - The medical imaging agent is not a biological product<sup>13, 14</sup>
    - The medical imaging agent does not predominantly emit alpha or beta particles

327 Note that under the safety margin criteria (see section IV.B), medical imaging agents that are  
328 administered in low mass doses to humans (e.g., diagnostic radiopharmaceuticals) usually are  
329 more likely to be considered Group 1 than those administered in higher mass doses.<sup>15</sup> There  
330 are important exceptions, including cases where the medical imaging agents are likely to be  
331 immunogenic (e.g., biological products) when the pharmacologic response exists at a low  
332 mass dose, or when the medical imaging agents cause adverse reactions that are not dose-  
333 related (e.g., idiosyncratic drug reactions).

334 We recommend that standard clinical safety evaluations be performed in all clinical  
335 investigations of medical imaging agents, but we suggest that, for Group 1 agents, reduced  
336 human safety monitoring may be appropriate in subsequent human trials.

- 337
- For example, human safety monitoring may be limited to recording adverse events and monitoring only particular organs or tissues of interest for toxicity (such as organs that showed toxicity in the animal studies, or the organs and tissues in which the medical imaging agent localizes, which usually would include the liver and kidneys).

342

343 Persons having questions about whether a medical imaging agent is a Group 1 agent are  
344 encouraged to contact FDA to discuss. Whether a medical imaging agent should be considered a  
345 Group 1 or Group 2 agent may change during the course of a product's development. For  
346 example, even if an agent is initially thought to be Group 1, the subsequent identification of  
347 safety concerns could be reason to treat that agent as a Group 2 agent for the remainder of the  
348 product's development.

### 2. *Group 2 Medical Imaging Agents*

351

352 For purposes of this guidance, Group 2 medical imaging agents are generally medical imaging  
353 drugs or biological products that do not fall under the considerations for Group 1 medical  
354 imaging agents. All biological products are assumed to be Group 2 agents unless the sponsor  
355 demonstrates that its product lacks immunogenicity. Medical imaging agents that are

---

<sup>13</sup> Biological medical imaging products (e.g., radiolabeled cells, monoclonal antibodies, monoclonal antibody fragments; see 21 CFR 600.3(h) for definition of a biological product) have the potential to elicit an immunogenic response. Because the development of antibodies following repeat or intermittent administration can alter the safety, pharmacokinetics, and biodistribution of such agents, we regard biological medical imaging products as Group 2 agents.

<sup>14</sup> See also the final regulation Adverse Experience Reporting Requirements for Licensed Biological Products (59 FR 54042; October 27, 1994).

<sup>15</sup> For example, the approved PET drug products meet the Group 1 criteria.

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356 biologically active in animal studies or in human studies when administered at dosages that are  
357 similar to those intended for clinical use should also be considered Group 2 agents.<sup>16</sup>  
358

359 For Group 2 medical imaging agents, *standard clinical safety evaluations* should include serial  
360 assessments of patient symptoms, physical signs, clinical laboratory tests (e.g., blood chemistry,  
361 hematology, coagulation profiles, urinalyses), other tests (e.g., electrocardiograms as  
362 appropriate), and adverse events. We recommend that additional specialized evaluations be  
363 performed when appropriate (e.g., immunological evaluations, creatine kinase isoenzymes), or if  
364 a particular toxicity is deemed possible based on animal studies or the known chemical or  
365 pharmacological properties of the medical imaging agent. Although the extent of clinical  
366 monitoring cannot be predetermined, we recommend that it be of sufficient duration to identify  
367 possible effects that may lag behind those predicted by pharmacokinetic analyses. If some of  
368 these standard clinical safety evaluations are felt to be unnecessary, this should be discussed with  
369 the reviewing division. We recommend that sponsors seek FDA comment on the clinical safety  
370 monitoring plans in clinical studies before such studies are initiated.  
371

### **B. Considerations For Groups 1 or 2**

#### *1. Safety-Margin Considerations*

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375  
376 Under the safety-margin considerations, medical imaging agents can be considered Group 1 if  
377 the results of nonclinical studies **and** initial human experience are consistent with the conditions  
378 outlined below:

##### a. Results of nonclinical studies

380  
381  
382 To be considered a Group 1 agent under the safety-margin considerations, we  
383 recommend that a medical imaging agent have an adequately documented margin  
384 of safety as assessed in the nonclinical studies outlined in the following list.<sup>17</sup>  
385

- 386 • We recommend that the no-observed-adverse-effect level (NOAEL)<sup>18</sup> in  
387 expanded-acute, single-dose toxicity studies in suitable animal species be at  
388 least one hundred times (100x) greater than the maximal mass dose to be used  
389 in human studies. We further recommend that such expanded, acute, single-  
390 dose toxicity studies be completed before the medical imaging agent is  
391 introduced into humans (see section III.B.1).

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<sup>16</sup> Group 2 diagnostic radiopharmaceuticals can also include radionuclides and carriers that are known to be biologically active. This group includes radionuclides and carriers used at radiation doses or mass dosages that are higher than those used previously, including radionuclides and carriers that have been documented to produce adverse reactions.

<sup>17</sup> In addition, the medical imaging agent should meet the conditions described for the results of initial human experience (see section IV.B.1.b).

<sup>18</sup> For purposes of Groups 1 and 2 in this section of this guidance, the term *no-observed-adverse-effect-level (NOAEL)* is defined as the highest mass dose tested in animals with no adverse effects. (See guidance *A Harmonized Approach to Estimating the Safe Starting Dose for Clinical Trials of Therapeutics in Healthy Volunteers.*)

## *Contains Nonbinding Recommendations*

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- We recommend that the NOAEL in safety pharmacology studies in suitable animal species be at least one hundred times (100x) greater than the maximal mass dose to be used in human studies. We further recommend that such safety pharmacology studies be completed before the medical imaging agent is introduced into humans (see section III.B.1).
  - We recommend that the NOAEL in short-term, repeat-dose toxicity studies in suitable animal species be at least twenty-five times (25x) greater than the maximal mass dose to be used in human studies.<sup>19</sup> Short-term, repeat-dose toxicity studies are conducted to evaluate the effects of exaggerated dose regimens. Such regimens can reveal effects not detected in studies of small numbers of patients, suggest effects to be monitored in clinical studies, and reveal effects that might occur in sensitive individuals. Short-term, repeat-dose toxicity studies can be performed either before the medical imaging agent is introduced into humans, or concurrently with early human studies, but we recommend that they be completed before phase 2 (see section III.B.1).

410 To establish these margins of safety, we recommend that the NOAELs be  
411 assessed in properly designed and conducted studies and be appropriately  
412 adjusted. *Appropriately adjusted* means that mass dose comparisons between  
413 animals and humans should be suitably modified for factors such as body size  
414 (e.g., body surface area) and otherwise adjusted for possible pharmacokinetic and  
415 toxicokinetic differences between animals and humans (e.g., differences in  
416 absorption for products that are administered orally).<sup>20</sup>

417

418 We recommend that Group 1 medical imaging agents also undergo other  
419 nonclinical toxicological studies as described in section III.B.1, such as  
420 genotoxicity, reproductive toxicity, irritancy studies, and drug-drug interaction  
421 studies. See section III.B.1 for details and timing sequence.

### i. Additional considerations

422

423

424

425 FDA may still consider a medical imaging agent Group 1 even if its NOAELs are  
426 slightly less than the multiples specified above. For example, FDA will also take  
427 into consideration, among other things, how close the NOAELs are to the  
428 multiples specified above, the amount of safety information known about  
429 chemically similar and pharmacologically related medical imaging agents, the

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<sup>19</sup> Short-term, repeated-dose toxicity studies may identify toxicities associated with accumulation of a medical imaging agent or its metabolites. In addition, even if such accumulation is not anticipated (e.g., non-metabolized medical imaging agents with short half-lives), short-term repeated-dose toxicity studies may identify toxicities caused by repeated toxic insults, each of which may be below the threshold of detection in expanded-acute, single-dose toxicity studies.

<sup>20</sup> For example, if drug elimination is based on a physiologic function that reflects blood flow, we then recommend that scaling on body surface area be used.

## *Contains Nonbinding Recommendations*

430 nature of observed animal toxicities, and whether adverse events have occurred  
431 during initial human experience, including the nature of such adverse events (see  
432 section IV.B.1.b).

433  
434 ii. Formulations used in nonclinical studies

435  
436 We recommend that the formulation used to establish safety margins in  
437 nonclinical studies be identical to the formulation that will be used in clinical  
438 trials and that is intended for marketing. We also recommend that any differences  
439 in the formulations used in the clinical trials and nonclinical studies be specified  
440 so that any effect on the adequacy of the nonclinical studies can be determined.  
441 Bridging studies may be helpful when changes in the formulation are apt to  
442 change the pharmacokinetics, the pharmacodynamics, or safety characteristics of  
443 the drug.<sup>21</sup>

444  
445 In some cases, it may be infeasible or impractical to administer the intended  
446 clinical formulation to animals in multiples of the maximal human mass dose  
447 specified above (e.g., the volume of such an animal mass dose may be excessive).  
448 We recommend that sponsors discuss their plans with FDA before studies are  
449 initiated. In these cases, alternative strategies can be employed, such as dividing  
450 the daily mass dose (e.g., into a morning and evening dose), or by using a more  
451 concentrated formulation of the medical imaging agent, or the maximal feasible  
452 daily mass dose can be administered.

453  
454 b. Results of initial human experience

455  
456 In addition to those considerations described above for nonclinical studies, FDA  
457 also intends to consider the following when evaluating whether a medical imaging  
458 agent is a Group 1 agent.

- 459
- 460 • Whether safety issues were identified during initial human use of the medical  
461 imaging agent in appropriately designed studies that include adequate and  
462 documented standard clinical safety evaluations. Identification of any adverse  
463 events during initial human use that were not predicted from effects observed  
464 in animals could be considered significant, regardless of severity. If adverse  
465 events occur at any time during human studies, we intend to conduct a risk  
466 assessment to determine whether the medical imaging agent should be  
467 reconsidered as a Group 2 medical imaging agent. This risk assessment will  
468 examine the type, frequency, severity, and potential attribution of the adverse  
469 events with respect to what is known about the pharmacology of the drug. For  
470 example, the safety profile of a specific drug class may be well known, so that  
471 the occurrence of a common, nonserious adverse event, such as headache,  
472 would not be of particular concern. However, in a drug class in which  
473 microparticles of varying sizes are administered, the occurrence of the same  
474 adverse event might be a signal of microcirculatory compromise.

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<sup>21</sup> See guidance *S7A Safety pharmacology studies for human pharmaceuticals*.

## *Contains Nonbinding Recommendations*

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- We recommend that human pharmacokinetic studies of the radiopharmaceutical be performed during phase 1 to collect information about the disposition of the radioactivity in humans. Such data help facilitate adequate comparisons of exposure between humans and the species used in the nonclinical studies and allow a more meaningful assessment of the relevance of the animal safety data (e.g., toxicokinetics).

### 2. *Clinical Use Considerations*

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484

485 Another way to be considered a Group 1 agent is by adequately documenting extensive  
486 prior clinical use without development of a safety signal. This means showing that there  
487 were no human toxicity or adverse events with clinical mass doses (and activities, if  
488 applicable) of the agent, under conditions of adequate safety monitoring, and that the lack  
489 of human toxicity was adequately documented. We recommend that the methods used to  
490 monitor for adverse events be documented. Literature may be of limited value in  
491 establishing the clinical safety of a drug because most published studies focus on  
492 efficacy, with little or no description of any safety assessments.

493  
494 An agent can be identified as Group 1 based on the clinical-use considerations at any  
495 time during drug development (e.g., after the conditions specified in this section have all  
496 been met).

## **C. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals**

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498  
499

### 1. *General Considerations*

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502 We recommend that an IND sponsor submit sufficient data from animal or human studies  
503 to allow a reasonable calculation of the radiation absorbed dose to the whole body and to  
504 critical organs upon administration to a human subject (21 CFR 312.23(a)(10)(ii)). At a  
505 minimum, we recommend that radiation absorbed dose estimates be provided for all  
506 organs and tissues in the standardized anthropomorphic phantoms established in the  
507 literature (e.g., by the Medical Internal Radiation Dose (MIRD) Committee of the Society  
508 of Nuclear Medicine). For diagnostic radiopharmaceuticals, we also recommend  
509 calculation of the *effective dose* as defined by the International Commission on  
510 Radiological Protection (ICRP) in its ICRP Publication 60 (this quantity is not  
511 meaningful for therapeutic radiopharmaceuticals).

512  
513 When a diagnostic radiopharmaceutical is being developed for pediatric use, the radiation  
514 absorbed dose should be provided for all age groups in which the agent is intended to be  
515 used, as provided by standard anthropomorphic phantoms established in the literature  
516 (i.e., newborn, 1-year-old, 5-year-old, 10-year-old, and 15-year-old).

517  
518 We recommend that the amount of the radiation absorbed dose delivered by internal  
519 administration of diagnostic radiopharmaceuticals be calculated by standardized methods,  
520 such as the absorbed fraction method described by the MIRD Committee and the ICRP.

## *Contains Nonbinding Recommendations*

521  
522 We also recommend that the methodology used to assess radiation safety be specified  
523 including reference to the body models that were used. We recommend that the  
524 mathematical equations used to derive the time activity curves and the radiation absorbed  
525 dose estimates be provided along with a full description of assumptions that were made.  
526 We further recommend that sample calculations and all pertinent assumptions be listed  
527 and submitted. We recommend that the reference to the body, organ, or tissue model  
528 used in the dosimetry calculations be specified, particularly for new models being tested.  
529 If a software program was used to calculate the radiation doses, we recommend that you  
530 provide (1) a full description of the code, including official name, version number, and  
531 computing platform; (2) a literature citation for the code; and (3) photocopies of the  
532 code's output, preferably showing all of the user input data and model choices.

533  
534 We recommend that safety hazards for patients and health care workers during and after  
535 administration of the radiolabeled product be identified, evaluated, and managed  
536 appropriately.

### 537 538 2. *Calculation of Radiation Absorbed Dose to the Target Organs or Tissues*

539  
540 For established radionuclides used with a diagnostic agent (e.g., Tc-99m, In-111), we  
541 recommend that the following items be determined based on the average patient as  
542 defined by the MIRD phantom:

- 543
- 544 • The tissue or organ in which a significant accumulation of radioactivity occurs (i.e.,  
545 *source* organ)
  - 546 • The amount of radioactivity that accumulates in these tissues, expressed as a  
547 percentage of the administered activity
  - 548 • The times at which radioactivity accumulation was observed in these tissues. We  
549 recommend that observations be made at two or more times during each phase of  
550 radioactivity accumulation or clearance from the source regions. If there is rapid  
551 accumulation in a region and nonexponential clearance, two to three time points may  
552 be sufficient to characterize the kinetic behavior. If there are two phases of clearance,  
553 we recommend at least two points of observation during each phase to adequately  
554 characterize the biokinetics. A description of the kinetic behavior of the activity  
555 accumulation and clearance from these tissues. This is most typically shown as  
556 *biological half-times* for accumulation and clearance, although other representations  
557 may be used.
  - 558 • The time-integral of activity for the accumulation of radiopharmaceutical in these  
559 source tissues or organs. For purposes of this guidance, this *time-integral* is defined  
560 as the “cumulated activity” or “residence time” by the MIRD Committee in various  
561 publications.
  - 562 • A description of how this time-integral was calculated. This should be based  
563 primarily on the accumulation and kinetic behavior in the source organs. We  
564 recommend that you specify the method used to calculate the time-integrals (e.g.,

### *Contains Nonbinding Recommendations*

565 numerical integration, regression analysis, or compartment model analysis). We also  
566 recommend that you provide a description of how the terminal portion of the time-  
567 activity curve for a given source region was integrated (e.g., assuming only physical  
568 decay after the last data point, some rate of biological elimination estimated by two or  
569 more of the later data points, or a fitted function continued to infinite time).

570 • A description of how these time-integrals for source regions were combined with  
571 dose conversion factors to calculate the radiation absorbed dose to all target regions.  
572 If hand calculations were performed, we recommend that you specify the source of  
573 dose conversion factors and provide copies of all calculations. If an electronic  
574 spreadsheet was used, we recommend that you provide printouts and electronic copies  
575 of the spreadsheets to verify the formulas used. If a computer program was used, we  
576 recommend that you provide a complete description of the code and version number  
577 as well as documentation of the code input and output.

578 For new radionuclides used with diagnostic agents, the same principles apply and we  
579 recommend that you provide the same information. If you want guidance on these  
580 calculations, we recommend that you consult the appropriate review division.

#### 581 3. *Maximum Radiation Absorbed Dose*

582  
583 We recommend that the amount of radioactive material administered to human subjects  
584 be the smallest radiation absorbed dose practical to perform the procedure while  
585 providing an adequate diagnostic examination for evaluation by the physician.  
586

587 We recommend that calculations include the radiation absorbed dose contributions made  
588 by all potential radionuclide contaminants that may be present in the product.  
589

590 We recommend that you perform calculations to anticipate possible changes in dosimetry  
591 that might occur in the presence of diseases in organs that are critical in metabolism or  
592 excretion of the diagnostic radiopharmaceutical. For example, renal dysfunction may  
593 cause significant, slow-clearing accumulation in one or both kidneys (and thus a high  
594 dose to kidneys and adjacent tissues) and/or a larger fraction of the administered activity  
595 to be cleared by the hepatobiliary system (or vice versa).  
596

597 We recommend that possible changes in dosimetry resulting from patient-to-patient  
598 variations in antigen or receptor mass be considered in dosimetry calculations. For  
599 example, a large tumor mass may result in a larger-than-expected radiation absorbed dose  
600 to a target organ from a diagnostic radiopharmaceutical that has specificity for a tumor  
601 antigen. (For the purposes of dose calculation, a primary tumor, without metastases, can  
602 be regarded as part of the organ in which it arises and its activity can be added to that of  
603 the organ.)  
604

605 We recommend that the mathematical equations used to derive the estimates of the  
606 individual organ time activity curves and the radiation absorbed doses be provided along  
607 with a full description of assumptions that were made. We recommend that sample  
608 calculations and all pertinent assumptions be listed.  
609

### *Contains Nonbinding Recommendations*

610 We recommend that calculations of radiation absorbed dose estimates be performed  
611 assuming freshly labeled material (to account for the maximum amount of radioactivity)  
612 as well as the maximum shelf life of the diagnostic radiopharmaceutical (to allow for the  
613 upper limit of accumulation of radioactive decay contaminants). We recommend that  
614 these calculations:

- 615
- 616 • Include radiation absorbed doses from x-ray procedures that are part of the study (i.e.,  
617 would not have occurred but for the study). The possibility of follow-up studies  
618 should be considered for inclusion in the dose calculations.
- 619 • Be expressed as milligray (mGy) per megabecquerel (MBq) and as rad per millicurie  
620 (mCi) of the administered radiopharmaceutical
- 621 • Be expressed as mGy and rad for a typical administered quantity of the  
622 radiopharmaceutical
- 623 • Be presented in a tabular format and include individual radiation absorbed doses for  
624 the target tissues or organs and the organs listed above in section IV.D.1

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626

**GLOSSARY**

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**Effective dose:** The sum of the weighted equivalent doses in all the tissues and organs of the body, given by the expression  $E = \sum WTHT,R$ , where WT is the weighting. Effective dose, defined in 1990 by the International Commission on Radiological Protection, allows the conversion of the risk from partial body irradiations to those of whole body irradiations.

**Mass dose:** The mass or weight of the ligand or carrier, including the radionuclide, administered to the subject.

**No observed adverse effect level (NOAEL):** The highest radiation absorbed dose tested in an animal species without adverse effects detected.

**No observed effect level (NOEL):** The highest radiation absorbed dose tested in an animal species with no detected effects.

**Radiation absorbed dose:** The energy absorbed per unit mass. This is the fundamental dosimetric quantity in radiological protection. Its unit is the joule per kilogram, which is given the special name gray (Gy). The older quantity was the rad, where 1 Gy = 100 rads.

**Repeat-dose toxicity study:** A study that investigates the toxicities produced when a pharmaceutical is administered repeatedly during a given period of more than 24 hours. A repeat-dose toxicity study evaluates the effects of exaggerated dose regimens. Usually all animals in a repeat-dose toxicity study are terminated the day after the final dose; however, a recovery period may be included in the design to test the reversibility of effects. An interim sacrifice is sometimes included to detect effects that may occur after a few doses.

**Safety pharmacology study:** A study that investigates the potential undesirable pharmacodynamic effects of a substance on physiologic functions in relation to exposure levels.

**Special toxicology study:** A study conducted when something about the nature of the drug or how it is used raises a concern, or when previous nonclinical or clinical findings on the product or a related product have indicated special toxicological concerns. Examples include a local irritation study conducted to test the effects of potential misadministration or extravasation.

**Standard/expanded acute toxicity study:** A study that investigates toxicities produced by a pharmaceutical when it is administered in one dose. During a period not exceeding 24 hours, doses may be split due to large volumes or high concentrations. An expanded acute toxicity study includes more measures of toxicities than a standard acute toxicity study.