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)

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Clinical Medical

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I. INTRODUCTION

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

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

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

[1] 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.

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

II. SCOPE — TYPES OF MEDICAL IMAGING AGENTS

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

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

A. Contrast Agents

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

B. Diagnostic Radiopharmaceuticals

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

[2] 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.

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

Diagnostic radiopharmaceuticals are generally radioactive drug or biological products that contain a radionuclide that typically is linked to a ligand or carrier.[4] These products are used in nuclear medicine procedures, including planar imaging, single photon emission computed tomography (SPECT), positron emission tomography (PET), or in combination with other radiation detection probes.

Diagnostic radiopharmaceuticals used for imaging typically have two distinct components.

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

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

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

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

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

III. GENERAL CONSIDERATIONS FOR SAFETY ASSESSMENTS OF MEDICAL IMAGING AGENTS

A. Medical Imaging Agent Characteristics Relevant to Safety

[3] 21 CFR 315.2 and 601.31.

[4] In this guidance, the terms *ligand* and *carrier* refer to the entire nonradionuclidic portion of the diagnostic radiopharmaceutical.

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

1. Mass Dose

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

2. Route of Administration

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

3. Frequency of Use

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

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

[5] 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.

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

4. Biological, Physical, and Effective Half-Lives

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

B. Performance of Nonclinical Safety Assessments

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

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

1. Nonclinical Safety Assessments for Nonbiological Drug Products

a. Timing of Nonclinical Studies Submitted to an IND Application

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

[6] *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.

other resources.[7] The recommended timing of nonclinical studies for medical imaging drugs is summarized in Table 1.

b. Contrast Agents

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

- Long-term (i.e., greater than 3 months), repeat-dose toxicity studies in animals usually can be omitted. (Exceptions are products with long residence time, e.g., > 90 days.)

- Long-term rodent carcinogenicity studies usually can be omitted.[8]

- Reproductive toxicology studies required under § 312.23(a)(8)(ii)(*a*) often can be limited to an evaluation of embryonic and fetal toxicities in rats and rabbits and to evaluations of reproductive organs in other short-term toxicity studies.[9] If you determine that such reproductive studies are not needed, we are prepared to grant a waiver under § 312.10 if you provide adequate justification.

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

[7] 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.

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

[9] 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*.

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

Study Type	Before Phase 1	Before Phase 2	Before Phase 3	Before NDA
Safety pharmacology	Major organs,[a] and organ systems the drug is intended to visualize			
Toxicokinetic pharmacokinetic	See ICH guidances			
Expanded single-dose toxicity	Expanded acute single dose [b]			
Short-term (2 to 4 weeks) multiple dose toxicity		Repeat-dose toxicity		
Special toxicology	Conduct as necessary based on route-irritancy, blood compatibility, protein flocculation, misadministration, extravasation			
Radiation dosimetry	If applicable			
Genotoxicity	In vitro [d]	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 [d]	
Drug interaction				As needed
Other based on data results				As needed

(a) See the guidances *S7A Safety Pharmacology Studies for Human Pharmaceutical* and *S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (note that *S7B* allows for phase evaluation of the required studies).
(b) See the guidance *Single Dose Acute Testing for Pharmaceuticals*.
(c) When repeat-dose toxicity studies have been performed, but single-dose toxicology studies have not, dose selection for initial human studies will likely be based on the results of the no-adverse-effect level (NOAEL) obtained in the repeat-dose study. The likely result will be a mass dose selection for initial human administration that is lower than if the dose selection had been based on the results of acute, single-dose toxicity studies.
(d) See radiopharmaceutical discussion in section III.B.1.c of this document.

c. Diagnostic Radiopharmaceuticals (Nonbiological Products)

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

- Long-term, repeat-dose toxicity studies in animals typically can be omitted.

- Long-term rodent carcinogenicity studies typically can be omitted.

- Reproductive toxicology studies can be waived when adequate scientific justification is provided.[10]

- Genotoxicity studies should be conducted on the nonradioactive component because the genotoxicity of the nonradioactive component should be identified separately from that of the radionuclide. Genotoxicity studies can be waived if adequate scientific justification is provided.[11]

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

2. Nonclinical Safety Assessments for Biological Products

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

- *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

[10] See footnote 11.

[11] See guidances *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals*.

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

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

IV. CLINICAL SAFETY ASSESSMENTS

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

A. Group 1 and 2 Medical Imaging Agents

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

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

1. Group 1 Medical Imaging Agents

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

[12] 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).

- 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).
- The medical imaging agent is not a biological product[13, 14]
- The medical imaging agent does not predominantly emit alpha or beta particles

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

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

- 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).

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

2. Group 2 Medical Imaging Agents

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

[13] 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.

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

[15] For example, the approved PET drug products meet the Group 1 criteria.

biologically active in animal studies or in human studies when administered at dosages that are similar to those intended for clinical use should also be considered Group 2 agents.[16]

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

B. Considerations For Groups 1 or 2

1. Safety-Margin Considerations

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

a. Results of nonclinical studies

To be considered a Group 1 agent under the safety-margin considerations, we recommend that a medical imaging agent have an adequately documented margin of safety as assessed in the nonclinical studies outlined in the following list.[17]

- We recommend that the no-observed-adverse-effect level (NOAEL)[18] in expanded-acute, single-dose toxicity 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 expanded, acute, single-dose toxicity studies be completed before the medical imaging agent is introduced into humans (see section III.B.1).

[16] 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.

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

[18] 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.*)

- 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.[19] 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).

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

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

i. Additional considerations

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

[19] 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.

[20] 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.

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

ii. Formulations used in nonclinical studies

We recommend that the formulation used to establish safety margins in nonclinical studies be identical to the formulation that will be used in clinical trials and that is intended for marketing. We also recommend that any differences in the formulations used in the clinical trials and nonclinical studies be specified so that any effect on the adequacy of the nonclinical studies can be determined. Bridging studies may be helpful when changes in the formulation are apt to change the pharmacokinetics, the pharmacodynamics, or safety characteristics of the drug.[21]

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

b. Results of initial human experience

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

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

[21] See guidance *S7A Safety pharmacology studies for human pharmaceuticals.*

- 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

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

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

C. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals

1. General Considerations

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

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

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

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

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

2. Calculation of Radiation Absorbed Dose to the Target Organs or Tissues

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

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

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

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

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

3. Maximum Radiation Absorbed Dose

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

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

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

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

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

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

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

GLOSSARY

Effective dose: The sum of the weighted equivalent doses in all the tissues and organs of the body, given by the expression $E = \sum W_T H_{T,R}$, 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.