Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

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

June 2018
Pharmacology/Toxicology

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

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

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

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

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

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

This guidance discusses the following concepts:

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

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

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

In general, FDA's guidance documents 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.

II. BACKGROUND

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

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

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

III. PHARMACOLOGY

A. Primary Pharmacology

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

B. Safety Pharmacology

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

IV. ANIMAL BIODISTRIBUTION AND DOSIMETRY

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

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

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

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

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

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

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

V. TOXICOLOGY

A. General Toxicology

1. Toxicology Studies to Support the FIH Therapeutic Phase

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

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

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

2. Long-Term Toxicity Assessments to Support Marketing

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

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

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

B. Genotoxicity, Reproductive Toxicology, and Carcinogenicity Studies

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

VI. FIH DOSE SELECTION

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

A. Radiation Administered Dose

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

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

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

B. Mass Dose

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

VII. LABELING RECOMMENDATIONS

A. Genotoxicity, Reproductive Toxicology, and Carcinogenicity

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

[4] See 21 CFR 201.57.

[5] See 21 CFR 201.57(c)(14)(i).

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

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

- Female patients should be advised to use contraception during treatment and then for at least a period of time that equals five effective half-lives and an additional 6 months after the last dose of the radiopharmaceutical. The half-life of daughter decays also should be considered. The five effective half-lives allow elimination of approximately 97 percent of the radioactivity and the additional 6 months is to ensure that damaged follicles and oocytes are released before fertilization.

- Male patients with female partners of reproductive potential should be advised to use contraception during treatment and then for at least a period of time that equals five effective half-lives and an additional 3 months after the last dose of the radiopharmaceutical. The half-life of daughter decays also should be considered. The five effective half-lives allow elimination of approximately 97 percent of the radioactivity and the additional 3 months takes into account the duration of spermatogenesis and the residence time of unejaculated sperm.

B. Lactation

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

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

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

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

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

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

GLOSSARY

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

1 MBq = 27 μCi; 1 mCi = 37 MBq

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

Dose

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

Radiation Dose

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

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

1 Gy = 100 rad; 1 cGy = 1 rad

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

1 Sv = 100 rem

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

H (Sv) = RBE. D (Gy)

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

Half-life

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

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

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

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

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

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

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

Organ

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

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

Parameters from animal biodistribution and dosimetry and extrapolation to human

Cumulated activity or *time-integrated activity (Ã):* The activity as a function of time in each organ (µCi-h or MBq-s). Activity time curves can be obtained by measurements of activity over time and it is a function of the initial activity A_0 (Ci or Bq unit) and the residence time τ (hour).

$$\tilde{A} = A_0 . \tau$$

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

$$\tau(human) = \tau\ (animal).\frac{Organ\ weight\ (human)}{Organ\ weight\ (animal)}\ \frac{BW(animal)}{BW\ (human)}$$

$$\%ID\ (human) = \%ID\ (animal).\frac{Organ\ weight\ (human)}{Organ\ weight\ (animal)}\ \frac{BW(animal)}{BW\ (human)}$$

Or:

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

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

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

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