事　　務　　連　　絡
令 和 ７ 年 １１ 月 １１ 日

各都道府県衛生主管部（局）　御中

厚生労働省医薬局医薬品審査管理課

「治療用放射性医薬品の非臨床試験と臨床試験デザインに関するガイドライン」等
の英文版の送付について

標記について、別添１及び２のとおり取りまとめましたので、貴管下関係業者に対して周知方お願いします。

また、本事務連絡の写しについて、別記の団体等宛てに連絡するので、念のため申し添えます。

別添１ Guideline for the Nonclinical Studies and the Design of Clinical Studies of Therapeutic Radiopharmaceuticals

別添２ Questions and Answers on Guideline for the Nonclinical Studies and the Design of Clinical Studies of Therapeutic Radiopharmaceuticals (Q&A)

別記

日本製薬団体連合会
日本製薬工業協会
米国研究製薬工業協会在日執行委員会
一般社団法人欧州製薬団体連合会
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国立医薬品食品衛生研究所
各地方厚生（支）局

（別添１）

# Guideline for the Nonclinical Studies and the Design of Clinical Studies of Therapeutic Radiopharmaceuticals

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## 1. Introduction

### 1.1 Background

For the purpose of this guideline, radiopharmaceuticals refer to pharmaceuticals provided in Article 2, Paragraph 1, of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960), which are unsealed compounds and their products that contain radioisotopes (radionuclides) and emit the radiation provided in Article 3, Item 5, of the Atomic Energy Basic Act (Act No. 186 of 1955) as structural elements.

Radiopharmaceuticals are used for diagnosis and treatmentin nuclear medicine and have the following characteristics:

- For both diagnosis and treatment, the indications are based on the radiation emitted by nuclear decay or the nuclear transition of radionuclides contained in an active ingredient. Non-radionuclide portions of radionuclide-labeled compounds play a role in delivering and accumulating radionuclides to the target sites which include targeting moieties, such as small molecule, peptides, or antibodies. If radionuclides have characteristics by themselves directed to a particular organ or tissue neat radionuclides may be used for diagnosis or treatment.[1]
- Diagnostic radionuclides are used to visualize the expression of the target molecules, function of organs and tissues, and the state of blood flow by utilizing highly penetrating photons, such as gamma or X-rays. For therapeutic radionuclides, highly cytotoxic radiation, such as beta or alpha radiation, is generally utilized for anticancer treatments. Although affected by the pharmacokinetics of compounds, such as the time required for accumulation to target sites, in general, radionuclides with a short physical half-life are selected for diagnosis for the purpose of reducing radiation exposure, and radionuclides with a long physical half-life are selected for treatment for the reason of the potential for therapeutic benefits.
- The administered dose of radiopharmaceuticals as compounds is generally extremely small, and compounds are by themselves often less likely to have biological effects.
- Diagnostic radiopharmaceuticals are primarily administered as a single dose, while therapeutic radiopharmaceuticals are commonly administered as multiple doses at regular intervals.[2]
- The recommended clinical doses of both diagnostic radiopharmaceuticals and therapeutic radiopharmaceuticals must be determined with consideration for radiation exposure doses to the nontarget organs, as well as efficacy. In particular, exposure doses to normal tissue must be considered when using highly cytotoxic radionuclides from the perspective of safety.
- In recent years, the radiopharmaceuticals based on the concept of theranostics have been developed. Theranostics has a concept that integrates diagnostics and therapeutics, which binds different radionuclides to molecules (including linkers in some cases) that have functional roles in delivery to the

[1] Including iodine, which is a thyroid seeker, and radium, which is a bone seeker.

[2] Radium chloride ($^{223}$Ra) solution for injection: Up to six doses at four-week intervals; lutetium oxodotreotide ($^{177}$Lu) solution for injection: up to four doses at eight-week intervals; strontium chloride ($^{89}$Sr) solution for injection: at intervals of at least three months when a rechallenge is administered.

same target sites, by utilizing the differences in the properties of radiation.[3]

1.2 Purpose

Considering that the conditions of application of nonclinical and clinical evaluations of radiopharmaceuticals are not clarified in the guideline for nonclinical and clinical studies required for the application for marketing authorization of general pharmaceuticals, this guideline provides basic considerations for the conduct of the nonclinical studies required for the application for marketing authorization and the initiation of clinical studies, and the conduct of clinical studies of new therapeutic radiopharmaceuticals. Although therapeutic radiopharmaceuticals are used for anticancer treatment in most cases, the guideline can cover the development of radiopharmaceuticals for the treatment of other diseases.

In this guideline, therapeutic radiopharmaceutical is defined as a drug that contains a radionuclide, and is administered systemically or locally for the treatment of disease with alpha radiation, beta radiation or others (hereinafter referred to as "radiation") emitted upon the decay of radionuclides.

This guideline is intended to avoid the unnecessary use of animals and other resources according to the principle of the 3Rs (reduction, refinement, and replacement) and to promote and accelerate the development of therapeutic radiopharmaceuticals as well as to protect clinical study participants from unnecessary adverse drug reactions.

1.3 General Principle

In the development of therapeutic radiopharmaceuticals, nonclinical and clinical studies should be conducted considering the characteristics of radionuclides, from which efficacy is expected, and other nonradioactive components (including molecules playing a functional role in the delivery to target sites or linker molecules; see the Glossary and Table 1). In light of the target diseases and physicochemical characteristics of nonradioactive components, it is possible to apply the ICH guidelines to the conduct of nonclinical and clinical evaluations.

Because of their diversity in terms of radionuclides and compound forms, therapeutic radiopharmaceuticals may need to be evaluated in a flexible manner on a case-by-case basis in nonclinical safety studies. In addition, if radionuclides and/or nonradioactive components of therapeutic radiopharmaceuticals under development are already approved as pharmaceuticals, results with them may be used for the waiver of new studies. If the results of nonclinical studies of compounds with a similar structure are used, the potential effects of different chemical structures on nonclinical evaluations should be carefully considered.

In nonclinical safety studies of therapeutic radiopharmaceuticals, data on studies must be collected and generated in accordance with Good Laboratory Practice (GLP) principles. However, if radionuclides are used for nonclinical studies, it may be difficult to conduct GLP studies in some cases. In such cases, studies have to be conducted under conditions that can ensure the adequate reliability as approval application data, with

[3] Burkett BJ, et al., A Review of Theranostics: Perspectives on Emerging Approaches and Clinical Advancements. *Radiol Imaging Cancer*. 2023;5(4):e220157.

the reason that studies cannot be conducted under GLP principles.

This guideline provides a summary of basic approaches based on current scientific knowledge. Thus, it does not necessarily require an evaluation using the methods shown in this guideline if the methods are based on scientific rationale reflecting advances in science and technology.

### 1.4 Scope

This guideline is appliable to therapeutic radiopharmaceuticals, including oncology therapeutic radiopharmaceuticals. The basic approaches provided in this guideline may be useful in the development of diagnostic radiopharmaceuticals.

## 2. Nonclinical Evaluation Studies and Endpoints

The nonclinical evaluation of therapeutic radiopharmaceuticals has to focus on the effects of radiation produced by radionuclide decay and the effects of *in vivo* exposure to nonradioactive components. For the effects based on exposure to radiation emitted by radionuclide decay, it is possible to determine the necessity of endpoints for nonclinical safety studies considering the type and level of radiation. The toxicity associated with radiation exposure can also be evaluated through information provided by the appropriate literature or other resources. In contrast, if radionuclide elements for labeling (including non-radionuclides) and/or non-element portions of nonradioactive components have a highly novel substance, such as those with limited clinical use as pharmaceuticals in humans, nonradioactive components (stable isotopologues of elements used for labeling or unlabeled substances if no stable isotope is available; see the Glossary and Table 1) must be evaluated by nonclinical safety studies in line with novel active ingredients of pharmaceuticals. In this case, the necessary endpoints for a nonclinical safety evaluation of novel nonradioactive components may be determined by reference to the ICH M3, ICH S6, and ICH S9 guidelines, depending on the physicochemical properties[4] and the intended pharmaceutical indication.

### 2.1 Primary Pharmacodynamics

Prior to the initiation of phase I clinical studies, the pharmacology of therapeutic radiopharmaceuticals to be used in clinical studies of the target diseases must be evaluated on the basis of *in vitro* and/or *in vivo* study results. In addition, results from *in vivo* pharmacology studies using disease models may provide information on the biodistribution of therapeutic radiopharmaceuticals and information for the selection of relevant animal species to be used in toxicology studies. *In vivo* pharmacology study results could also be used to determine the maximum tolerated radiation dose in animals. Furthermore, nonradioactive components could also be used to assess the binding or uptake by the target molecules such as receptors, or target cells.

### 2.2 Safety Pharmacology

[4] Including low-molecular compounds, synthetic peptides, or biotechnology-derived pharmaceuticals.

If the effects of nonradioactive components on the function of vital organs[5] and the biological effects on radionuclide elements used for labeling (including nonradioactive isotopes) have been well characterized, the significance of conducting safety pharmacology studies with therapeutic radiopharmaceuticals is low. In contrast, if radionuclide elements used for labeling (including nonradioactive isotopes) and/or nonradioactive components have not been used clinically as pharmaceuticals, the effects on the function of vital organs[5] must be evaluated, mainly with nonradioactive components, in accordance with the ICH S7A and S7B guidelines before the initiation of phase I clinical studies in the same manner as the novel active ingredients of pharmaceuticals. The necessary study endpoints should be selected by reference to the ICH M3, ICH S6, and ICH S9 guidelines, as appropriate, depending on the physicochemical properties and intended pharmaceutical indication of the therapeutic radiopharmaceuticals.

2.3 Pharmacokinetics

The results of biodistribution and dosimetry in pharmacokinetic studies in animals may be enable to determine of human doses. In pharmacokinetic studies, it is useful to evaluate absorption, distribution, metabolism, and excretion, depending on the physicochemical properties of the therapeutic radiopharmaceuticals in accordance with the ICH S3A guideline, the guideline for nonclinical pharmacokinetic studies, or the ICH S6 guideline. Distribution should be evaluated in terms of organs and tissues throughout the body. As substances for administration, therapeutic radiopharmaceuticals or nonradioactive components with appropriate radiolabeling should be used to assess their activity. In addition, mass balance can be evaluated with substances in which a radionuclide is replaced with a nonradioactive isotope. The selection of substances for administration should take into consideration the evaluation of their disposition as compounds. Although a single dose is typically used, repeated dose studies may be necessary considering the persistence of radioactivity or changes in distribution in the living body if repeated doses are administered in clinical practice. A single animal species to be used in general toxicology studies is usually sufficient. In addition, if unlabeled substances have not been used clinically as pharmaceuticals, their effects on drug metabolism and drug interactions may have to be evaluated along the physicochemical properties of the unlabeled substance in the same manner as pharmaceuticals with novel active ingredients.

In the case of single-dose administration, a radioactivity-time curve should be prepared with an adequate sampling time after the administration of the pharmaceutical (e.g., 5 × effective half-life) to assess the activity in organs over time. The duration and frequency of sampling should be determined on the basis of a scientific rationale so that reliable pharmacokinetic parameters can be calculated from the radioactivity-time curve.

The design of pharmacokinetic studies in animals should incorporate aspects of the planned clinical schedule in humans that might affect the pharmacokinetics of a radiopharmaceutical. For instance, if the planned clinical study includes pretreatment with thyroid-blocking agents to reduce the radioiodine uptake by the thyroid gland, it is recommended that a biodistribution study in animals be conducted mimics dosing regimen as that in humans.

Of note, if there are any progeny nuclides, not only radionuclides contained in the active ingredients but

[5] Cardiovascular system, respiratory system, and central nervous system.

also the radioactive progeny nuclides produced by the decaying of these radionuclides should be considered in pharmacokinetic studies of therapeutic radiopharmaceuticals and dosimetry studies based on these PK studies. Therefore, when designing these studies, the periods of observations or the method of measurement must be selected considering progeny nuclide decay and their half-lives.

2.4 Dosimetry

A single dose of an active ingredient is typically administered to animals, and the organs and tissues throughout the body of both male and female animals are generally assessed for time-integrated radioactivity. It is acceptable to use at least one animal species (animal species exhibits the intended pharmacological activity) for studies. The selection of organs and tissues to be assessed should be scientifically justified. However, the organs to be assessed should include bone marrow (generally greatly affected by radiation), kidneys and the liver (organs of excretion), and male and female reproductive organs, regardless of target binding. In addition, the assessment of urinary and fecal excretions are also recommended as needed.

Activity-time curves in the organs and tissues of animals can be used to estimate the percent administered activity (%ID), residence time, and time-integrated radioactivity in the organs and tissues of humans. See the Glossary (Estimation of human values of activity and residence time in source organs) for examples of the methods used for animal-to-human extrapolations. If any other methods are used, the details and justification of the calculation methods must be described in the final report.

2.5 Toxicology

2.5.1 General Toxicology Studies

Depending on the physicochemical properties and intended pharmaceutical indication of the therapeutic radiopharmaceuticals, studies must be conducted by reference to the ICH M3, ICH S6, and ICH S9 guidelines for the selection of the duration of administration, dose level, and animal species, and the ICH S4 guideline for the study method. Given that the expected pharmacology is cytotoxicity induced by radiation exposure, the significance of determining the non-observed-adverse-effect-level (NOAEL) based on the study results is low. For example, it is also acceptable that the dose levels to enable the appropriate assessment of dose-responsive toxicity of nonradioactive components in a novel active ingredient are selected and planned to determine the tolerability in humans (e.g., $STD_{10}$ and HNSTD). If the potential effects of the decay of radionuclides to be used on human organs and tissues and the safety of unlabeled substances in humans have been well characterized, the significance of conducting general toxicology studies with therapeutic radiopharmaceuticals is considered low. In contrast, if the safety of unlabeled substances in humans has been well characterized, but the safety of radionuclide decays on human organs and tissues has not been well characterized,[6] systemic toxicity and tolerability in humans can be evaluated in general single-dose toxicology studies with therapeutic radiopharmaceuticals[7] in some cases. In addition, if the elements of radionuclides for labeling (including nonradioactive isotopes) and/or unlabeled substances have not been

[6] If a radionuclide with a high level of novelty is used, the scenario in which its biological effects are unknown is assumed.
[7] For study methods, refer to the extended single dose toxicity study (Table 3, Section 7.3, ICH M3).

used clinically as pharmaceuticals, it should be noted that general toxicology studies with nonradioactive components need to be conducted as with the novel active ingredients of pharmaceuticals.

2.5.2 Genotoxicity, Reproductive and Developmental Toxicity, and Carcinogenicity Studies

Since the radiation emitted from therapeutic radiopharmaceuticals causes deoxyribonucleic acid (DNA) damage, it is considered genotoxic and carcinogenic, and has potentially adverse effects on male and female germ cells and fetal development. Thus, no genotoxicity, reproductive and developmental toxicity, or carcinogenicity study is warranted.

2.5.3 Immunotoxicity Evaluation

Adverse immune effects associated with radiation exposure are well known, and the significance of conducting immunotoxicity studies with therapeutic radiopharmaceuticals is low. If the nonradioactive components have the potential effects for the immune system, in addition to adverse immune effects associated with radiation exposure, an evaluation may be required in accordance with the ICH S8 guideline.

2.5.4 Photosafety Evaluation

If the photosafety of unlabeled substances has been well characterized, the significance of conducting a photosafety evaluation with therapeutic radiopharmaceuticals is low. In contrast, if nonradioactive components have not been used clinically as pharmaceuticals in humans, an initial assessment of the phototoxicity potential should be conducted before the conduct of clinical studies in outpatients, and an experimental evaluation should be undertaken before the conduct of phase III clinical studies, if appropriate, with nonradioactive components in accordance with the ICH S10 guideline. Of note, if unlabeled biotechnology-derived pharmaceuticals with only functional role of delivery to the target sites are used, the significance of conducting assessments in accordance with the ICH S6 guideline is low.

2.5.5 Local Tolerance Studies

The assessment of local tolerance is desirable by using the proposed clinically relevant routes of administration as part of general toxicology study, and its assessment in a stand-alone study is not recommended.

2.5.6 Metabolite Characterization

Metabolites should be characterized by reference to the ICH M3, ICH S6, and ICH S9 guidelines, depending on the physicochemical properties and the intended indication of therapeutic radiopharmaceuticals. However, if the radioactive metabolites are different between animals and humans (including significantly different ratios), safety may be affected by a different distribution from that of the active ingredient and thus should be evaluated considering the levels of radiation and the distributions of the active ingredient and its metabolites, and safety should be evaluated in nonclinical studies if it is difficult to evaluate in terms of radiation exposure.

2.5.7 Impurity Assessment

The safety of impurities should be evaluated by reference to the ICH Q3A and Q3B guidelines, depending on the physicochemical properties and the intended indication of the therapeutic radiopharmaceuticals. The impurities produced during the steps of the synthesis of an active ingredient or degradation products present in formulations should be evaluated for safety based on these guidelines. If an active ingredient contains nonradioactive components where safety has been well characterized in toxicology studies with nonradioactive components, no further toxicology study with these components as impurities in accordance with the ICH Q3A and Q3B guidelines is required. In the case of therapeutic radiopharmaceuticals, the significance of conducting genotoxicity evaluations as shown in the ICH Q3A and Q3B guidelines and safety evaluations of mutagenic impurities as described in the ICH M7 guideline is low because radiation exposure induces genotoxicity. For radionuclide impurities different from an active ingredient, safety should be evaluated on the basis of the characteristics of the radionuclide by comparing the level of radiation with the active ingredient. An evaluation in nonclinical studies should be considered if safety is difficult to evaluate in terms of radiation exposure.

2.5.8 Evaluation of Late Radiation Toxicity

Late radiation toxicity is caused by high levels of ionizing radiation onto normal organs and tissues brought by therapeutic radiopharmaceuticals and is generally irreversible. Late-onset radiation toxicity must be evaluated when patients have a long life expectancy that may be affected by the late adverse effects of radiation. The risk assessment can be evaluated through a review of the literature on radiation distribution (obtained from the biodistribution in animals and dosimetry in humans) and late radiation toxicity or the conduct of animal studies. Although the evaluation of late radiation toxicity should be completed prior to the initiation of dose-escalation clinical studies, a phase I clinical study may be initiated before completion of the late radiation toxicity study based on a benefit-risk perspective.

If late radiation toxicity is evaluated in animal studies, both the acute effects (occurring within several weeks after dosing) and late effects (occurring after a long-term period of latency) of radiation should be evaluated using the single animal species used in general toxicology studies by reference to 2.5.1 “General Toxicology Studies.” If general toxicology studies are conducted with an active ingredient, late toxicity can be evaluated by the occurrence of toxicity in recovery groups when an appropriate recovery period is included in the study. In general, the time to the occurrence of late radiation toxicity in animals is considered to be shorter than that in humans, but long-term observation may be necessary, depending on the character of the toxicity observed. Thus, the dosing method and interval, as well as appropriate post-dosing observation period must be planned in consideration of a clinical study strategy. Study methods should be consistent with those for general toxicology studies, and 2.5.1 “General Toxicology Studies” can be a useful reference. Although evaluation of selected target organs is also acceptable, the selection of the target organs must be justified on the basis of the results of distribution and general toxicology studies. Utilization of relevant biomarkers is also acceptable to identify late radiation toxicity. Dose levels for a definitive study must be

selected to ensure that they can identify radiation dose-related late radiation toxicity. In addition, it is also useful to include a nonradioactive component group as a control group, in addition to a vehicle control group, in order to accurately investigate the effects of radiation causing late toxicity or the effects of nonradioactive components.

2.6 Nonclinical Safety Evaluation Required Prior to the Conduct of Phase I Clinical Studies

The required studies must be conducted by reference to the ICH M3, ICH S6, and ICH S9 guidelines, in addition to this guideline, depending on the physicochemical properties and intended indication of therapeutic radiopharmaceuticals. In the case of therapeutic radiopharmaceuticals, a clinical trial can usually be initiated if safety pharmacology, dosimetry, general toxicology, and primary pharmacodynamics studies have been conducted that ensure the validity on the safety or tolerability in humans and the initiation of a clinical evaluation.

2.7 Required Toxicity Evaluation Prior to Marketing Authorization Application

The required studies must be conducted by reference to the ICH M3, ICH S6, and ICH S9 guidelines, in addition to this guideline, depending on the physicochemical properties and intended indication of therapeutic radiopharmaceuticals. Refer to the relevant sections of this guideline for the necessity of the conduct of studies according to the characteristics of therapeutic radiopharmaceuticals.

## 3. Clinical Study Design

3.1 Initial Dose in First-in-human Study

The initial dose of therapeutic radiopharmaceuticals in a first-in-human study must be determined on the basis of the radioactive administered dose (administered radioactivity) and mass dose of an active ingredient. Generally, in the case of therapeutic radiopharmaceuticals, the initial dose should be determined in consideration of the level of radiation exposure mainly based on the result of dosimetry in nonclinical studies because the effects of radiation are dose-limiting toxicities.

3.1.1 Radiation Administered Dose

For the first-in-human dose, the radiation administered dose (radiation per body weight, per body surface area, or the fixed administered activity [Bq]) must be determined on the basis of pharmacokinetic and dosimetry data in animals, the estimated absorbed radiation doses in human organs, and tolerance of normal human organs to radiation. As described in the Glossary and 2.3 “Pharmacokinetics (Biodistribution)”,as well as 2.4 “Dosimetry,” the activity over time in each source organ is extrapolated from animals to humans to obtain the estimated absorbed doses in the human target organs. The radiation dose administered in subjects should be adjusted on the basis of the tolerated absorbed radiation doses in the human organs.

Organ tolerance doses for systemically administered therapeutic radiopharmaceuticals can differ from the tolerance doses for external radiation beams. However, because there currently are no accepted criteria for

organ tolerance doses for internal radiation from therapeutic radiopharmaceuticals in humans, the tolerance doses described in published articles obtained for external beams is used for therapeutic radiopharmaceuticals. Since these values are for external beams, caution should be exercised in extrapolating the data to organ tolerance doses for alpha decay. Because there is a report that results from clinical studies with therapeutic radiopharmaceuticals suggest that tolerance doses of external beams may be conservative,[8] attention should be paid to the potential for changes in the global consensus. For estimating the equivalent dose of alpha-emitting therapeutic radiopharmaceuticals, the absorbed dose with an appropriate value of relative biological effectiveness (RBE) must be calculated. When using organ tolerance dose data generated with external beam radiation, an RBE of 5 is recommended for alpha radiation for the time being, and an RBE of 1 is applied to beta and gamma radiations. Results of dosimetry in subjects can then guide the selection of a reasonably safe therapeutic radiation administered dose.

For dose selection, radiation doses in a specific organ in a biodistribution study can be assessed using data on two related radiopharmaceuticals. Based on clinical study data from one radiopharmaceutical, the initial dose of the other radiopharmaceutical for the assessment of radiation doses in humans can be selected.

3.1.2 Mass Dose

For the first-in-human dose focusing on mass dose, the results of nonclinical studies of nonradioactive components must be considered. If general toxicology studies have been conducted with nonradioactive components, appropriate doses must be determined in terms of safety based on the general toxicology study results by reference to "Guidance for Establishing Safety in First-in-Human Studies during Drug Development" or the concept of ICH S9 guideline for pharmaceuticals for advanced cancer.

3.2 Dose Escalation Scheme and Maximum Dose in Clinical Studies

The ICH E8 guideline, "Guidance for Establishing Safety in First-in-Human Studies during Drug Development," and the concept of ICH S9 guideline (for pharmaceuticals for advanced cancer) should be used as references.

3.3 Concomitant Use of Pharmaceuticals

The ICH E8 guideline, "Guidance for Establishing Safety in First-in-Human Studies during Drug Development," and the concept of ICH S9 guideline (for pharmaceuticals for advanced cancer) should be used as references.

**4. Other Considerations**

4.1 Contraception

To minimize the adverse effects of genotoxicity and reproductive and developmental toxicity of

[8] Bergsma H, et al., Nephrotoxicity after PRRT with $^{177}$Lu-DOTA-octreotate. *Eur J Nucl Med Mol Imaging*. 2016;43(10):1802-1811. Cremonesi M, et al., Correlation of dose with toxicity and tumour response to $^{90}$Y- and $^{177}$Lu-PRRT provides the basis for optimization through individualized treatment planning. *Eur J Nucl Med Mol Imaging*. 2018;45(13):2426-2441.

therapeutic radiopharmaceuticals, a period of contraception during and after completion of treatment is necessary.

As described in the "Guidance on the Need for Contraception Related to Use of Pharmaceuticals," female subjects of childbearing potential need contraception during treatment and then for at least a period of time that equals five effective half-lives after completion of treatment and for an additional six months after the last dose of therapeutic radiopharmaceuticals. In such cases, the safety should be judged in consideration of the half-lives, radiation intensity, and amount produced of the progeny nuclides. In addition, male subjects with a female partner of childbearing potential need contraception during a clinical study and then for at least a period of time that equals five effective half-lives and for an additional three months after the last dose of therapeutic radiopharmaceuticals.

4.2 Lactation

Infants have higher sensitivity to radiation than adults and may exhibit adverse effects at lower exposure dose than adults. Thus, to avoid or minimize exposure to therapeutic radiopharmaceuticals in a nursing child, lactating women must carry out the measure of not breastfeeding during treatment with a therapeutic radiopharmaceutical and, if applicable, for a specific period of time after the last dose. The period during which a woman should not breastfeed should be defined to limit the radiation effective dose to the nursing child to no more than 1 mSv.[9] In addition, the risk of infants on exposure to a nonradioactive component via breast milk should be assessed as per an assessment of conventional prescription drugs.

[9] ICRP Publication 60 (ICRP 1990 recommendation) recommends that protection should be provided to ensure that the public radiation exposure dose limit does not exceed an effective dose of 1 mSv.

**Glossary**

**Radioactivity:** 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 the becquerel (Bq), which is one decay per second.

**Material** (see Table 1)

**Active ingredient:** Refers to a therapeutic radiopharmaceutical molecule that is expected to be approved and contains radionuclides. (1) in Table 1.

**Stable isotopologue:** A material in which a radionuclide contained in an active ingredient is substituted with a stable isotope. (2) in Table 1. Coexists in formulations manufactured using isotope exchange reaction or radionuclide raw materials with low specific activity.

**Unlabeled substance:** A material in which a radionuclide contained in an active ingredient is substituted with a nonradioactive nuclide reaction group, or no nuclide is present. (3) in Table 1. Usually may coexist in formulations manufactured by methods other than isotope exchange reaction. No nuclide is present if a specific metal does not coordinate with a chelating agent.

**Nonradioactive component:** For the purpose of this guideline, a general term for stable isotopologues [(2) in Table 1] and unlabeled substances [(3) in Table 1].

**Dosimetry**: For the purpose of this guideline, dosimetry means measuring and characterizing effects of radiation on organs, including radioactivity or absorbed radiation dose in an organ and its biological effects, after administration of a therapeutic radiopharmaceutical.

**Organ**

**Source organ:** The organ that takes up the therapeutic 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 radioactivity or time-integrated radioactivity (Ã)**: The radioactivity as a function of time in each organ (MBq) that is integrated over time. Radioactivity time curves can be obtained by measurements of radioactivity over time. Cumulated radioactivity is a function of the initial radioactivity $A_0$ (Bq unit) and the residence time $\tau$ (hours).

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

**Estimation of human values of radioactivity 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/body weight ratios, as shown below:

$$\tau\ (\text{human}) = \tau\ (\text{animal}) \times \frac{\text{Organ weight (human)}}{\text{Organ weight (animal)}} \times \frac{\text{Body weight (animal)}}{\text{Body weight (human)}}$$

$$\%\text{ID (human)} = \%\text{ID (animal)} \times \frac{\text{Organ weight (human)}}{\text{Organ weight (animal)}} \times \frac{\text{Body weight (animal)}}{\text{Body weight (human)}}$$

where

%ID (human): the fraction of the administered radioactivity in human organ

%ID (animal): the fraction of the administered radioactivity 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.

**Dose**

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

**Radiation Administered Dose**: The amount of radioactivity administered to animals or to patients and expressed as the unit of radioactivity (e.g., in units of megabecquerel [MBq]).

**Absorbed dose (**D**)**: The ionizing-radiation energy deposited per unit mass of an organ or tissue. The SI unit of absorbed dose is the gray (Gy), where 1 Gy = 1 J/kg.

**Equivalent dose (H):** A measure of biological effect of the radioactive dose that takes into account both the absorbed dose and the biological effectiveness of the radiation and depends on the radiation type. The SI unit is the sievert (Sv).

The equivalent dose is dependent on the relative biological effectiveness (RBE).

$$H\ (Sv) = RBE \times D\ (Gy)$$

**Relative biological effectiveness (RBE):** When a radiation of interest and a reference radiation bring the same biological change, an RBE is a value obtained by dividing the absorbed dose of the former by the absorbed dose of the latter. Usually, the reference radiation used includes X-rays or gamma radiation. This indicates that even the same absorbed dose causes quantitative differences in biological effects, depending on the type of radiation. For therapeutic radiopharmaceuticals, a RBE of 5 is can be assigned to alpha radiation for the time being. This means that alpha radiation shows toxicity that is five times greater than the gamma radiation providing the same absorbed dose (Gy).

**Half-life**

**Biological half-life:** Half-life 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 that takes into consideration both the physical half-life and the biological half-life.

The effective half-life can be obtained by calculation as shown below or obtained experimentally. Based on the physical half-life Tp and biological half-life Tb, the effective half-life Te is calculated as shown in the following formula:

$$1/Te = 1/Tp + 1/Tb$$

Table 1. Types of compounds used in nonclinical studies of therapeutic radiopharmaceuticals

| Classification in this guideline | Active ingredient | Cold pharmaceutical | |
|---|---|---|---|
| Type of compounds | (1) Active ingredient | (2) Stable isotopologue | (3) Unlabeled substance |
| Structure | ●-◇-Ar | ●-◇-As | ●-◇-(Xs) |
| Radionuclide | Contained | Not contained | Not contained |
| Presence in formulations | Present | Absent/present | Present/absent |
| Example: With linker, | ●-◇-$^{90}$Y | ●-◇-$^{89}$Y | ●-◇-(Xs) |
| without linker, | ●-$^{131}$I | ●-$^{127}$I | ●-(Xs) |
| inorganic substance | ◇-$^{89}$Sr | ◇-$^{88}$Sr | — |

●: Molecule that plays a functional role in delivery to target sites (including the absence cases)

◇: Linkers or ion pair in inorganic salt (including the absence cases)

Ar: Radionuclide of Element A

As: Stable nuclide of Element A

Xs: Stable nuclide or reaction group of Element X other than Element A (including the absence cases)

It should be noted that for the purpose of this guideline, linkers contain chelating sites, as needed.

**References**


- ICH Q3A: Partial Revision of the "Guideline for Impurities in New Drug Substances," PFSB/ELD Notification No. 1204001 dated December 4, 2006, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH Q3B: Revision of the "Guideline for Impurities in New Drug Products," PFSB/ELD Notification No. 0703004 dated July 3, 2006, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S3A: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies, PAB/ELD Notification No. 443 dated July 2, 1996, issued by the Director of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
- ICH S4: Revision of the "Guideline for Single and Repeated Dose Toxicity Studies," PAB/NDD Notification No. 88 dated August 10, 1993, issued by the Director of the New Drugs Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
- ICH S4: Partial Revision of "Guideline for Repeated Dose Toxicity Studies," PMSB/ELD Notification No. 655 dated April 5, 1999, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare
- ICH S6 (R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, PFSB/ELD Notification No. 0323-1 dated March 23, 2012, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S7A: Guideline for Safety Pharmacology Studies of Human Pharmaceuticals, PMSB/ELD Notification No. 902 dated June 21, 2001, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S7B: The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, PFSB/ELD Notification No. 1023-4 dated October 23, 2009, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S8: Guideline for Immunotoxicity Studies for Human Pharmaceuticals, PFSB/ELD Notification No. 0418001 dated April 18, 2006, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S9: Guideline for Nonclinical Evaluation for Anticancer Pharmaceuticals, PFSB/ELD Notification No. 0604-1 dated June 4, 2010, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH S10: Guideline for Photosafety Evaluation of Pharmaceuticals, PFSB/ELD Notification No. 0521- 1 dated May 21, 2014, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
- ICH E8 (R1): Revision of the General Considerations for Clinical Studies, PSEHB/ELD Notification No. 1223-5 dated December 23, 2022, issued by the Director of the Pharmaceutical Evaluation Division, the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

・ICH M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, PFSB/ELD Notification No. 0219-4 dated February 19, 2010, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

・Guideline for Nonclinical Pharmacokinetic Studies, PMSB/ELD No. 496 dated June 26, 1998, issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare

・Revision etc. of "Guidance for Establishing Safety in First-in-Human Studies During Drug Development," PSEHB/PED Notification No. 1225-1 dated December 25, 2019, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

・Guidance on the Need for Contraception Related to Use of Pharmaceuticals, PSEHB/PED Notification No. 0216-1, PSEHB Notification No. 0216-1 dated February 16, 2023, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare and Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour

If the ICH guidelines are revised, please see the revised versions.

Guideline Development

FY2023–2024: Evaluation promotion project on radiopharmaceuticals

FY2025: Japan Agency for Medical Research and Development, Research on Regulatory Science of Pharmaceuticals and Medical Devices: "Evaluation of testing requirements for theranostic radiopharmaceuticals" (Principal Investigator: Yoshiro Saito, Director General, National Institute of Health Sciences)

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# Questions and Answers on Guideline for the Nonclinical Studies and the Design of Clinical Studies of Therapeutic Radiopharmaceuticals (Q&A)

2.1 Primary Pharmacodynamics

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|---|---|
| Q1. | For primary pharmacodynamics studies, what types of test systems are assumed in *in vitro* and *in vivo* studies? |

A1. It is assumed that primary pharmacodynamics (and pharmacokinetics and dosimetry for *in vivo* studies) can be evaluated *in vitro* by studies using human cultured cells or others, and *in vivo* by studies using mice grafted with human cancer cells or rheumatoid tissues, or others.

2.3 Pharmacokinetics

| | |
|---|---|
| Q2. | For pharmacokinetic studies, what are the points to consider when selecting and using alternative radionuclides to the radionuclides in an active ingredient of therapeutic radiopharmaceuticals? |

A2. Alternative radionuclides to the nuclides in an active ingredient of therapeutic radiopharmaceuticals should be selected on the basis of the similarity of their element characteristics, and the applicant must justify the substitution.

2.5.7 Impurity Assessment

| | |
|---|---|
| Q3. | Even when a trace mass dose in microgram (μg) units is administered to humans, are the reporting, identification, and safety evaluation of impurities required to be performed? |

A3. Basically, assessments are required to be made. At the same time, for anticancer pharmaceuticals, some assessments and studies may be omitted by reference to the ICH S9 guideline.