Provisional Translation (as of March 2025)*

Considerations for Non-Clinical Studies in the Development of Diagnostic Radiopharmaceuticals (Early Consideration)

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Office of New Drug II

Pharmaceuticals and Medical Devices Agency

1. Introduction

The "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals" (hereinafter referred to as the "Guideline")[1)] has been issued as a general guideline summarizing the non-clinical study items and the planning, implementation, and evaluation methods of clinical studies required for the development of diagnostic radiopharmaceuticals. However, discussions frequently arise regarding the non-clinical study items specified in the Guideline and the timing of their implementation.

The purpose of this document is to make an additional explanation of the contents of the Guideline concerning the non-clinical studies required for the development of diagnostic radiopharmaceuticals. Furthermore, it aims to provide the current regulatory perspective based on newly issued ICH guidelines . It should be noted that the considerations outlined in this document are based on currently available knowledge and may be subject to change as new findings emerge in the future.

2. Considerations for Non-Clinical Studies

2.1 Data on Pharmacological Action

- Safety Pharmacology

According to the Guideline, in principle, safety pharmacology core battery studies should be conducted before the initiation of Phase I clinical studies. However, if the administered dose (total amount of active ingredients and non-radioactive ingredients†) is within the dose range for the microdose studies, this requirement may not be applicable.

When the clinically recommended dose is within the dose range for the microdose studies, the necessity of conducting safety pharmacology core battery studies (including safety pharmacology evaluations as part of toxicology studies) based on the ICH S7A and S7B guidelines[2)-3)] should be evaluated on a case-by-case basis. Considering the following factors, if it can be appropriately demonstrated that there is no impact on the functions of vital organs, omission of these studies may

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

† A collective term for stable isotopologues (a compound in which the radionuclide of the active ingredient is substituted to a stable isotope) and unlabeled substances

be considered. Therefore, consultation with the PMDA on a case-by-case basis is strongly recommended.

- Pharmacological properties of the investigational drug (e.g., properties related to on-target and off-target effects, such as binding specificity and affinity to various receptors, channels, transporters, and enzymes)
- Existing non-clinical safety study and clinical study results
- Clinical usage experience in other countries
- Safety information on related compounds (If extrapolation is deemed appropriate based on structural similarity (e.g., compounds labeled with different radionuclides))

2.2 Data on Absorption, Distribution, Metabolism, and Excretion

- Drug-Drug Interactions

Even for diagnostic radiopharmaceuticals, information on drug-drug interactions is valuable for ensuring appropriate use. Therefore, assessments of potential drug interactions should be conducted in a stepwise manner, considering the stage of development. When evaluating whether an investigational drug can act as a object (affected drug) or precipitant (interacting drug) in *in vitro* studies, the study methods and timing should follow the ICH M12 guideline[4)]. However, if the drug is administered as a single dose in clinical use and is rapidly eliminated from the body, it is not necessarily required to conduct *in vitro* studies to assess its potential to induce drug-metabolizing enzymes.

Additionally, when biologics such as monoclonal antibodies are used as diagnostic radiopharmaceuticals, the risk of pharmacokinetic drug-drug interactions is generally considered lower compared to small-molecule compounds. Since *in vitro* testing methods designed for chemical substances are not generally applicable for biologics, assessments of potential drug interactions should consider the following factors:

- The pharmacological action of the biologic
- Its clearance
- Concomitant medications commonly used in the patient population

By taking these factors into account, the mechanisms of potential drug interactions should be carefully evaluated.

2.3 Data on Acute, Subacute, Chronic Toxicity, Teratogenicity, and Other Toxicity Studies

- Repeated-Dose Toxicity

According to the Guideline, even if the clinical use involves single-dose administration and the clinically recommended dose is within the dose range for the microdose studies, a 4-week repeated-

dose toxicity study (conducted in two animal species, one rodent and one non-rodent) is generally required before submitting a marketing authorization application. However, considering the following factors, it may be acceptable to conduct a shorter-duration repeated-dose toxicity study or an extended single-dose toxicity study in a single species (typically rodents):

- Presence or absence of unexpected safety concerns in existing non-clinical safety study and clinical study results
- Clinical usage experience in other countries
- Safety information on related compounds (If extrapolation is deemed appropriate based on structural similarity (e.g., compounds labeled with different radionuclides))

However, it is important to note that if repeated dosing is planned in clinical use or if the compound has high novelty requiring careful consideration of off-target effects, evaluation using repeated-dose studies in multiple animal species is crucial.

Given these considerations, if toxicity evaluation is conducted without following the repeated-dose toxicity studies recommended in the Guideline, it is strongly recommended to consult with the PMDA before conducting the study to ensure the validity of the study plan.

- Safety evaluation of radiolytic products

Radiolytic products may be produced in large amounts in radiopharmaceuticals between production and administration to patients. The safety of impurities, including radiolytic products, should be evaluated in accordance with the principles outlined in the ICH Q3A, Q3B, and M7 guidelines[5)-7)]. Non-clinical studies using a product with decayed radioactivity may be useful for assessing the safety of impurities.

3. References

1) "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals" (PFSB/ELD Notification No. 0611-1 dated June 11, 2012) https://www.pmda.go.jp/files/000275076.pdf
2) ICH Harmonised Guideline. S7A: Safety Pharmacology Studies for Human Pharmaceuticals (8 November 2000)
3) ICH Harmonised Guideline. S7B: The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (12 May 2005)
4) ICH Harmonised Guideline. M12: Drug Interaction Studies (21 May 2024)
5) ICH Harmonised Guideline. Q3A(R2): Impurities in New Drug Substances (25 October 2006)
6) ICH Harmonised Guideline. Q3B(R2): Impurities in New Drug Products (2 June 2006)
7) ICH Harmonised Guideline. M7(R2): Assessment and Control of DNA Reactive (Mutagenic)

Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (3 April 2023)