Provisional Translation (as of April 2025)[1]

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To: Heads of Prefectural Public Health Bureaus (Departments)

From: Director, Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals

We have compiled a guideline concerning the evaluation methods of non-clinical and clinical studies for diagnostic radiopharmaceuticals conducted for the purpose of drug approval applications. Please inform relevant manufacture and marketing authorization holder under your jurisdiction about the application of this guideline.

Please note that this guideline represents the fundamental concepts based on the current scientific knowledge. It is not intended to mandate strict adherence to the methods described herein, provided that there is a scientifically rational basis that reflects academic progress or other advancements.

[1] This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

(August 13,2012: Partial revision)

Appendix

Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals

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1. Introduction

This guideline outlines general principles regarding the non-clinical study items, planning, conduct and evaluation methods of clinical studies necessary for the development of diagnostic radiopharmaceuticals.

The conduct of non-clinical and clinical studies for pharmaceuticals should, in principle, comply with the guidelines issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and relevant domestic standards and regulations, such as the Ministerial Ordinance on Good Clinical Practice (GCP), issued as Ministry of Health and Welfare Ordinance No. 28 in 1997. However, as described below, diagnostic radiopharmaceuticals. possess characteristics that differ from those of general pharmaceuticals. Therefore, their development must take these specific features into full consideration, and it may not always be appropriate to uniformly apply the standard non-clinical and clinical study methods used for general pharmaceuticals.

In Europe and the United States, guidances on clinical evaluation of diagnostic pharmaceuticals have already been presented, and development of diagnostic radiopharmaceuticals is proceeding in accordance with such guidances. In Japan as well, recognizing the need to establish standard clinical evaluation methods that consider the unique characteristics of diagnostic radiopharmaceuticals, this guideline has been developed.

Diagnostic radiopharmaceuticals are used to visualize and diagnose a wide range of organs and conditions, such as the brain, lungs, heart, bones, kidneys, liver, tumors, and inflammatory diseases. This guideline provides a general framework, but the specific evaluation items, implementation methods, and assessment approaches should be carefully examined according to the disease area targeted by the radiopharmaceutical under development. Furthermore, if there is a reasonable scientific basis that reflects academic advancements or other valid considerations, adherence to the methods described herein is not necessarily required.

2. Characteristics of Diagnostic Radiopharmaceuticals

Radiopharmaceuticals are a category of pharmaceuticals as defined in Article 2, Paragraph 1 of the Pharmaceutical Affairs Law (Law No. 145 of 1960), which emit radiation as specified in Article 3, Item 5 of the Atomic Energy Basic Act (Law No. 186 of 1955). Specifically, they are unsealed compounds containing radioisotopes (hereinafter referred to as "RI") as structural elements, as well as preparations made from such compounds. In this guideline, " diagnostic radiopharmaceuticals." refers to radiopharmaceuticals that are administered to the body for the purpose of clinical diagnosis by detecting photons or positrons[2] emitted from RIs.

The term "clinical diagnosis" in this context refers to one or more of the following:

- Detection of specific diseases or pathological conditions under one or more defined clinical settings
- Evaluation of biochemical, physiological, or molecular biological functions—such as hypo- or hyper-function—that are commonly seen in various diseases or pathological conditions
- Selection of therapeutic strategies for a patient and monitoring of therapeutic response over time

diagnostic radiopharmaceuticals. have the following characteristics:

- Their efficacy is based on the specific accumulation of the compound at the target site and detection of photons emitted from the RI, rather than on the pharmacological action of the compound itself
- In many cases, the administered dose is extremely small, and the likelihood of biological effects is minimal
- They are, in principle, administered as a single dose
- The recommended clinical dosage must be determined with consideration of radiation exposure

[2] The accurate meaning is: radiation emitted from the annihilation of positrons.

3. Non-clinical Studies

3.1 Conduct of Non-clinical Studies

Non-clinical studies are required for the following purposes:

- Screening of drugs effective for the target disease
- Clarification of the characteristics of the drug
- Evaluation of safety prior to human administration
- Investigation of drug interactions
- Collection of information necessary for designing appropriate clinical trials

Before a drug used in clinical trials (hereinafter referred to as an "investigational product") is administered to humans for the first time, non-clinical data related to the product must be thoroughly reviewed in order to predict its efficacy and safety in humans. Data to be reviewed includes the following items (①～⑥). Non-clinical studies should follow appropriate guidelines, such as the "ICH M3(R2): Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" (19 February 2010), and appropriate experimental systems should be selected accordingly. These data must be developed in alignment with the clinical trial phases.

For diagnostic radiopharmaceuticals, non-clinical studies must be conducted appropriately considering their specific characteristics:

- Doses may be expressed in both radioactivity (unit: MBq) and mass (unit: μg). Except for temporal changes in biodistribution, radioactivity decreases over time due to physical half-life, while mass remains constant. The administered dose (radioactivity) can be adjusted based on the time between preparation and administration. Furthermore, since imaging devices that detect photons from RIs are highly sensitive, the investigational diagnostic radiopharmaceuticals are administered in trace amounts of both radioactivity and mass.
- The efficacy is based on specific accumulation of the compound at the target site, rather than on its pharmacological effect.
- In principle, diagnostic radiopharmaceuticals are administered as a single dose.

The notification "Points to Consider for Marketing Authorization Applications for Pharmaceuticals" (PSEHB/PSD Notification No. 0331009, dated March 31, 2005) allows omission of some data related to pharmacological action, acute toxicity, subacute toxicity, chronic toxicity, teratogenicity, and other toxicities when scientifically justified. Additionally, if the administered dose qualifies, the “Guidance for Microdose Clinical Trials” (PSEHB/PSD Notification No. 0603001, dated June 3, 2008) may be applicable. These notifications should be referenced when planning non-clinical and clinical trials.

The data to be reviewed includes:

① Documentation on origin or history of discovery, use in foreign countries, and other information

② Documentation on manufacturing process, specifications, and test procedures

③ Documentation on Stability data

④ Documentation on Pharmacological data

1） Primary pharmacodynamics (*in vitro, in vivo*)

2） Secondary pharmacology and safety pharmacology (See Explanation 1)

3） Other pharmacological data

⑤ Documentation on absorption, distribution, metabolism, and excretion (ADME)

In addition to standard pharmacokinetic information, radiation dosimetry estimates (absorbed dose and effective dose in humans) should be calculated using the results of biodistribution studies in animals before Phase I clinical studies.

Radiation exposure should be evaluated by extrapolating the results of animal biodistribution studies using RI-labeled compounds to humans and estimating the absorbed and effective doses using the MIRD (Medical Internal Radiation Dose) method.

⑥ Documentation on Toxicological data, including acute, subacute, chronic toxicity, teratogenicity, and others

1） Single-dose toxicity

- Maximum tolerated dose may not always be required, but safety must be confirmed at exposure levels significantly higher than the clinical exposure.
- If the administered dose is within the dose range for the microdose studies and no repeated-dose toxicity study has been conducted before Phase I clinical studies, an extended single-dose toxicity study using at least one mammalian species (typically rodents) is required.
- If repeated-dose toxicity studies (2–4 weeks) have been conducted in two mammalian species (one non-rodent) before Phase I clinical studies, usual single-dose toxicity study is sufficient.
- If repeated-dose toxicity studies were conducted in compliance with Good Laboratory Practice (GLP), the single-dose toxicity study need not be GLP-compliant.

2） Repeated-dose toxicity

- If the clinical study is a single-dose trial and an appropriate extended single-dose toxicity study has been conducted, repeated-dose toxicity data before Phase I clinical studies may not be required.
- However, if the total dose is ≤500 μg, with up to five doses and ≤100 μg per dose (each dose <1/100 of NOAEL), a 7-day repeated-dose toxicity study in rodents (one species)

must be conducted.

- For drugs administered as a single dose in clinical practice, a 4-week repeated-dose toxicity study prior to the marketing application is acceptable.
- At the maximum dose safety must be demonstrated at exposure levels significantly higher than clinical exposure.

3） Reproductive and developmental toxicity

Due to radiation risks, diagnostic radiopharmaceuticals should only be administered to pregnant or breastfeeding women if the diagnostic benefit outweighs the radiation risk.

In addition, they are, in principle, administered as a single dose and the administered dose is extremely small, if pathological examination of reproductive organs in extended single-dose or repeated-dose toxicity studies show no abnormalities, and genotoxicity, structure, and distribution pose no reproductive concerns, reproductive and developmental toxicity studies may not be required.

4） Genotoxicity

If sufficient scientific rationale is available, genotoxicity study may not be necessary. However, any test results or structure-activity relationship data must be submitted with the clinical trial notification.

5） Local tolerance

Local tolerance should be evaluated in general toxicity studies.

3.2 Test Substances for Non-clinical Studies

It is not always easy to evaluate the "active ingredient containing RI as a structural element" as the test substance in diagnostic radiopharmaceuticals.

i. For efficacy-supporting studies, secondary pharmacology, and pharmacokinetic studies, the test substance may include:
   - The active ingredient itself
   - A non-radioactive compound with the same structure as the active ingredient
   - A compound labeled with an appropriate radionuclide

ii. For safety pharmacology and toxicity studies, a non-radioactive compound with the same chemical structure as the active ingredient should be used. However, in cases where a non-radioactive compound with the same structure cannot be obtained (e.g., Tc-99m labeled compounds), the ligand before labeling may be used as a substitute for evaluating the safety of the active ingredient.

In addition, if single clinical dose of non-radioactive components exceeds the maximum dose allowed in microdose studies, safety evaluation of those components is recommended.

4. Clinical Evaluation Methods

4.1 Basic Considerations on Evaluation Methods

The efficacy of diagnostic radiopharmaceuticals is demonstrated from two points: the accuracy of the information obtained from the images, and the clinical significance of that information.

The accuracy of the information obtained by the investigational product is validated in phase III clinical studies. This is done by comparing the results of image evaluations with the standard of truth information, expressed by the final diagnosis and disease condition (see section 4.2.4), and evaluating diagnostic performance indicators such as sensitivity and specificity. If obtaining the standard of truth is difficult, accuracy may be estimated based on findings from existing diagnostic technologies, other test results, or clinical follow-up.

If a technique that provides the same type of information as the investigational product already exists, and its clinical significance is well-established, the clinical significance of the information obtained by the investigational product can be inferred from existing medical and pharmacological knowledge. Clinical significance can also be inferred from the results of a comparative study with the existing technique.

The method for demonstrating the clinical significance of information obtained by the investigational product should be thoroughly discussed using appropriate consultation systems during the planning stage of the clinical trial.

4.2 Efficacy Evaluation

4.2.1 Evaluation from Image Findings

For diagnostic radiopharmaceutical images, evaluation is performed based on objective image findings, image interpretation, and subjective image findings. Considering the indications for the investigational product and potential clinical usage scenarios, these findings are set as [primary endpoints] and [secondary endpoints] according to the clinical trial's objectives.

Objective image findings refer to measurable image characteristics such as the target/background ratio, uptake rate, or the size and number of lesions. In this case, factors that could influence the measured values of image findings must be pre-defined, such as how the ROI (Region of Interest) is set or how lesion size is measured. If the clinical significance of objective image findings is clear, they can be used as [primary endpoints], but if further interpretation is needed, they should be considered [secondary endpoints].

Image interpretation refers to the clinical judgment made based on objective image findings, such as the presence of lesions, lesion characteristics (benign/malignant, degree of ischemia, etc.). Image interpretation itself holds clinical significance and can be incorporated as a [primary endpoint] in confirmatory trials.

Subjective image findings refer to the diagnostic confidence perceived by the reader based on their

experience, and can be included as [secondary endpoints] in confirmatory trials.

4.2.2 Image Evaluation by Investigator (Facility Evaluation)

In image evaluation conducted by the investigator at the participating medical institution (facility evaluation), there is a possibility that participant information not specified in the trial protocol may be added, which could introduce bias into the evaluation. Therefore, the results of image evaluation by the investigator are typically considered [secondary endpoints] of efficacy.

4.2.3 Image Evaluation by Third Parties (Blinded Evaluation)

To avoid bias in facility evaluations, blinded image evaluation by a third party is recommended. Diagnostic performance indicators (such as sensitivity and specificity) based on blinded evaluations by a third party should be interpreted carefully, as these results are obtained under different conditions from those in clinical practice.

4.2.3.1 Readers

To ensure objectivity and reproducibility in image evaluation, at least two readers independent of the participating medical institution (preferably three or more) are required. Each reader should perform image evaluation independently from the others.

4.2.3.2 Randomization in Image Evaluation

In third-party image evaluations, to avoid bias due to the order of evaluation, images should be evaluated in a randomized order.

4.2.3.3 Information Disclosure in Image Evaluation

When third-party image evaluations are conducted, any information that could identify the participants on the images should be anonymized. The level and scope of information disclosure should be specified in advance in the clinical trial protocol. The degree of information disclosure in image evaluation can be classified into four categories:

① Complete Blinding: No information is provided to the readers, such as selection/exclusion criteria, patient background (medical history, clinical test results, other image test results, etc.), investigational product information (type and dose of drug administered for each image), or final results (evaluation results based on standard of truth, final diagnosis, patient outcome, etc.).

② Partial Blinding: Information regarding the patient's background necessary for image evaluation is provided, but information on the investigational product administered (type and dose for each image) and final results is withheld.

③ Stepwise Unblinding: The information given to the readers increases gradually, assuming clinical

diagnostic algorithms that may occur in practice. It must be pre-specified in the clinical trial protocol which stage of image evaluation is the primary endpoint.

④ Non-Blinding: All information, except for those that could identify the participants, is provided to the readers.

4.2.3.4 Methods of Image Evaluation

① Individual Image Evaluation: Evaluate the images from the investigational product and those from comparison groups independently.

② Combined Image Evaluation: For example, images from CT and the investigational product, or images from an already approved diagnostic radiopharmaceutical and the investigational product, can be obtained simultaneously (or nearly simultaneously) and evaluated.

4.2.4 Standard of Truth

A standard of truth is an index that can independently evaluate (or is believed to be able to evaluate) the true state of the disease or condition that the investigational product is aiming to assess, and could include the following:

- Test results with confirmed validity
- Follow-up results or clinical outcomes (used as substitutes for the true state at the time of testing)
- A combination of clinical findings and test results

The standard of truth must be carefully selected and should be established independently from the diagnosis by the investigational product. To minimize variability between institutions or readers, the content, timing, and evaluation criteria for the standard of truth should be specified in advance in the clinical trial protocol.

4.2.5 Statistical Analysis

In efficacy evaluation, it is recommended to develop an appropriate statistical analysis plan at the planning stage and clearly state it in the clinical trial protocol.

4.2.5.1 Evaluation of Reliability in Image Evaluation

The reliability of the image evaluation for the investigational product is ensured by obtaining reproducible image evaluation results. (See Explanation 2)

4.2.5.2 Evaluation of Diagnostic Performance

Indicators of diagnostic performance for image diagnostic drugs include sensitivity, specificity,

positive predictive value, and negative predictive value. It is recommended to calculate the confidence intervals for sensitivity and specificity. Positive and negative predictive values are influenced by the prevalence of the disease under diagnosis, so careful interpretation is required.

4.2.5.3 Comparison of Diagnostic Performance

In comparing the diagnostic performance of the investigational product with that of the other diagnostic technique, the consistency between the results of each diagnostic method and the standard of truth is compared. (See Explanation 3)

5. Clinical Studies

In the development of diagnostic radiopharmaceuticals, when multiple diseases are considered for the intended clinical application, separate subject groups are needed for each disease according to the number of applicable diseases. However, in the development of diagnostic radiopharmaceuticals intended to diagnose common pathological, biochemical, physiological, molecular biological, or immunological changes (common factors) across multiple diseases, it may be possible to evaluate multiple diseases together, or to evaluate one representative disease and extend the evaluation results to other diseases. In such cases, it must be proven that common factors exist in multiple diseases, based on established medical knowledge or empirical studies. For diseases other than the representative disease, it is recommended to collect exploratory data from a small number of individual cases in preliminary studies, if possible.

Diagnostic radiopharmaceuticals can usually achieve diagnostic purposes with very small doses (on the order of micrograms or less). As a result, they are typically administered in the lower range of the dose-response curve, making them unlikely to cause dose-dependent adverse events. Therefore, the factors that usually define the dose (radioactive dose) of diagnostic radiopharmaceuticals are radiation exposure to the subject and the optimal imaging time required to obtain high-quality images while the subject remains at rest. Increasing the radioactive dose shortens the imaging time, but it also increases the subject's radiation exposure. By the time of Phase III clinical studies, it is necessary to establish an appropriate dose based on both radiation exposure and imaging time.

The dose, number of doses, and duration of administration of diagnostic radiopharmaceuticals in clinical trials differ from those in conventional clinical trials for therapeutic drugs. Therefore, clinical trials should be designed appropriately, taking these differences into account.

Note: In the following clinical trials, dose and administration amounts are expressed in terms of "radioactive dose."

5.1 Phase I Clinical Studies

5.1.1 Purpose

Phase I clinical studies are the initial phase of clinical development in which the investigational product is administered to humans based on non-clinical data. The primary objectives of Phase I clinical studies are to determine the dosage, safety, pharmacokinetics, absorbed dose, imaging methods, and criteria for image evaluation. Additionally, exploratory objectives may include investigating imaging methods that simulate clinical use.

5.1.2 Investigators and Medical Institutions

The trials should be conducted under the supervision of physicians with adequate knowledge and experience in handling and evaluating radiopharmaceuticals, as well as clinical pharmacologists who are familiar with the field. The medical institution must have the necessary equipment, approval for

the nuclear species used in the trial, and the ability to adequately observe and manage subjects, with sufficient measures in place for emergencies.

5.1.3 Subjects

Pregnant women or those who may become pregnant should be excluded from Phase I clinical studies. For first-in-human trials, refer to the " Guidance for Establishing Safety in First-in-Human Studies during Drug Development" (PFSB/ELD Notification No. 0402-1 dated April 2, 2012). For elderly individuals without severe diseases, refer to the " ICH E7: Studies in Support of Special Populations: Geriatrics" (2 December 1993) and ensure that the trials are conducted with careful consideration.

5.1.4 Study Design

Phase I clinical studies are typically conducted with a single dose. Whole-body imaging is required to assess radiation exposure. Additionally, imaging methods simulating clinical use (e.g., SPECT imaging of target areas) may be explored. This exploration may provide preliminary data for dose setting and imaging data collection conditions for subsequent Phase II clinical studies . The data collected from healthy subjects during Phase I clinical studies can be used to evaluate diagnostic performance in later trials (e.g., Phase II clinical studies) and can help set cutoff values for diagnosis.

5.1.4.1 Dosage and Administration

To avoid unnecessary radiation exposure to subjects, a single dose should be considered. Based on the toxicity test results from non-clinical studies and estimated human absorbed doses, as well as the approved doses of radiopharmaceuticals using the same isotopes, the most appropriate dose should be selected, assuming safety and efficacy.

From the perspective of setting dosage and administration, it is necessary to establish multiple dosage levels. However, in order to minimize radiation exposure to subjects, it is desirable to set as few dosage and administration groups as possible. Therefore, when results from clinical trials in foreign countries are available, the dosage may be selected based on data from those trials regarding safety, absorbed dose, and efficacy.

The dosage obtained from the results of the Phase I clinical study shall be defined as the [dose that can be safely administered based on the Phase I clinical study].

5.1.4.2 Safety

Safety is evaluated based on adverse events detected through appropriate tests and medical examinations conducted before and after the administration of the investigational product. General test and observation items include vital signs (blood pressure, heart rate, respiratory rate, temperature), electrocardiogram, and clinical tests (hematological tests, blood biochemical tests, urinalysis). Based on the results of non-clinical studies or prior clinical studies, additional test items may be considered if necessary.

The timing, frequency, and observation period of medical interviews should be determined

considering the expected mechanism of action and characteristics of the investigational product.

5.1.4.3 Pharmacokinetics and Absorbed Dose

The pharmacokinetics of the active ingredient are clarified by measuring blood concentration over time and calculating pharmacokinetic parameters such as area under the curve (AUC), clearance, volume of distribution, and half-life. Additionally, urine excretion (and fecal excretion, if necessary) should be measured. Based on the organ/tissue radioactivity distribution rate and urinary radioactivity excretion rate obtained from the pharmacokinetic study, the absorbed dose and effective dose for major organs and tissues are calculated using the MIRD method.

5.2 Phase II clinical studies (Exploratory Trials)

5.2.1 Purpose

The main objective of Phase II clinical studies is to confirm the development concept predicted from non-clinical studies in humans and to investigate the appropriate dose and safety for Phase III clinical studies. Additionally, exploratory analysis of Phase II clinical studies results may help establish evaluation items, target patient populations, sample sizes, and diagnostic criteria for Phase III clinical studies.

5.2.2 Investigator and Medical Institutions

Phase II clinical studies should be conducted under the supervision of physicians with sufficient knowledge and experience in handling radiopharmaceuticals and expertise in the relevant disease areas. The medical institution must have the necessary equipment, approval for the nuclear species used in the trial, and the ability to adequately observe and manage subjects, with sufficient measures in place for emergencies.

5.2.3 Subjects

Phase II clinical studies may include patients with various conditions within the target disease population. The primary objective is to estimate the diagnostic performance of the investigational product in preparation for Phase III clinical study design. However, if the Phase Ⅲ clinical studies is expected to include subjects whose diagnosis has not yet been confirmed (e.g., cases suspected of having the target disease based on clinical symptoms), it may be difficult to conduct Phase II clinical studies with similar subjects. In such cases, it is possible to estimate diagnostic performance in a group where abnormalities in the target areas have been confirmed through other diagnostic methods (e.g., tissue diagnosis, imaging, follow-up surveys).

5.2.4 Study Design

5.2.4.1 Dosage and Administration

In Phase II clinical studies, multiple doses should be administered to perform a comparison and determine the appropriate dose. If sufficient data exists for the relationship between the administered radioactive dose, the amount of substance administered, radioactivity distribution, diagnostic image

quality, diagnostic performance, and the primary endpoint of the confirmatory trial, and an appropriate confirmatory hypothesis can be established, it may be possible to assess this relationship without using multiple doses by evaluating images generated using different amounts of acquired data (acquisition counts), because image quality for diagnostic radiopharmaceuticals depends on the number of photons or positrons emitted from the target.

5.2.4.2 Efficacy

To verify the hypothesis of efficacy for Phase III clinical studies, exploratory evaluations of the investigational product's effectiveness should be conducted, including comparisons with existing diagnostic technologies. In general, efficacy should preferably be evaluated using measures of diagnostic performance (sensitivity and specificity) based on a standard of truth, such as pathological findings, clinical outcomes, or follow-up observations.

5.2.4.3 Safety

Safety evaluations should be conducted using common test and observation items such as subjective symptoms, objective findings, vital signs, and clinical tests. If adverse events specific to the investigational drug are identified in prior clinical studies, additional tests or observation items may be added.

5.3 Phase III Clinical Studies (Confirmatory Trials)

5.3.1 Purpose

The primary purpose of Phase III clinical studies is to confirm the hypothesis of efficacy and expand the safety database. The efficacy hypothesis derived from prior studies should be tested in the patient population where the investigational product is expected to be used.

5.3.2 Investigator and Medical Institutions

Investigator and medical institutions should follow the same guidelines as Phase II clinical studies.

5.3.3 Subjects

The subjects for a Phase III clinical study should be a patient population for which the use of the investigational product is anticipated. However, since the drug is a diagnostic pharmaceutical, for example, while a Phase III clinical study may target patients with confirmed diagnoses, post-marketing use may involve patients at the stage where the target disease is suspected based on symptoms, meaning the target patient population may not always align. In such cases, the scientific validity and feasibility of the clinical study should be thoroughly considered, and diagnostic performance can be verified using a population in which abnormalities or normality in the target site or function have been confirmed through other diagnostic methods (e.g., histological diagnosis, imaging, follow-up studies). The target number of subjects for a confirmatory trial should be calculated based on findings from previous studies (e.g., diagnostic performance, detectable differences) using appropriate statistical methods, and should be clearly stated in the clinical study protocol together with the rationale for

setting the number of subjects.

5.3.4 Study Design

5.3.4.1 Dosage and Administration

The dose confirmed in Phase II clinical studies should be used.

5.3.4.2 Comparator

When comparing the investigational product with an existing diagnostic technology, it may be necessary to conduct comparative studies using within-subject or parallel group designs.

These study designs are determined by considering the properties of the drug and the advantages and limitations of each design.

5.3.4.3 Efficacy

Efficacy should be tested based on the hypothesis developed in Phase II clinical studies, using appropriate measures of diagnostic performance (sensitivity, specificity) and third-party image evaluations.

5.3.4.4 Safety

Safety evaluations should follow the same guidelines as Phase II clinical studies.

Explanatory Notes

Explanation 1: Secondary Pharmacology and Safety Pharmacology

Core battery safety pharmacology studies should generally be conducted before Phase I clinical studies. However, if the administered dose is within the dose range for the microdose studies, this requirement may not be applicable.

Explanation 2: Reproducibility of Image Evaluation

To generalize the findings from a study, ensuring reproducibility in image evaluation is crucial. When multiple readers are involved in image assessment, reproducibility is typically expressed in terms of inter-reader consistency. To minimize variability among readers, it is essential to set objective evaluation criteria whenever possible. If needed, reader training may be conducted beforehand.

When multiple readers perform image evaluations, a representative indicator of reproducibility is the inter-reader consistency (for categorical data, the kappa coefficient, and for continuous data, the Intraclass Correlation Coefficient (ICC) are commonly used).

Explanation 3: Statistical Analysis for Diagnostic Performance Comparison

When diagnostic results are assessed using several ordinal scales and multiple thresholds can be set, it is possible to compare the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curve, which is created by varying the thresholds.

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