Provisional Translation (as of May 2026)*

Points to Consider in the Clinical Development of *In Vivo* Diagnostics (Early Consideration)

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Office of New Drug II

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1. Introduction

In vivo diagnostics are medicinal products that are directly administered to the human body, such as via blood vessels, the gastrointestinal tract, the respiratory tract, or subcutaneous tissue, for the purpose of diagnosing or supporting the diagnosis of diseases. These products are broadly classified into radiopharmaceuticals used in nuclear medicine examinations (e.g., PET, SPECT), contrast agents, and functional imaging/diagnostic agents[1)] .

Since no guidelines have been issued that specifically address methods for the clinical evaluation of *in vivo* diagnostics, development strategies are currently considered on a case-by-case basis through individual consultations. Although general principles for the clinical evaluation of diagnostic radiopharmaceuticals are provided in the "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals" (hereinafter referred to as the "Diagnostic Radiopharmaceuticals Guideline")[2)], recent advances in global development including multi-regional clinical trials（MRCTs） and the use of foreign clinical trial data have led to discussions on development strategies that were not originally envisaged in the guideline.

The purpose of this document is to outline fundamental considerations for the clinical development of *in vivo* diagnostics, including diagnostic radiopharmaceuticals, and to supplement the Diagnostic Radiopharmaceuticals Guideline by focusing on issues that are frequently discussed during clinical trial planning. 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. Key Considerations for Overall Development Strategy (Clinical Data Package)

2.1 Basic Principles of Clinical Evaluation

The clinical utility of *in vivo* diagnostics should be demonstrated from the following two perspectives: (1) the accuracy of the obtained information appropriate to the intended purpose of the examination, and (2) the clinical significance of that information.

Points to consider regarding confirmatory trials to demonstrate the accuracy of the obtained

* 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.

information are described in Section 3, while points to consider regarding the policy for explaining clinical significance are described in Section 4.

2.2 Considerations in Formulating Development Strategy

To ensure the timely availability of effective and safe *in vivo* diagnostics in Japan, participation in MRCTs should be considered at an early stage of development, if it is deemed appropriate. When participating in MRCTs, ethnic factors† that may affect diagnostic performance should be considered, based on "Basic Principles on Global Clinical Trials" [3] and related notifications. For *in vivo* diagnostics whose development has progressed ahead overseas, when results from foreign confirmatory trials are already available, it is considered possible to conduct exploratory domestic trials with designs similar to foreign confirmatory trials to confirm that comparable diagnostic performance and safety can be expected in Japanese subjects as non-Japanese subjects. Upon such confirmation, a development strategy may be adopted in which a clinical data package is constructed with the results of the foreign confirmatory trials serving as the primary evidence.

In addition, for diagnostics whose diagnostic principle involves specific accumulation in target sites and for which no other extrinsic or intrinsic ethnic factors affecting diagnostic performance are anticipated, a development strategy relying primarily on foreign confirmatory trial data may also be considered, provided that pharmacokinetic similarity between Japanese and non-Japanese subjects has been confirmed, for example, in Phase I studies. This strategy may be applicable to imaging-based diagnostics such as radiopharmaceuticals used in nuclear medicine examinations (e.g., PET, SPECT) and contrast agents. Even in such cases, evaluating diagnostic performance in Japanese subjects in Phase I or exploratory trials is considered useful for explaining diagnostic performance in the Japanese population. Furthermore, as clinical experience in Japanese medical practice during the development stage is expected to be limited, it is recommended that images obtained in foreign confirmatory trials be evaluated by image readers within a Japanese clinical setting and that, based on the results of these evaluations, training materials for image interpretation and assessment be developed.

It is recommended to consult with PMDA regarding the development plans utilizing foreign confirmatory trial data.

3. Considerations for Confirmatory Trials

3.1 Study Design

When planning confirmatory trials for *in vivo* diagnostics, it is necessary to clearly define the

† Intrinsic ethnic factors: physiological functions (circulatory dynamics, renal function, etc.), distribution and expression levels of target molecules, height and weight, etc.
Extrinsic ethnic factors: diagnostic criteria (including diagnostic algorithms, pathological classification systems), equipment used (including devices, analysis software, and settings), image reading and interpretation methods (including procedures, training content, and proficiency of readers/assessors), surgical techniques (including surgical approach, resection extent, and surgeon proficiency), etc.

intended clinical use of the product (e.g., assessment of patient condition, such as presence/absence of disease or disease staging; identification of the location of tissue or lesions targeted for surgery or biopsy),) and to consider its clinical positioning in comparison with existing diagnostic methods.

If established diagnostic methods provide information comparable to that of the investigational products, a comparative study is recommended. With regard to comparative study design, both within-subject and parallel group designs may be considered, and the choice of study design should be determined by the characteristics of the product. If a comparative study is not feasible, a single arm study evaluating diagnostic performance based on predefined threshold may be acceptable. In such cases, however, the validity of the threshold should be adequately justified based on prior clinical trial results of the product, clinical trial results of established diagnostic methods, and relevant literature.

3.2 Primary Endpoints

In confirmatory trials, it is recommended that diagnostic performance based on the Standard of Truth (hereinafter referred to as the "SOT") be set as the primary endpoint.

The SOT refers to the results obtained by diagnostic methods that are considered capable of evaluating the true disease or pathological condition independently of the investigational Sensitivity and specificity are among the measures used to evaluate diagnostic performance.

product. While the method considered most appropriate at the time may be selected as the SOT, careful consideration should be given to whether it reflects, or reasonably serves as a surrogate for, the true disease or pathological condition.

Sensitivity and specificity are among the measures used to evaluate diagnostic performance. To demonstrate that accurate information regarding diseases or pathological conditions can be obtained, it is generally recommended to set both sensitivity and specificity as primary endpoints. Depending on the intended use of investigational product, however, sensitivity alone may be set as the primary endpoint and specificity evaluated secondarily. For example, when complete detection of lesions is clinically important even if some false positives occur, such as when the product is used to support biopsy or for screening and the final diagnosis is confirmed by existing diagnostic methods, sensitivity alone may be considered as the primary endpoint. In other situations, clinical utility may be demonstrated using primary endpoints other than sensitivity and specificity.

When both sensitivity and specificity are not set as primary endpoints, the appropriateness of the development plan should be discussed with PMDA.

For *in vivo* diagnostics that detect multiple lesions or sites within the same patient, the primary endpoint should be defined on a patient basis or on a lesion/site basis, depending on which approach more directly informs physicians' decision-making in clinical practice. For example, when the

diagnostic objective is to accurately diagnose the patient's overall condition, it is generally appropriate to set patient basis evaluation as the primary endpoint and lesion/site basis evaluation as a secondary endpoint. Conversely, when the objective is to accurately localize target tissues or lesions, it is generally appropriate to set lesion/site basis evaluation as the primary endpoint.

3.3 Image Evaluation

To ensure objectivity and reproducibility in image interpretation, it is appropriate to appoint at least two independent evaluators (three or more is preferable) who are not affiliated with the investigational sites. In cases of discrepant assessments, the final judgment should be determined using an objective method, such as majority voting. Preparation of evaluation manuals and implementation of pre-study training are recommended to reduce variability among evaluators.

4. Considerations for Explaining Clinical Significance

The clinical significance of *in vivo* diagnostics should be explained based on the clinical benefits obtained by individuals undergoing the examination using such diagnostics.

Examples of clinical benefit include enabling more appropriate selection of treatment options and the safe and appropriate performance of surgical procedures through accurate diagnosis of the patient's condition and precise identification of the location of tissues or lesions. The methods for demonstrating these clinical benefits vary depending on the current medical practice system, including the availability of existing diagnostic methods and established treatment options. Where sufficient medical consensus has been established based on clinical guidelines or literature that the use of *in vivo* diagnostics enables optimal treatment selection and facilitates the safe and appropriate performance of surgical procedures, additional clinical trials to demonstrate the clinical benefits of the investigational product may not be necessary. Conversely, if the clinical significance of treatment interventions based on the diagnostic results has not been established in the current treatment algorithm, the clinical utility of such interventions (e.g., improvement in prognosis compared with existing treatments) should be evaluated through clinical trials. Based on the results of these trials, it is necessary to demonstrate the clinical significance of performing the diagnostic examination.

1） Yoshinori Tsukumo, et al. Current Status and Trends of *In Vivo* Diagnostics. RSMP 2019; 9: 5-15

2） "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals" (PFSB/ELD Notification No. 0611-1 dated June 11, 2012) (August 13, 2012: Partial revision)
https://www.pmda.go.jp/files/000275076.pdf

3）"Basic principles on Global Clinical Trials "（PFSB/ELD Notification No.0928010 dated September 28, 2007）
https://www.pmda.go.jp/files/000153265.pdf