Provisional Translation (as of March 2026)*

Points to Consider in the Clinical Development of Radiopharmaceuticals for Positron Emission Tomography Targeting Prostate-Specific Membrane Antigen (PSMA-PET) (Early Consideration)

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Office of New Drug II

Pharmaceuticals and Medical Devices Agency

1. Introduction

Prostate-specific membrane antigen (hereinafter referred to as "PSMA")-targeted positron emission tomography (hereinafter referred to as "PSMA-PET") has been reported to demonstrate superior diagnostic performance for the initial staging and detection of biochemically recurrent prostate cancer compared with conventional imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy[1)-2)]. PSMA-PET is also recommended as one of the major imaging modalities in foreign clinical practice guidelines. The use of imaging methods with higher diagnostic performance is expected to contribute to determining appropriate treatment strategies and, consequently, improving patient prognosis. Against this background, early adoption of PSMA-PET in clinical practice in Japan has been anticipated[3)]; however, at present, no radiopharmaceuticals for PSMA-PET intended for the initial staging and detection of biochemically recurrent prostate cancer have been approved in Japan.

The purpose of this document is to outline considerations for clinical development to facilitate the introduction into Japanese clinical practice of radiopharmaceuticals for PSMA-PET that are approved in Europe and/or the United States, with recommended use in the initial staging and detection of biochemically recurrent prostate cancer.

2. Points to Consider for Clinical Development

As with other *in vivo* diagnostic pharmaceuticals, the clinical performance of radiopharmaceuticals for PSMA-PET should be evaluated by confirming the adequate sensitivity and specificity in their intended clinical use. Therefore, verification of diagnostic performance based on sensitivity and specificity is generally required[4)].

On the other hand, among radiopharmaceuticals for PSMA-PET used for the initial staging and detection of biochemically recurrent prostate cancer in Europe and/or the United States, some have been approved based on exploratory evaluations of sensitivity and specificity. For those products that

* 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.

have been approved overseas, have been on the market for a certain period, and are recommended as one of the major imaging modalities in foreign clinical practice guidelines, it may be considered that a certain level of diagnostic performance has been established through accumulated clinical experience in Europe and/or the United States.

In addition, for radiopharmaceuticals for PSMA-PET, it may be considered acceptable to evaluate the efficacy and safety in Japanese patients primarily based on foreign clinical trial data, provided that no clinically significant differences in pharmacokinetics between Japanese and non-Japanese populations are identified. This consideration is based on the following points:

- In PSMA-PET, PSMA-positive lesions are detected by imaging γ rays emitted from radiopharmaceuticals that are taken up into prostate cancer cells by binding to PSMA, which is highly expressed on prostate cancer cells.
- Except for the availability of PSMA-PET, there are no substantial differences in the clinical framework for prostate cancer between Japan and other countries.

Based on the above considerations, radiopharmaceuticals for PSMA-PET that meet the following criteria may be considered to have the potential to satisfy the requirements for application of the conditional approval system for pharmaceuticals as described in the "Handling of Conditional Approval of Drugs" (PSB/PED Notification No. 0227-6 dated February 27, 2026, issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare; hereinafter referred to as the "Director's Notification"):

- The product has been approved in Europe and/or the United States, has been in use for a certain period since approval, and its standard use in the initial staging and detection of biochemically recurrent prostate cancer can be objectively confirmed based on clinical practice guidelines.
- Based on the results of Phase I studies or equivalent data, it can be confirmed that there are no clear differences in pharmacokinetics between Japanese and non-Japanese populations.
- Agreement has been reached with the Pharmaceuticals and Medical Devices Agency (PMDA) on the clinical trial design intended to verify diagnostic performance.

For consultations regarding the application of the conditional approval system, sponsors are encouraged to utilize the PMDA's consultation in accordance with the Director's Notification. Furthermore, for radiopharmaceuticals for PSMA-PET that meet the above requirements and subject to the conditional approval system, clinical experience in Japanese medical practice during the development stage is expected to be limited. Therefore, it is recommended that images obtained in foreign clinical 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.

3. Others

Radiopharmaceuticals for PSMA-PET are expected to be used not only for initial staging and detection of biochemically recurrent disease but also to support the determination of eligibility for specific medicinal products. However, it is anticipated that it may not be straightforward for medical institutions to selectively use multiple radiopharmaceuticals according to different clinical purposes. Accordingly, for radiopharmaceuticals for PSMA-PET, it is desirable to pursue development as a companion diagnostic in parallel with development for initial staging and detection of biochemically recurrent prostate cancer.

4. Reference

1） National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Prostate Cancer version 5. 2026

2） EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer 2025

3） Clinical Guideline for Prostate Cancer, 2023, Japanese Urological Association, ed.

4） Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals（PFSB/ELD Notification No. 0611-1 Dated June 11, 2012; Partially revised on August 13, 2012, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare）