

Points to Consider for the Development of Companion Diagnostics Developed in Parallel with Anti-cancer Drugs
(Early Consideration)

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Pharmaceuticals and Medical Devices Agency

Office of New Drug V

Office of Software as a Medical Device

Office of In Vitro Diagnostics

1. Purpose and Background

In the development of anti-cancer drugs, *in vitro* diagnostic products or medical devices (hereinafter referred to as "diagnostic products") that detect specific gene mutations or protein expression may be used at the time of drug administration to identify patients who are expected to benefit from the treatment, to identify patients who are at high risk of developing a specific adverse reaction, or to determine the appropriate dosage and administration for individual patients.

The "Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products" (PFSB/ELD Notification No. 0701-10, dated July 1, 2013) provides that, in principle, marketing approval applications for companion diagnostics (hereinafter referred to as "CDx") and their corresponding therapeutic products should be submitted at approximately the same time.¹⁾ However, to align the schedules for development, application, and approval of both, it is essential that the respective developers identify issues at an early stage from the clinical trial planning phase and establish an appropriate development strategy through consultation with the Pharmaceuticals and Medical Devices Agency (PMDA).

This document summarizes the considerations for assessing the necessity of diagnostic products in the administration of anti-cancer drugs and for determining whether such products qualify as a CDx, with respect to diagnostic products being considered in conjunction with the development of anti-cancer drugs. It also outlines practical development considerations, including the timing of consultations with PMDA. It should be noted that the contents of this document are based on the scientific knowledge available to date and may be subject to change based on new information or advances in science in the future.

2. Considerations for Determining the Need for Diagnostic Products and Assessing Whether They Qualify as a CDx

1) Perspectives for Determination and Assessment

In the development of anti-cancer drugs, developers should determine whether a diagnostic product

is needed to identify patients for treatment with the drug, and whether the diagnostic product qualifies as a CDx, considering the following perspectives.

- Whether the diagnostic product is used for identifying patients who are expected to benefit from the anti-cancer drug, optimizing dosage and administration, or determining whether treatment should be discontinued is considered essential for the use of the anti-cancer drug. Note that diagnostic products used for the purpose of diagnosing the target disease or classifying disease types are excluded.
- The relationship between the proteins, genes, etc. to be detected or measured and the mechanism of action of the anti-cancer drug, as well as their biological significance in tumors (contribution to cancer development and progression).
- Whether the use of the diagnostic product is required for patient or dose selection in pivotal clinical trials (e.g., confirmatory trials) of the anti-cancer drug. Note that when both biomarker-positive and biomarker-negative patients can be enrolled in pivotal clinical trials, the necessity of patient selection using a diagnostic product should be carefully determined based on the benefit-risk balance in the overall population, positive population, and negative population, considering the pharmacological mechanism of the anti-cancer drug and other relevant factors.

2) Practical Considerations

- Whether a diagnostic product qualifies as a CDx should be determined based on a comprehensive assessment of the considerations described above. If there is uncertainty regarding CDx qualification, consultation with PMDA should be considered.
- Developers of anti-cancer drugs should assess the need for a CDx from the early stages of development and, where appropriate, share relevant information with developers of diagnostic products. They should also collaborate and coordinate with such developers, considering the timelines for the development, application, and approval of both the anti-cancer drug and the CDx (see Section 4).
- Developers should consider whether the analytical performance and clinical performance of the diagnostic products used in pivotal clinical trials have been appropriately evaluated.
- To enable identification in clinical practice of a patient population comparable to that in which efficacy was demonstrated in the clinical trials, the diagnostic product used in the pivotal clinical trials should be submitted for approval as a CDx; however, if for some reason the diagnostic product used after approval (post-marketing) is expected to differ from that used in clinical trials, developers should consider whether the analytical equivalence between the diagnostic products can be demonstrated based on the results of a concordance study.
- The necessity of an approval application (or a partial change approval application) as a CDx

should also be considered in the following cases.

- Even when a diagnostic product capable of measuring the biomarkers that are the test targets for the anti-cancer drug under development has already been approved, if there is no description regarding use as a CDx for the related anti-cancer drug in the intended use section (the intended use section for *in vitro* diagnostic products, or the intended use or effects section for medical devices).
- When diagnostic products are required to identify the patient population eligible for treatment with a specific medicinal product that must be used in combination with the anti-cancer drug under development.
- When confirmation of specific patient characteristics (genetic factors, etc.) is required to ensure the safe use of the anti-cancer drug.

3. Timing of Consultation with PMDA

Once the need for a CDx has been identified based on the considerations described in Section 2, developers are encouraged to share the development plan with PMDA and seek consultation as early as possible, and no later than the consultation on the proposed design of the pivotal clinical trial. The following information should be included in the consultation materials submitted for the consultation. Depending on the subject matter, consultation should be directed to the appropriate division (Office of New Drug V, Office of Software as a Medical Device, or Office of In Vitro Diagnostics).²⁾

- The rationale for considering a CDx necessary (e.g., the mechanism of action of the anti-cancer drug, tumor biological significance of the target biomarker, efficacy and safety data in biomarker-positive and biomarker-negative patients, proposed data package).
- Details of the diagnostic product planned for the approval application (e.g., assay principle, definition of biomarker positivity in the CDx, including relevant genetic variants or mutations, analytical and clinical performance, regulatory approval status in Japan and overseas, and development status in Japan and overseas).
- The relationship between the diagnostic product used in pivotal clinical trials of the anti-cancer drug and the diagnostic product planned for the approval application (if different, details of the diagnostic product used in pivotal clinical trials should also be provided).

Additionally, if changes may occur in the clinical necessity or positioning of the diagnostic product during development, developers are encouraged to consult PMDA as appropriate.

4. Considerations Regarding Application and Approval Timing

In principle, a CDx should be covered by insurance by the time when the corresponding anti-cancer

drug is listed on the National Health Insurance drug price list (for drugs already listed, by the time of regulatory approval; the same applies hereinafter). Therefore, the development schedule, including the planned timing of the application for the CDx, should be established considering the period required for insurance coverage of the CDx, the (scheduled) timing of the anti-cancer drug's listing on the National Health Insurance drug price list, and the standard review period based on the CDx application category.

In establishing the development schedule, the developers of the anti-cancer drug and the CDx need to closely collaborate to confirm the scheduled approval timing for each, etc. If delays are anticipated relative to the schedule established based on the above considerations, developers should consult PMDA as early as possible.

A notification has been issued regarding cases in which it is difficult to submit a CDx application at approximately the same time as the application for a drug developed in investigator-initiated clinical trials in patients with rare cancer.³⁾

5. References

- 1) Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products (PFSB/ELD Notification No. 0701-10, July 1, 2013)
- 2) Implementation Guidelines for Face-to-Face Consultations, Certification Confirmation Investigations, etc. Conducted by the Pharmaceuticals and Medical Devices Agency (PMDA Notification No. 0303070, March 2, 2012 (last amended May 29, 2026))
- 3) Revision of "Points to consider for application for approval of drugs to be administered based on specific biomarkers that were developed by investigator-initiated clinical trials in patients with rare cancer" (PSB/PED Notification No. 0319-1, PSB/MDED Notification No. 0319-1, March 19, 2024)