Provisional Translation (as of [November 2026])*

Points to Consider for the Development of Companion Diagnostics for Drugs with Efficacy and Safety Demonstrated in Clinical Trials in Which Patients Were Enrolled Using Tests Selected by Clinical Trial Sites
(Early Consideration)

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Pharmaceuticals and Medical Devices Agency
Office of Software as a Medical Device
Office of New Drug V
Office of In Vitro Diagnostics
Companion Diagnostics Working Group

1. Purpose and Background

Progress has been made in the development of drugs used in personalized medicine, and in recent years, their molecular targets have diversified. As a result, patient selection based on particular biomarkers has subdivided the patient population, making target patient populations progressively smaller. This has made randomized controlled trials with adequate power for statistical hypothesis testing within a single country or region difficult to conduct. Therefore, the use of multi-regional clinical trials, which are clinical trials conducted in several countries or regions, is being promoted as a study methodology to ensure the sample size required to demonstrate the efficacy of drugs. In multi-regional clinical trials, when enrolling biomarker-positive patients, a uniform test or central review may be used to increase the homogeneity of patient backgrounds; however, a variety of tests selected and prepared at individual sites or in individual regions (hereinafter referred to as "local laboratory tests (LLTs)") may also be used.

In principle, when companion diagnostics (hereinafter referred to as "CDx") are developed, the CDx planned for development is required to be used for patient enrollment in the pivotal clinical trial (e.g., confirmatory trial) of the drug. If LLTs are used for any reason, it is common practice to collect samples from all enrolled patients wherever possible, subsequently conduct a central review of those samples, and develop, as a CDx, either the test used in the central review or a test confirmed to be concordant with that test. If no central review is conducted, one possible approach is to test samples of all enrolled patients (some samples may be missing if reasonably justified) using the diagnostics planned for

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development and, if a high positive percent agreement with the LLTs is demonstrated, to use those diagnostics as the CDx.

In this case, from the perspective of CDx development, it must be evaluated whether the CDx can be used to aid in identifying patients eligible for treatment with the target drug (i.e., whether it can identify the population in which the efficacy and safety of the drug are expected; hereinafter referred to as "clinical performance"). On the other hand, from the perspective of drug development, if the efficacy and safety of a drug were demonstrated in a relatively heterogeneous population enrolled using LLTs, it could be interpreted that patients may be selected using any test that meets a certain level of analytical performance. From this perspective, the CDx development policy could be streamlined.

This document primarily covers the development of anti-cancer drugs for which patients have been enrolled using LLTs, and summarizes points to consider for the development of CDx. It should be noted that the contents of this document are based on current scientific knowledge and may be subject to change based on new information or advances in science in the future.

2. CDx Development Policy

For drugs intended for personalized medicine targeting specific molecules, a single test is usually used in pivotal clinical trials to enrich the patient population in order to increase the homogeneity of patient backgrounds. In addition, the single test used to enrich the patient population is usually developed as the CDx. When developing a CDx, the appropriateness of the clinical cut-off of the CDx planned for development needs to be explained based on the clinical cut-offs, etc., of the test used to enroll patients during the clinical trial of the drug. The clinical performance of the CDx needs to be evaluated, for example, by confirming analytical concordance between the diagnostics. However, if patients were enrolled using LLTs, the clinical cut-offs, etc., used for enrollment vary, and the drug is administered to a relatively heterogeneous population. If the efficacy and safety of the drug were demonstrated even in such a population, it is considered possible to develop a test similar to the LLTs as a CDx. For example, a subgroup analysis of the efficacy and safety of a drug may be performed for each assay principle of LLTs used in the pivotal clinical trial (e.g., DNA sequencers, PCR, immunohistochemistry). If an assay principle is determined to be acceptable for use in patient selection from the perspective of the efficacy and safety of the drug, it may be possible to submit a marketing approval application (or a partial change approval application) for a test based on that principle without demonstrating concordance with any specific test. However, it needs to be justified that the proposed CDx has a certain level of analytical performance, and information on the LLTs may be used for this justification, if available. In addition, if the clinical trial protocol specifies performance requirements, etc., for the tests such that the enrolled population is homogeneous, it may be necessary to justify that the CDx planned for development meets those requirements.

For drugs that were approved based on a clinical trial that enrolled patients using LLTs, it is desirable

to include information, such as a list of gene mutations detected at enrollment in the clinical trial and a list of gene mutations defined as positive in the protocol, in the package insert of the drug to facilitate the use of CDx by users.
Similar actions can also be taken for approved drugs for which efficacy and safety were demonstrated in populations enrolled using LLTs.

3. Handling of CDx Approved Based on These Points to Consider

Information indicating that direct concordance has not been confirmed between a CDx approved based on these Points to Consider and the test used in the pivotal clinical trial of the corresponding drug is useful for users when selecting a test. Therefore, it is desirable to include such information in the package insert of the CDx.
Tests approved based on these Points to Consider qualify as CDx because they are essential for the use of the drug, in accordance with the definition of CDx in the "Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products" (PFSB/ELD Notification No. 0701-10, dated July 1, 2013).

4. Consultation with the Pharmaceuticals and Medical Devices Agency (PMDA)

When developing CDx using the concept described in Section 2, developers are encouraged to share their development plans with PMDA and seek consultation as early as possible, but no later than the consultation on the proposed design of the pivotal clinical trial. The following information, to the extent available at that time, needs to be included in the consultation materials in addition to the points described in "Points to Consider for the Development of Companion Diagnostics Developed in Parallel with Anti-cancer Drugs (Early Consideration)" (Administrative Notice dated October 5, 2026).
Depending on the subject matter, developers should consult the appropriate office (Office of New Drug V, Office of Software as a Medical Device, or Office of In Vitro Diagnostics).

- Summary and inclusion criteria of the pivotal clinical trial for the drug in development.
- List of enrollment tests that are expected to be used or have been used in the pivotal clinical trial (including product names, assay principles, sample types, number of enrolled patients, etc.).
- Requirements for enrollment tests specified in the clinical trial protocol, etc. (if specific requirements are established).
- Product name, assay principle, sample type, etc., of the CDx planned to be developed concurrently with the drug.