Provisional Translation (as of [November 2026])*

Points to Consider for Concordance Evaluation of Companion Diagnostics Using DNA Sequencers (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

When it is necessary to confirm the status of a specific biomarker using companion diagnostics (hereinafter referred to as "CDx") prior to the administration of a drug, the development of CDx is required in conjunction with the development of the drug ("Notification on Approval Application for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products" (PFSB/ELD Notification No. 0701-10, dated July 1, 2013)). In CDx development, unless the CDx planned for a marketing approval application (hereinafter referred to as "approval application") was used in the pivotal clinical trial (e.g., confirmatory trial) of the drug, concordance between the test used for patient enrollment in the clinical trial (hereinafter referred to as "clinical trial assay (CTA)") and the CDx planned for an approval application needs to be evaluated. In this context, CDx development may become necessary close to the time of the approval application, for example, when efficacy is demonstrated only in the biomarker-positive population, pre-specified as one of the primary analysis populations, in a phase 2 or phase 3 trial that allowed enrollment regardless of biomarker status. In such cases, there is a concern that CDx development may be delayed, resulting in drug lag or drug loss.

In addition, when developing products following an approved CDx (hereinafter referred to as "follow-on CDx"), concordance with the approved CDx that is linked to the clinical trial results of the relevant drug (hereinafter referred to as "original CDx") needs to be evaluated. However, in some cases, such as when the original CDx constitutes one of the test items in cancer genomic profiling, it may be difficult to evaluate concordance between CDx products using samples collected from the same patients at the same time points.

As one approach to addressing the issues described above, this document summarizes the concept of concordance evaluation when the assay principle of the CTA or the original CDx is based on DNA

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sequencers (i.e., next-generation sequencers) and a product that uses a DNA sequencer is being developed as a CDx for an anti-cancer drug. This approach is based on review experience to date with products using DNA sequencers. Since DNA sequencers mainly analyze gene mutations, microsatellite instability, etc., related to cancer, this document mainly covers CDx for anti-cancer drugs that may require confirmation of the relevant biomarker prior to administration. 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. Concept of Concordance Evaluation Between Products Using DNA Sequencers

For products using DNA sequencers, a result is determined to be positive when a gene mutation with a variant allele frequency greater than or equal to the "limit of detection" is detected, and the detected gene mutation meets the "criteria for positivity", such as the list of gene mutations defined for patient enrollment in the pivotal clinical trial of the drug. In other words, the scope of gene mutations determined to be positive by the relevant product (hereinafter referred to as "CDx-positive mutation set") is defined by the "limit of detection" and the "criteria for positivity". The purpose of a concordance study between CDx products is to demonstrate that the CDx under development can identify a population similar to the population that is determined to be positive by the CTA or the original CDx, and in which the efficacy and safety of the drug are expected, that is, to confirm the concordance between CDx-positive mutation sets.

Regarding the "limit of detection" of products using DNA sequencers, coverage in the target region (read depth), uniformity of coverage, the percentage of the region in which a certain level of coverage is obtained, etc., are confirmed as part of the analytical evaluation. On this basis, it can be interpreted that, if the limit of detection is evaluated for a representative gene mutation, other gene mutations would show a generally similar limit of detection. Therefore, by explaining the concordance in the "limit of detection" and the "criteria for positivity" for a representative gene mutation, it may be possible to explain the concordance between the CDx-positive mutation sets without conducting a concordance study.

3. Future CDx Development

1) Direction of Development

As mentioned above, the development of an original CDx may require concordance studies with the CTA, and the development of follow-on CDx has required concordance studies with the original CDx. In the future, for products using DNA sequencers, it may be acceptable to omit concordance studies if the concordance in the "limit of detection" and the "criteria for positivity" can be explained in accordance with the concept described in Section 2. In such cases, it is appropriate to state in the package insert that the product was evaluated based on the concordance in the "limit of detection" and the "criteria for positivity", and that direct concordance with the CTA or the original CDx has not been

confirmed. However, this concept is premised on analytical performance having been ensured. If a CDx is developed for analysis targets or cancer types outside the previously approved scope, a separate evaluation of analytical performance will be required. In cases of particularly high medical need where the detection frequency of the target gene mutation is extremely low and it is difficult to conduct a concordance study, a similar concept may also be applicable to PCR-based tests.

In addition, the concept described in Section 2 is premised on the publication of the "criteria for positivity" and the "limit of detection" (or the clinical cut-off) of the CTA, as well as appropriate information sharing between drug developers and CDx developers. To facilitate CDx development during drug development, it is desirable that information such as the product name, assay principle, and validation results of the CTA used for patient enrollment in the pivotal clinical trial of the drug, as well as the list of gene mutations defined as positive, be made publicly available or that the relevant developers coordinate appropriately.

As another application, the concept described in Section 2 may serve as the scientific basis for the provisional use of cancer genomic profiling or tests used for patient enrollment in clinical trials as CDx, in accordance with "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, dated March 19, 2024).

2) 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 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).

- Assay principle of the CDx planned for an approval application, as well as similarities and differences in principle from the CTA or the original CDx.
- "Limit of detection" and "criteria for positivity" of the CTA or the original CDx based on published information.
- Policy for evaluating concordance in the "limit of detection" and "criteria for positivity".
- Information to be provided to users and CDx developers.