Provisional Translation (as of March 2025) *

Administrative Notice
May 22, 2024

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Pharmaceutical Evaluation Division, Medical Device Evaluation Division, Pharmaceutical Safety Division, and Compliance and Narcotics Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare

Partial revision of "Guidance on Drug-Agnostic Companion Diagnostics"

We have recently received from the Pharmaceuticals and Medical Devices Agency a report on the topic mentioned above as shown in the corresponding attached document. Please inform the relevant industries under your jurisdiction to refer this report in their business operations.

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* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Appendix

PMDA Notification No. 1244
May 15, 2024

To: Director of Pharmaceutical Evaluation Division,
Director of Medical Device Evaluation Division,
Director of Pharmaceutical Safety Division,
Director of Compliance and Narcotics Division,
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Chief Executive
Pharmaceuticals and Medical Devices Agency

Partial revision of "Guidance on Drug-Agnostic Companion Diagnostics"

The guidance regarding the evaluation for eligibility for drug-agnostic companion diagnostics and points to be considered for concepts when developing relevant in vitro diagnostics and drugs is provided in "Guidance on Drug-Agnostic Companion Diagnostics." (PMDA Notification No. 0628013, dated June 28, 2022, issued by the Chief Executive, Pharmaceuticals and Medical Devices Agency; hereinafter referred to as "Guidance").

The Pharmaceuticals and Medical Devices Agency has recently compiled the points to consider in compliance with the Ministerial Order on Quality Management System (QMS) for Medical Devices and In Vitro Diagnostics (Order of MHLW No. 169 of 2004) in the development of drug-agnostic companion diagnostics, etc. and has partially revised the Guidance. Please refer to the following materials.

Old/New Comparison Table

(The underlined parts are revised parts.)

After the revision	Before the revision
3. Points to be considered when changing conventional CDx to drug-agnostic CDx (Omitted) A drug-agnostic CDx should be developed in compliance with the requirements of the Ministerial Order on Quality Management System (QMS) for Medical Devices and In Vitro Diagnostics (Order of the MHLW No. 169 of 2004; hereinafter referred to as the "Ministerial Order on QMS"). To comply with the requirements of the Ministerial Order on QMS, it is necessary to take necessary measures related to design and development, etc. based on the contents of the procedures, records, etc. managed by the marketing authorization holder, manufacturer, etc. who develop the drug-agnostic CDx. In this case, it is necessary to review and verify that the product can be used as aid in identifying the eligible patients for treatment with relevant therapeutic products in accordance with the company's quality management system based on the results of evaluation for eligibility for drug-agnostic CDx, and to take actions such as preparation and storage of records of review and verification in accordance with the procedure. In this process, where therapeutic products requiring identification of the eligible patients are expected to be added to the CDx in the future, design and development or changing the design and development of the drug-agnostic CDx product may be implemented so that it can detect the intended biomarkers, taking into consideration the scope of intended use of	3. Points to be considered when changing conventional CDx to drug-agnostic CDx (Omitted)

the CDx.	

(Attachment 1)

Guidance on Drug-Agnostic Companion Diagnostics

This guidance expounds "Notification on Handling of In Vitro Diagnostics and Medical Device Products aiming Drug-agnostic Companion Diagnostics" (Notification No. 0331-1 dated March 31, 2022, jointly issued by the Director of the Pharmaceutical Evaluation Division, the Director of Medical Device Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau) (hereinafter referred to as the "jointly issued notification") and provides the basic concept of eligibility for "drug-agnostic companion diagnostics" (hereinafter referred to as the "drug-agnostic CDx"), points to be considered when submitting an application for partial change of a conventional companion diagnostics to drug-agnostic CDx, submitting an application for a follow-on product to drug-agnostic CDx, as well as submitting an application for new therapeutic products relevant to drug-agnostic CDx. The purpose of this document is to facilitate development and review of drug-agnostic CDx and relevant therapeutic products.

It should be noted that the following concepts are based on the scientific knowledge at present, and should be reviewed and revised as necessary in accordance with the change of circumstances, advances in science and technology, and accumulation of knowledge in the future.

1. Basic concept of drug-agnostic CDx

According to Article 1 of the jointly issued notification, when multiple companion diagnostics (hereinafter referred to as "CDx") products are approved for the same intended use (i.e. the target disease, biomarkers and specimen type) but for different corresponding therapeutic products, these CDx products could be designated as drug-agnostic CDx, if it is considered scientifically reasonable to use the test results of any of the CDx products interchangeably to be used as aid in identifying the eligible patients for treatment with the other relevant therapeutic products. The basic concept regarding the scientifically reasonable range of interchangeable use could be interpreted as follows, although it should be noted that the concepts in individual cases are determined on a case-by-case basis, taking into consideration the characteristics of the biomarker and assay principle to be analyzed, etc.

A high percentage of concordance to predicate CDx in the equivalence study evaluated at the time of application for approval could be the basis for the validity of interchangeable use noted in the requirement in Article 1 (3) of the jointly issued notification. For CDx that detects multiple variants of a specific gene, it is assumed

that there may be cases in which variants to be detected are not completely the same between products. In such cases, if the equivalence studies using specimens from the typical patient population subject to the corresponding drug demonstrate a high percentage of concordance between CDx products, and the differences between products are recognized only in rare variants that are detected infrequently in the target patients, these CDx products are considered to meet Article 1 (3) of the jointly issued notification.

When multiple CDx products based on the different assay principles (i.e. immuno-histochemical staining, *in situ* hybridization, genetic test using a next-generation sequencer, etc.) are approved as CDx for corresponding therapeutic products with the same indication, it could be assumed that equivalence studies indicate some discrepancies of the test results due to the differences in the assay principles. In such cases, these CDx products could be considered to meet the requirements of Article 1 (3) of the jointly issued notification, if a physician with sufficient knowledge and experience can appropriately identify the eligible patients for the treatment with relevant therapeutic products based on the test guidance provided by the relevant academic societies etc., with the understanding of the characteristics and limitations of the assay principle of each CDx product.

2. Flow of eligibility evaluation for drug-agnostic CDx

The eligibility for drug-agnostic CDx is evaluated based on the following (i) and (ii), which are included in the submitted dossier of each candidate CDx product at the time of regulatory review. Peer-reviewed published papers, demonstrating concordance between approved CDx products, could also be the basis as reference information. The test guidance for CDx developed by the relevant academic societies and opinions from medical experts could also be considered as reference information.

(i) Percentage of concordance in equivalence studies between approved CDx products
(ii) Percentage of concordance in equivalence studies between approved CDx and laboratory validated tests established as a standard method (see Section 3.2. of "Technical Guidance on Development of In Vitro Companion Diagnostics and Corresponding Therapeutic Products" (Administrative Notice dated December 26, 2013))

3. Points to be considered when changing conventional CDx to drug-agnostic CDx

According to the jointly issued notification, when CDx is determined to be eligible for drug-agnostic CDx, the MAHs of the designated in vitro diagnostics products or medical device products are requested to submit an application for partial change to

modify the intended use to the contents which is not limited to identify eligible patients for treatment with a specific therapeutic product. When changing the intended use of conventional CDx to drug-agnostic CDx, the additional precaution statements in the package inserts etc. and risk management based on the assessment report on the eligibility for drug-agnostic CDx are required. Those changes of product design or revalidation of the performance of CDx products should be considered as necessary.

Revision of precautions in the package inserts etc. should be considered from the following perspectives, for example.

- If the test guidance for the target biomarker has been issued by relevant academic societies, health care professionals should follow it.
- It is necessary to caution health care professionals that specific characteristics of the diagnostic products should be fully considered when selecting an assay method and interpreting test results.
- For in vitro diagnostic products, it should be cautioned that the product should be used to identify the eligible patients for the treatment with each relevant therapeutic product, based on thorough knowledge and understanding of the clinical and analytical performance of the product indicated in the package inserts etc. For medical devices, it should be cautioned that the product should be used to identify the eligible patients for treatment with relevant therapeutic products, based on thorough knowledge and understanding of the clinical performance and equivalence study result of the product in the package inserts etc.
- The PMDA website should be referred to in order to confirm which drug-agnostic CDx product could be used as aid in identifying the eligible patients for treatment with relevant therapeutic products.

When developing a drug-agnostic CDx, the requirements of the Ministerial Order on Quality Management System (QMS) for Medical Devices and In Vitro Diagnostics (Order of MHLW No. 169 of 2004; hereinafter referred to as the "Ministerial Order on QMS") shall be complied with. To comply with the requirements of the Ministerial Order on QMS, it is necessary to take necessary measures related to design and development, etc. based on the contents of the procedures, records, etc. managed by the marketing authorization holder, manufacturer, etc. who develop the drug-agnostic CDx. In this case, it is necessary to review and verify that the product can be used as aid in identifying the eligible patients for treatment with relevant therapeutic products in accordance with the company's quality management system based on the results of evaluation for eligibility for drug-agnostic CDx, and to take actions such as preparation and storage of records of review and verification in accordance with the procedure. In this process, where therapeutic products requiring identification of the eligible patients are expected to be added to the CDx in the future, design and

development or changing the design and development of the drug-agnostic CDx product may be implemented so that it can detect the intended biomarkers, taking into consideration the scope of intended use of the CDx.

4. Development of follow-on drug-agnostic CDx products

For the application for follow-on drug-agnostic CDx products, it is acceptable to submit the results of an equivalence study result with one of the products approved as drug-agnostic CDx as a rationale for its clinical performance. In principle, a predicate product with the same assay principle should be selected as reference for the equivalence study. It is possible to develop follow-on products with a novel assay principle as drug-agnostic CDx; however, the acceptance criteria for the percentage of concordance in the equivalence studies should be determined on a case-by-case basis according to the characteristics of the product to be developed and discussed with PMDA in advance.

5. Development of therapeutic products using drug-agnostic CDx to identify the eligible patients

According to the jointly issued notification, if it can be adequately explained that approved drug-agnostic CDx can be used as aid in identifying the eligible patients for treatment with a new therapeutic product, an application for partial change for drug-agnostic CDx is not required in association with the filing of the application of the new therapeutic product. Representative cases in which it is considered possible to use drug-agnostic CDx products as CDx for a new therapeutic product are as follows. In case (1), prior confirmation with PMDA is not required. In cases (2) and (3), it is recommended that the marketing authorization holder of the therapeutic product consults with the Office of New Drug and Office of In Vitro Diagnostics and/or Office of Medical Devices I of PMDA in advance to discuss the strategy of the development and/or the application for approval of the drug.

(1) A product approved as drug-agnostic CDx is used as the clinical trial assay (hereinafter referred to as the "CTA") to identify the subjects to evaluate efficacy and safety of the therapeutic product in the pivotal clinical trial.

(2) An equivalence study has been conducted between the CTA used in the pivotal clinical trial and one of the products approved as drug-agnostic CDx, and the analytical equivalence has been demonstrated between them.

(3) No equivalence study has been conducted between the CTA used in the pivotal clinical trial and drug-agnostic CDx; however, the analytical equivalence between the CTA and drug-agnostic CDx could be explained based on the comparison of the analytical validation reports of the CTA with the published information on the analytical performance of approved drug-agnostic CDx.

(Attachment 2)

Q&A on the "Guidance on Drug-Agnostic Companion Diagnostics"

1. Flow of eligibility evaluation for drug-agnostic CDx

Q1: If it is considered scientifically reasonable to use interchangeably the test results of multiple in vitro diagnostic products approved as complementary diagnostics, is it possible to apply to the same procedures as drug-agnostic CDx for submitting an application for partial change of the intended use to that not to identify patients for the corresponding therapeutic product?

A1: Yes, it is possible.

2. Development of therapeutic products using drug-agnostic CDx to identify the eligible patients

Q2: We are planning to use drug-agnostic CDx as the CDx for a new therapeutic product. Which consultation category should we apply in cases of 5 (2) and (3) of the "Guidance on Drug-Agnostic Companion Diagnostics"?

A2: In cases of 5 (2) and (3) of the "Guidance on Drug-Agnostic Companion Diagnostics," it is acceptable to include the consultation items addressing the appropriateness of a development plan using drug-agnostic CDx in conjunction with other consultation items for a major clinical trial or clinical data package of the therapeutic product. The equivalence study plans of drug-agnostic CDx and CTA and related items are recommended to be consulted on using the category of "CDx development package consultation" of Office of In Vitro Diagnostics and/or the category of "clinical trial necessity consultation" of Office of Medical Device I, in cooperation with the marketing authorization holder of drug-agnostic CDx product, as necessary. The minutes of consultation should be attached to the application dossier for approval of a new therapeutic product.