

Provisional Translation (as of April 2023)\*

Administrative Notice

March 31, 2022

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

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

Questions and answers (Q&A) on Drug-agnostic Companion Diagnostics

"Notification on Handling of In Vitro Diagnostics and Medical Device Products for use of 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) has been issued, whereas "Questions and answers (Q&A) on Drug-agnostic Companion Diagnostics" has been compiled as attached about Q&A on handling of them. Please notify related industries under the jurisdiction of this administrative notice.

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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.

(Attachment)

## Questions and answers (Q&A) on Drug-agnostic Companion Diagnostics

### 1. Scope of the notification

Q1: Are CDx for diseases other than malignant tumors and CDx for detection of biomarkers (hereinafter referred to as "BM") such as circulating tumor DNA (ctDNA) in plasma samples included in the scope of the notification?

A1: Yes.

Q2: IVD products A, B and C are immunostaining kits for the same BM of the same cancer type, and each is approved as a CDx to be used as aid in identifying the eligible patients for treatment with a different corresponding drug. The analytical equivalence A and B have been confirmed, but C does not show equivalence to A and B. In this case, is it possible to designate only A and B to drug-agnostic CDx?

A2: In such a case, A and B are designated to drug-agnostic CDx because they meet all requirements of jointly issued notification 1. The product C is not designated to drug-agnostic CDx because it does not meet the requirements of the jointly issued notification 1. (3).

Q3: If a new therapeutic product is developed for the same specimen type and BM as drug-agnostic CDx but for a new cancer type, is an application for approval of new CDx necessary?

A3: When developing a new therapeutic product for a cancer type that is not included in the intended use of drug-agnostic CDx, it is necessary to develop new CDx and apply for approval. When adding a new cancer type to the specimen types and BMs that have already been approved as drug-agnostic CDx, submit an application for partial change approval of the intended use to add that to be used as aid in identifying the eligible patients for treatment with the corresponding therapeutic product for a new cancer type listed to that already approved as drug-agnostic CDx.

### 2. Procedures for changing conventional CDx to drug-agnostic CDx

Q4: Is it acceptable for a CDx product (including a follow-on product) that has been determined to be designated as drug-agnostic CDx not to submit an application for partial change approval and keep the intended use unchanged as before, if the

marketing authorization holder (hereinafter referred to as "MAH") desires?

A4: It is possible for an MAH to keep the intended use as conventional CDx as before for business reasons etc. However it should be noted that a CDx product which keeps the same intended use as before (hereinafter referred to as "non-compliant CDx") is subject to the following (1) and (2).

(1) Approved drug-agnostic CDx products can be used as aid identifying the eligible patients for treatment with the drug, which is indicated as corresponding drugs to identify the eligible patients in the intended use of the non-compliant CDx.

(2) When submitting new application data for a follow-on product to drug-agnostic CDx, it is acceptable to treat the non-compliant CDx as a predicate of drug-agnostic CDx and use it as a reference in equivalence studies.

Note that CDx that are determined not to be designated as drug-agnostic CDx and corresponding therapeutic products developed using such CDx are not subject to (1) and (2) above.

### 3. Approval application of therapeutic products relevant to CDx

Q5: For an approved therapeutic product using corresponding CDx to identify the eligible patient, is any regulatory application for approval required when corresponding CDx is designated as drug-agnostic CDx? Is it necessary to revise the precautions in the package inserts etc.?

A5: No regulatory application for approval is required. The judgement of necessity for the revision of the precautions in the package inserts etc. and its detail would be announced in the administrative notice to each MAH for requesting for partial change approval of intended use to that of drug-agnostic CDx.

Q6: According to the jointly issued notification, if it can be adequately explained that approved drug-agnostic CDx can be used to identify the eligible patients of a new therapeutic product, an application for partial change approval of drug-agnostic CDx is not required in association with submission of the application of the new therapeutic product. For which part should such an explanation be included in the application dossier?

A6: It should be included in CTD 2.5 and/or 2.7 of submission dossier for application of the drug.