Administrative Notice
July 1, 2013

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

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and answers (Q&A) on CoDx and corresponding therapeutic products

"Notification on Approval Application for *In Vitro* Companion Diagnostics (CoDx) and Corresponding Therapeutic Products" (PFSB/ELD Notification No. 0701-10, Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 1, 2013) have been issued, whereas "Questions and answers (Q&A) on CoDx and corresponding therapeutic products" has been compiled as attached about Q&A on handling of them. Please notify related industries under the jurisdiction of this administrative notice.

(Attachment)

Questions and answers (Q&A) on CoDx and corresponding therapeutic products

Q1

Regarding the definition of CoDx, Section 1 of this Notification states that “A CoDx refers to an *in vitro* diagnostic agent or a medical device that is essential for using the pertinent therapeutic product (except *in vitro* diagnostic agents or medical devices intended simply for disease diagnosis).” What examples are there of such diagnostics?

A1

Whether a diagnostic is classified as a CoDx will be judged individually based on the trial notification, the proposal at the approval application, and the evaluation of necessity of a CoDx by the Pharmaceuticals and Medical Devices Agency (PMDA). For the time being, the judgment will be made based on the following points of view, which will be modified as appropriate based on findings accumulated in the future.

1) The diagnostic is used in the clinical study to judge the appropriateness of administering the therapeutic product or to adjust the dose, etc.

2) It is planned to state in “INDICATIONS AND USAGE,” “DOSAGE AND ADMINISTRATION,” “Precautions for Indications,” or “Precautions for Dosage and Administration” that the pertinent CoDx should be used to judge the appropriateness of administering the therapeutic product and/or to adjust the dose, etc.

For difficult-to-judge cases, it is recommended to consult the PMDA on a case-by-case manner.

Q2

Are *in vivo* diagnostics not included in CoDx?

A2

They should be evaluated individually. It is therefore recommended to consult the PMDA.

Q3

When a diagnostic is essential for administering an approved therapeutic product for the indication newly added

by partial change approval application, will the diagnostic be handled as a CoDx?

A3

Yes. Also, when a marketing authorization holder of a relevant therapeutic product intends to use an approved diagnostic as a CoDx by change or addition of Intended Use / Indications for Use, the marketing authorization holders of the therapeutic product and the pertinent CoDx are recommended to contemporaneously submit partial change approval applications.

Q4

What examples are there of "*in vitro* diagnostic agents or medical devices intended simply for disease diagnosis" described in Section 1 of this Notification?

A4

Examples may include *in vitro* diagnostics that are used for biochemical assays related to organ functions such as serum creatinine, transaminases, and blood glucose level, hematological assays such as prothrombin time kit, bacterial or viral identification and susceptibility tests for infections, as well as tests used to identify the disease, check the treatment effect, assist in follow-up observation, or evaluate the severity in routine clinical practice. However, diagnostics of these types may also be judged as CoDx depending on the clinical necessity, etc. For difficult-to-judge cases, it is recommended to consult the PMDA in advance.

Q5

Section 2 (1) of this Notification states that "If use of the therapeutic product requires patient selection by an unapproved CoDx, application for approval should be made contemporaneously for the pertinent CoDx and the therapeutic product." How much time elapse is considered 'contemporaneous'? What should be done if contemporaneous application is infeasible for an unavoidable reason?

A5

Contemporaneous application is desirable as a general rule. Approval application for a CoDx should be submitted within 1 month after the approval application for the corresponding therapeutic product, at the latest. It is desirable that the applicants of the corresponding therapeutic product and the CoDx cooperate with each other by sharing the development status for the approval application for the CoDx to be submitted at the right time. Delayed application for an unavoidable reason will be judged for its acceptability on a case-by-case basis. It is desirable that the applicant of the pertinent therapeutic product consults the office in charge of the approval review of therapeutic products, etc., in the PMDA at the earliest stage possible.

Q6

Section 2 (2) of this Notification states that “The development status of the pertinent CoDx should be summarized to the extent possible.” Is it only necessary to describe whether the pertinent CoDx is approved or not in and out of the country, the name of the company developing the CoDx, and progress of cooperation on the development?

A6

Yes, it is.

Q7

What points should be considered on the descriptions in the package insert of a CoDx and of a corresponding therapeutic product?

A7

The package insert of a corresponding therapeutic product should contain a clear description that it should generally be used with an approved CoDx in an appropriate place such as “Precautions for Indications”.

The package insert of a CoDx should contain descriptions of the nonproprietary name and the kinds of the corresponding therapeutic product(s). The package insert should also contain a description, as appropriate, that the device should not be used for purposes other than those for using the corresponding therapeutic product.

Q8

What kinds of considerations are necessary in the development stage in order to allow contemporaneous approval application for a therapeutic product and a CoDx?

A8

The applicant of the corresponding therapeutic product should thoroughly investigate necessity/possibility of developing a CoDx at the early stage of therapeutic product development. In order to investigate biomarkers, etc. as necessary, it is useful to consider that biological samples are collected and stored after taking necessary procedures prior to the start of clinical studies, such as obtaining the informed consent of subjects.

Q9

Regarding the PMDA’s review system described in Section 3 (1) of this Notification, in the actual review process, inquiries may be made on the performance of the CoDx during the review of the therapeutic product, or on the clinical utility of the therapeutic product during the review of the CoDx. For contemporaneously submitted products, is it possible to inquire regarding only the applied product by the coordination of concerned offices in the PMDA?

A9

No. The PMDA endeavors to coordinate among related review offices as much as possible. At the same time, in view of the definition and the objective of CoDx, necessary inquiries may be made regarding the CoDx even if it is not the direct subject of the review, in order to confirm the efficacy, safety, and performance of the therapeutic product and the corresponding CoDx. The PMDA encourages that the company developing the therapeutic product and the company developing the CoDx endeavor to coordinate and share necessary information.