

July 1, 2013

To: Directors of Prefectural Health Departments (Bureau)

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

**Notification on Approval Application
for *In Vitro* Companion Diagnostics and Corresponding Therapeutic Products**

With the recent progress of science and technologies, advances are being made in individualized or personalized medical therapy whereby the treatment method for each patient is selected by examining specific genes and proteins expressed in the patient, along with the development of molecularly-targeted drugs based on the expression of specific target molecules. The importance of diagnostics intended for selections of therapeutic products in treatment has been becoming recognized.

In order to facilitate more appropriate development of therapeutic products intended for personalized medical therapy and diagnostics that are companion with them, the guidance for handling of *in vitro* companion diagnostics (CoDx), the use of which for selections of therapeutic products supports personalized medical therapy, and of corresponding therapeutic products has been established as follows. Please inform the relevant industries under your jurisdiction regarding the application of this guidance.

Please also inform that consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) is recommended for specific matters related to individual cases, as appropriate.

1. Definition of CoDx

A CoDx refers to an *in vitro* diagnostic agent or a medical device that is used to improve the efficacy or safety of a specific therapeutic product, is essential for using the pertinent therapeutic product, and corresponds to either of the following (except *in vitro* diagnostic agents or medical devices intended simply for disease diagnosis, etc.).

- (1) An *in vitro* diagnostic agent or a medical device that is used to identify patients who are expected to respond better to a specific therapeutic product.
- (2) An *in vitro* diagnostic agent or a medical device that is used to identify patients who are likely to be at high risk of developing adverse events associated with a particular therapeutic product.
- (3) An *in vitro* diagnostic agent or a medical device that is necessary for optimizing the treatment including dose, schedule, and discontinuation of a particular therapeutic product.

2. Handling of approval application and clinical trial notification for CoDx and corresponding therapeutic products

(1) Points to consider on approval application

- a. 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 in principle. For this purpose, the applicant of the therapeutic product should make every effort to develop the CoDx in its own right or in collaboration with another company engaged in the development of CoDx by sharing the information necessary for the development and approval application.
- b. When both approval applications are submitted contemporaneously for the CoDx and corresponding therapeutic product co-developed as described above, each of the applicants should describe as such in the remarks column of the approval application form.

(2) Points to consider on clinical trial notification

- a. If a CoDx that corresponds to the therapeutic product to be subjected to a clinical trial is being developed, the remarks column of the trial notification of the drug should indicate as such. Also, the developmental status of the pertinent CoDx should be summarized to the extent possible. When the pertinent CoDx is imported by a company other than a sponsor of the clinical trial and needed to be provided to the sponsor after being verified the quality and given the indication, “for clinical trial use” (indication), the remarks column of the clinical trial notification should describe CoDx information such as names (brand names and active substances), quantity and intended use of the pertinent CoDx , and the name and address of the company giving the indication of CoDx .
- b. For medical devices for CoDx that require submission of clinical trial notification, the notification should contain a description that the medical devices are CoDx in the remarks column. The column should also summarize the developmental status of the corresponding therapeutic product to the extent possible. For the details of medical devices that require submission of clinical trial notification, please refer “Handling of the notification of the plan for clinical trial of equipment and devices” (PFSSB/ELD/OMDE Notification

No. 0329-10, dated March 29, 2013).

- c. In case of the description in “a” above, the PMDA or MHLW may ask the company submitting the trial notification about the developmental status of the CoDx.

3. Other

(1) PMDA’s review system

Regarding “2 (1)” above, the CoDx and the corresponding therapeutic product contemporaneously submitted for approval application will be reviewed by the therapeutic product review office and the CoDx review office of the PMDA under adequate mutual coordination. In a similar manner, the review process will be controlled and clinical trial consultation during the development stage will be addressed under the coordination of both offices, as appropriate.

(2) Revision of Japanese notifications *(not available English)*

…*omission*…

(3) Effective date

For therapeutic products for which the corresponding CoDx is under development, the guidance will be applied to the clinical trial notification submitted on or after February 1, 2014.

For other handling, the guidance will be applied to therapeutic products and corresponding CoDx that are submitted for approval application on or after July 1, 2014.

Clinical trial notification or approval application based on this notification is acceptable on or after July 1, 2013.