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Proposal on Maintaining Infrastructure of Companion Diagnostic Agents to Promote Personalized Medicine

Introduction

In order for each individual patient to achieve the best clinical outcome, it is important to select the medical treatment most appropriate for each patient. Today, with the progress of life science, personalized medicine is becoming available which enables the selection of regimens and agents appropriate for each patient by examining patient biomarkers such as genes and proteins before drug administration. Going forward, personalized medicine is expected to spread more and more, leading to improvement in the quality and safety of medical practices as well as effective use of financial medical resources.

To realize personalized medicine in pharmacotherapy, companion diagnostics (hereafter referred to as "CoDx")—drugs which test biomarkers to predict the effect and safety of agents, and optimize dosing—are essential. Our mission as diagnostic agent companies is to collaborate with pharmaceutical companies to develop and market CoDx as *in vitro* diagnostic products and contribute to the promotion of personalized medicine. To provide medical care based on this new concept, the processes of development, clinical evaluation, approval by the pharmaceutical affairs bodies, and entry in the NHI Reimbursement Price List and insurance coverage of new drugs, and *in vitro* diagnostic products needed for those new drugs, must all progress simultaneously so that the pharmaceutical products and CoDx can be provided in clinical settings without delay. However, because there is currently no system linking CoDx development and pharmaceutical products, the expeditious establishment of CoDx development infrastructure is a pressing issue that must be solved in order to promote appropriate use of pharmaceutical products which require CoDx (hereafter referred to as "pharmaceutical product-CoDx") in clinical settings.

We therefore propose the following items for establishing infrastructure related to CoDx approval by the pharmaceutical affairs bodies and insurance reimbursement, which are essential for realizing personalized medicine. In addition, we request the establishment of a setting for continuous exchange of opinions between government and

industry in order to facilitate improvement in the CoDx development/approval review processes.

We hope that this proposal will help to bring about and spread effective and safe medical practices, which will lead to the well-being of each patient.

1. Requirements for regulatory application and CoDx development/approval processes

In order to provide CoDx, which are closely related to the efficacy and safety of pharmaceutical products and, therefore, should as a precondition be used together with the products; we suggest the construction of new development and approval criteria and processes, which are linked to regulatory review of pharmaceutical products, for *in vitro* diagnostic products.

- (1) Constructing framework for the implementation of joint trials (clinical studies) of pharmaceutical products and CoDx

To enable verification of clinical diagnostic efficacy of CoDx simultaneously in a clinical study of pharmaceutical product-CoDx, we propose the construction of a framework that enables collaboration with pharmaceutical companies from the developmental stages of clinical studies, such as consultation.

- (2) Coordinated review and simultaneous approval of *in vitro* diagnostic products and pharmaceutical products

In principle, in the case of pharmaceutical product-CoDx, CoDx would be best developed simultaneously with their corresponding pharmaceutical product and each product would then be approved by the pharmaceutical affairs bodies at the same time. In addition, we propose that the system should be geared to review pharmaceutical products in conjunction with CoDx for greater review efficiency: for example, for CoDx which are developed simultaneously with a pharmaceutical product, the clinical efficacy of CoDx should be reviewed during the pharmaceutical product review; the quality of the reagent and its basic performance should be reviewed during the *in vitro* diagnostic product review.

(3) Development of pharmaceutical requirements including equivalence tests

When an *in vitro* diagnostic product is not developed at the time of pharmaceutical product development, a clinical study of a pharmaceutical product will be performed using an LDT (Laboratory Developed Test^{*}). If an *in vitro* diagnostic product is developed after the pharmaceutical product's development, its equivalence with the LDT used in the clinical study of the pharmaceutical product is given high importance in the application. Therefore, we propose the development of pharmaceutical requirements such as equivalence tests necessary for CoDx review.

* These are tests conducted at laboratories of medical institutions and registered clinical laboratories using techniques developed uniquely on-site. Tests are performed using reagents not approved by the regulatory authorities.

2. Insurance reimbursement for *in vitro* diagnostic products used in CoDx

CoDx will play an important role in the development of personalized medicine. To facilitate CoDx development and appropriate implementation in clinical settings, it is essential that CoDx insurance reimbursement be optimized and that a system be developed in which pharmaceutical products and CoDx can be simultaneously covered by insurance. Current insurance coverage processes differ between pharmaceutical products and specimen tests, which may lead to issues of time lag in insurance coverage timing. In addition, it has been pointed out that the current medical fee payment system for specimen tests does not take into account the technological innovations and developmental efforts of diagnostic agent companies in its evaluation: for example, the current system makes it difficult to directly reflect technologies of *in vitro* diagnostic products and their clinical efficacy on reimbursement pricing, and some genetic testing methods not approved by the pharmaceutical affairs bodies (LDT) are entered on the insurance price list while the fees for unapproved testing methods and approved testing methods are the same.

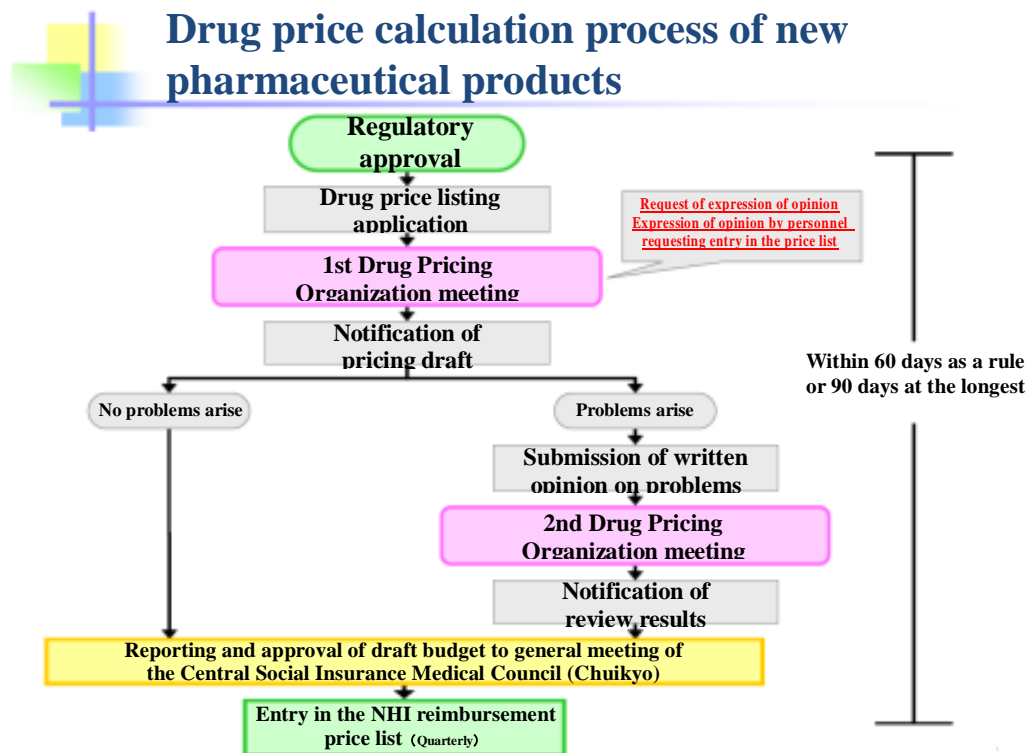
Based on these specimen test-related medical fee payment system issues, we make the following proposals for the promotion of CoDx:

(1) Constructing a CoDx insurance coverage review process that is synchronized with pharmaceutical product review

[1] When the drug price of a pharmaceutical product is listed and marketed, the

CoDx should be simultaneously covered by insurance and marketed. For this purpose, we propose that CoDx insurance coverage be reviewed as part of the same process as the drug price listing of each corresponding pharmaceutical product (see the attached figure), enabling simultaneous insurance coverage after approval by the pharmaceutical affairs bodies.

- [2] We propose that CoDx be subject to quarterly point allocation and item listing similarly to new drugs, instead of the current system of specimen tests, in which new items are listed in conjunction with the biannual medical fee payment revision and points are assigned based on items with similar insurance coverage.



- (2) Establishment of an insurance point allocation system that encourages the development and spread of CoDx which have been approved by the pharmaceutical affairs bodies

- [1] We propose the establishment of a new insurance point allocation system which incentivizes technological innovations in testing and product development, which are not clearly defined in current insurance coverage reviews.

- [2] Regarding CoDx which promote the effective use of pharmaceutical agents and, at the same time, bring about medical economic impacts, we request that the value of economic effects be more accurately reflected in the allocation of insurance points.
- [3] We request the establishment of a system which supports the development and introduction of CoDx approved by the pharmaceutical affairs bodies through the allocation of different amounts of insurance points than those of testing methods not approved by the regulatory authorities. At the same time, we request that unapproved testing methods covered by insurance be immediately removed from insurance coverage when regulatory body-approved *in vitro* diagnostic products of the same nature become covered.