Provisional Translation (as of February 2018) *

PSEHB/PED Notification No. 0915-1
HIB/MED Notification No. 0915-1
September 15, 2017

To: Directors of Prefectural Health Departments (Bureaus)
Directors of the National Health Insurance Departments (Divisions), Prefectural Welfare Departments (Bureaus)
Directors of Latter-Stage Elderly Healthcare Departments (Bureaus), Prefectural Latter-Stage Elderly Healthcare Departments (Bureaus)
Directors of Healthcare Departments, Regional Bureaus (Branches) of Health and Welfare

Director of the Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Director of the Medical Economics Division,
Health Insurance Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Handling of the Optimal Clinical Use Guidelines

The Basic Policy on Economic and Fiscal Management and Reform 2016 (adopted by the cabinet on June 2, 2016) also sets forth a plan to promote the optimal use of innovative pharmaceutical products. In response, the Optimal Clinical Use Guidelines (hereinafter referred to as "the Guidelines") have been prepared in a trial manner, to provide innovative pharmaceutical products to patients who really need them.

Based on the results of this trial, the handling policy for the Guidelines has been developed (see below). Please ensure that related parties are fully informed of this notification.

1. Purpose of the Guidelines

Ensuring the efficacy and safety of pharmaceutical products requires proper use in accordance with their corresponding package inserts. In light of recent scientific advancements having led to the regulatory approval of various innovative pharmaceutical products with novel mechanisms of action, such as antibody therapies, the most urgent priority is to provide access to such products to patients in need. Innovative and extremely high-priced pharmaceutical products have entered markets in recent years. However, the

impact of such products on public financial burden and healthcare costs has become an area of concern. Accordingly, the Basic Policy on Economic and Fiscal Management and Reform 2016 included a plan designed to promote the optimal use of innovative pharmaceutical products.

Innovative pharmaceutical products with novel mechanisms of action are often distinct from existing products in terms of pharmacological effects or safety profile. Therefore, until sufficient efficacy and safety data are gathered, such products should be prescribed only to patients in whom the anticipated benefits of use are substantial, and only at medical institutions capable of taking the necessary countermeasures in case of adverse reactions and that fulfill certain requirements.

In this regard, the Guidelines will be crafted to address pharmaceutical products with novel mechanisms of action, in conjunction with ongoing review for marketing approval and for partial changes to marketing approval conditions (hereinafter collectively referred to as "approval"), to promote the optimal use of such products consistent with the most current scientific data. The Guidelines will establish product use requirements, treatment approaches, and points to consider for both patients and medical institutions.

2. Procedures for designating pharmaceutical products subject to the Guidelines

(1) Preliminary consultation

Prior to submission for approval of a pharmaceutical product meeting any of criteria [1] to [3] (see below), the applicant shall consult the officer in charge of the Guidelines in the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (hereinafter referred to as the "Pharmaceutical Evaluation Division"), Ministry of Health, Labour and Welfare (MHLW), to discuss whether the Guidelines apply to the product in question (products determined to be within the scope of the Guidelines are hereinafter referred to as "Guideline Products.") Consultation may take place during the early stages of product development.

[1] Pharmaceutical products with a mechanism of action that differs from those of existing products available for the target disease
[2] Pharmaceutical products with a mechanism of action that is similar to those of existing products for which Guidelines have already been established
[3] Pharmaceutical products for which Guidelines have already been established as in criteria [1] or [2] above, and for which an application for expansion of indications will be submitted

To request a consultation, please complete and submit the request form (see Attachment) to the Pharmaceutical Evaluation Division. (FAX: 03-3597-9535)

Prior to a request for consultation by an applicant (i.e., an entity intending to submit an application for approval of a pharmaceutical product within the scope of criteria [1] - [3]), the Pharmaceutical Evaluation Division may ask the applicant to explain whether the product in question should be selected as a Guideline Product.

(2) Designation of Guideline Products

A Guideline Product is a drug for which requirements for eligible patients or medical institutions must be defined to ensure efficacy and safety, until sufficient efficacy and safety data can be gathered, pursuant to Section 1 (“Purpose of the Guidelines”).

A pharmaceutical product meeting criterion [1] in Section (1) is designated as a Guideline Product if it has a very large number of target patients and is expected to be used in many medical institutions. A product’s eligibility for classification as a Guideline Product must also be determined based on a comprehensive evaluation with respect to the following criteria:

- Significantly different pharmacological mechanisms/effects from those of existing products
- Significantly different safety profile from that of existing products necessitating special care during use
- Markedly greater efficacy than comparable existing pharmaceutical products
- Different clinical positioning from existing pharmaceutical products and high potential for use by a broader patient population
- Possibility of expanding the eligible population through development of the product for other diseases (e.g. additional indications)

In principle, a pharmaceutical product meeting the criterion [2] or [3] in Section (1) is designated as a Guideline Product because the product or existing products with similar mechanisms of action already have corresponding Guidelines to promote optimal use.

Pharmaceutical products with clearly identified patient eligibility (e.g., drugs used for a specific hereditary disorder) with a small target population are used only by a limited number of medical institutions. Such products are not designated as Guideline Products, because defining requirements for eligible patients or medical institutions by the Guidelines is unlikely to offer benefits.

Products that have been designated as Guideline Products shall be reported to the forthcoming relevant committee of the Pharmaceutical Affairs and Food Sanitation Council.

(3) Notification request for information

The Pharmaceutical Evaluation Division will send a notification to the applicants of products designated as Guideline Products, to request that they provide information to support the development of the Guidelines (hereinafter referred to as “Reference Information”). The applicants will receive the notification between the submission for approval and the receipt of inquiries (i.e., “inquiries before the initial meeting” or “inquiries on key issues [if no initial meeting is held]”) from the Pharmaceutical and Medical Devices Agency (PMDA). The notification will include the following instructions regarding Reference Information.

- Format

- Submission deadline (in principle, within 1 month after receipt of notification)
- Recipient
- Submission procedure

3. Procedures for Guideline development

(1) Submission of Reference Information

The applicants of Guideline Products should submit Reference Information to the recipient by the deadline (both the recipient and the deadline are specified in the notification).

Reference Information should be prepared based on the existing Guidelines, and include the following:

1) Name, non-proprietary name, indication(s), dosage and administration of the Guideline Product; name of the academic society or societies closely related to the product; and the contact person in charge of the submission for approval
2) Characteristics and mechanism of action of the Guideline Product
3) Clinical studies
   - Efficacy and safety data from the pivotal clinical studies (e.g., trials that evaluated the efficacy of the product) should be provided.
   - If any analysis indicates difference in efficacy or safety between subgroups and the overall population, the analysis results should also be provided.
4) Requirements for medical institutions to use the Guideline Product

   From the standpoint of efficacy and safety, information for the following categories should be provided.
   - Requirements for necessary medical care system and examination devices
   - If treating physicians using a Guideline Product are required to have relevant expertise, clarify the expertise.
5) Patients eligible for the Guideline Product

   From the standpoint of efficacy and safety, information for the following categories should be provided.
   - Conditions of patients to whom the product must not be prescribed (contraindications)
   - Conditions of patients to whom the product should be administered with care or for whom other treatment options should be considered first from the perspective of safety
   - Conditions of patients in whom the product has been shown to be effective
   - Conditions of patients unsuitable for treatment with the product because the product has not been shown to be effective in such patients or for other reasons
   - Conditions of patients for whom the necessity of use should be carefully considered
6) Warnings concerning Guideline Product use

(2) Development of the draft Guidelines

Pursuant to Section 1, the Pharmaceutical Evaluation Division will request that relevant academic societies and PMDA review the draft Guidelines for applicable Guideline

Products according to the procedures set forth in Section 2. The review will be conducted from a scientific and clinical standpoint based on the Reference Information.

Relevant academic societies should recommend specialists capable of contributing to the review. A specialist's eligibility to participate in the review will be determined based on an evaluation of any conflicts of interest involving such specialist conducted in accordance with the regulations of the Pharmaceutical Affairs and Food Sanitation Council.

The applicant should promptly respond to any inquiries or requests for additional data from the academic societies or PMDA. In the event of a change in the Reference Information during the review for regulatory approval, the applicant should notify the recipient of the Reference Information of the change without delay.

MHLW will explain the draft Guidelines to the Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as the "Committee on Drugs") and at the general meeting of the Central Social Insurance Medical Council, in order to seek endorsement for the draft Guidelines from the Committee and Council. (The purpose of the Committee on Drugs is to discuss, or receive reports on, whether pharmaceutical products including Guideline Products should be approved for marketing.) However, as for the Guidelines to be prepared because of additional indications (through partial change of the marketing approval), MHLW will submit reports on the Guidelines to the general meeting of the Central Social Insurance Medical Council after the issuance of the Guidelines (see Section (3) below).

The Pharmaceutical Evaluation Division should in principle present the draft Guidelines to the applicant to hear the opinion of the applicant prior to the Committee on Drugs.

(3) Issuance of the Guidelines

The Guidelines should be issued before the Guideline Product is listed in the National Health Insurance drug price list.

Pursuant to the Guidelines, the director of the Medical Economics Division, Health Insurance Bureau, MHLW will issue a notification offering points to consider regarding health insurance coverage as well as items required by the healthcare insurance system to ensure the effectiveness of the Guidelines, the ideal model of insurance coverage from the perspectives of economic efficiency and product characteristics, and the medical judgment of clinicians.

For Guideline Products seeking a change or expansion of indications (through partial change of the marketing approval), the Guidelines and "the notification of points to consider regarding health insurance coverage" in principle will be issued when the expansion or change is approved.

4. Revision to the Guidelines

(1) Timing of revisions to the Guidelines

From time to time, existing Guidelines should be revised in light of most current scientific knowledge, such as when a new dosage form is added, product indications or dosages are modified, the product package insert is revised, or when any other findings that result in a materially different standpoint on optimal use are obtained.

(2) Guideline revision procedures

The manufacturers of pharmaceutical products likely to meet the above (1) should consult the officer in charge of Guidelines in the Pharmaceutical Evaluation Division about revision to the Guidelines.

If revision is required, the Guidelines should be revised in accordance with the procedures specified in Section 3. However, revision due to additional dosage forms, etc. will be processed by MHLW alone if the revision involves no change in the indication, the dosage and administration, or the conditions of eligible patients or medical institutions, or if the revision is associated with change in the precautions in the package insert. In such cases, MHLW will not request relevant academic societies or PMDA to review the draft Guidelines, or submit reports on the Guidelines to the Pharmaceutical Affairs and Food Sanitation Council or the Central Social Insurance Medical Council.

5. Others

Pharmaceutical products submitted for marketing approval on or after September 15, 2017 will be handled in accordance with this notification.

Attachment

Form of Request for Optimal Clinical Use Guidelines Consultation

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
To: Officer in charge of the Optimal Clinical Use Guidelines

Name of company	Name of applicant (names of participants and their departments)
Contact information Tel: ( ) - Fax: ( ) - E-mail:	Preferred consultation dates 1st preference: mm/dd/yyyy, time (AM/PM) 2nd preference: mm/dd/yyyy, time (AM/PM) 3rd preference: mm/dd/yyyy, time (AM/PM)
Proposed brand name and non-proprietary name of the product	
Planned indication(s)	
Summary of the product and target disease(s)	

Note:

1. The request form must be prepared on A4 size paper.
2. The summary of the product and target disease(s) should be specific but brief, and should include the following product information:
    - Structural formula (or definition of biotechnology products)
    - Mechanism of action (comparison with similar existing drugs)
    - Planned indication and dosage and administration
    - Pivotal clinical study results
    - Expected clinical positioning (first discuss the existing treatments for the target disease(s), then compare the product against the treatments)
    - Efficacy and safety characteristics
    - Summary of the target disease(s) and the number of patients (as well as the number of patients eligible for treatment with the product)
    - Future development plan (provide any details concerning plans for additional indications or dosages)
3. If arranging a consultation on your preferred dates is not feasible, the Pharmaceutical Evaluation Division will contact the applicant to resolve scheduling.