PSB/PED Notification No. 1222-6
December 22, 2023

To: Commissioners of Prefectural Health Departments (Bureaus)

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

Partial Revision of "Handling of Designation of Innovative Pharmaceutical products under the SAKIGAKE system"

Designation of innovative pharmaceutical products based on Article 77-2 (2) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as "the Act") has been handled in accordance with "Handling of Designation of Innovative Pharmaceutical Products under the SAKIGAKE system" (PSEHB/PED Notification No. 0831-6 dated August 31, 2020 issued by the Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, hereinafter referred to as the "Notification by Director").

Handling of the designation of innovative pharmaceutical products under the SAKIGAKE system (hereinafter referred to as "SAKIGAKE pharmaceutical products") has been revised as shown in the attached new/old comparison table. We ask you to understand this revision and inform related parties under your jurisdiction of this matter.

The revised Notification by Director is attached for reference.

Appendix

Comparison Table of Revisions to "Handling of Designation of Innovative Pharmaceutical Products under the SAKIGAKE system"

(revised parts are underlined)

New	Old
1. Requirements for designation of SAKIGAKE pharmaceutical products SAKIGAKE pharmaceutical products shall meet all of the following 4 requirements. Even if all of the 4 requirements are met, the following cases will not be designated in principle: • Cases in which an additional indication is intended to be designated for a certain product previously designated as SAKIGAKE pharmaceutical products and the mechanism of action is the same for both the previously designated indication and additional indication. • Cases in which the proposed indication has been already designated under the SAKIGAKE system for other pharmaceutical products with the same mechanism of action. 1) Requirement 1: Innovativeness of therapeutic pharmaceutical products In principle, the therapeutic pharmaceutical product has any of the following features: The mechanism of action is novel and distinct from that of the approved drugs; the therapeutic pharmaceutical product has the same mechanism of action as that of the approved drugs but is planned to be indicated for the target disease for the first time; or the therapeutic pharmaceutical product employs an innovative drug delivery system. <u>The approved drugs include those approved only in foreign countries.</u>	1. Requirements for designation of SAKIGAKE pharmaceutical products SAKIGAKE pharmaceutical products shall meet all of the following 4 requirements. Even if all of the 4 requirements are met, the following cases will not be designated in principle: • Cases in which an additional indication is intended to be designated for a certain product previously designated as SAKIGAKE pharmaceutical products and the mechanism of action is the same for both the previously designated indication and additional indication. • Cases in which the proposed indication has been already designated under the SAKIGAKE system for other pharmaceutical products with the same mechanism of action. 1) Requirement 1: Innovativeness of therapeutic pharmaceutical products In principle, the therapeutic pharmaceutical product has any of the following features: The mechanism of action is novel and distinct from that of the approved drugs; the therapeutic pharmaceutical product has the same mechanism of action as that of the approved drugs but is planned to be indicated for the target disease for the first time; or the therapeutic pharmaceutical product employs an innovative drug delivery system.

4) Requirement 4: Intent and organizational capacity for development and application in Japan ahead of the rest of the world In recognition of the priority placed on early-stage development within Japan, the applicant is required to demonstrate plans to submit the approval application in Japan either earlier than anywhere in the world (countries with the approval system equivalent to that in Japan) or in Japan and the other countries at the same time (submission within 3 months from the date of the world-first submission, which is used as the initial date in reckoning, shall be regarded as simultaneous submission). In addition, the applicant is required to have organizations that can achieve the approval application and respond to inquiries and requests from the expedited approval review, by utilizing the "SAKIGAKE comprehensive assessment consultation" (hereinafter referred to as "SAKIGAKE consultation") provided by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"). It is desirable for therapeutic pharmaceutical products applied for designation to meet both of the following conditions that ensure that progress of development in Japan can be tracked. - First In Human (FIH) study has been conducted in Japan. - Proof Of Concept (POC) study has been conducted in Japan. The applicant of a drug requiring companion diagnostics for its use, if applicable, is required to have organizations that can achieve the approval application of the concerned companion diagnostics in parallel (including a collaborative organization with the other companies).	4) Requirement 4: Intent and organizational capacity for development and application in Japan ahead of the rest of the world In recognition of the priority placed on early-stage development within Japan, the applicant is required to demonstrate plans to submit the approval application in Japan either earlier than anywhere in the world (countries with the approval system equivalent to that in Japan) or in Japan and the other countries at the same time (submission within 30 days from the date of the world-first submission, which is used as the initial date in reckoning, shall be regarded as simultaneous submission. In countries where both the date of submission and the date of receipt of submitted data are in place, the latter date shall be used as the initial date in reckoning). In addition, the applicant is required to have organizations that can achieve the approval application and respond to inquiries and requests from the expedited approval review, by utilizing the "SAKIGAKE comprehensive assessment consultation" (hereinafter referred to as "SAKIGAKE consultation") provided by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"). It is desirable for therapeutic pharmaceutical products applied for designation to meet both of the following conditions that ensure that progress of development in Japan can be tracked. - First In Human (FIH) study has been conducted in Japan. - Proof Of Concept (POC) study has been conducted in Japan. The applicant of a drug requiring companion diagnostics for its use, if applicable, is required to have organizations that can achieve the approval application of the concerned companion diagnostics in parallel (including a collaborative organization with the other companies).

4. Procedure for designation of SAKIGAKE pharmaceutical products 1) Application for designation as eligible product Those who intend to apply for designation of SAKIGAKE pharmaceutical products shall submit the application form using Form 107-2 specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961, hereinafter referred to as "Regulation") and attachment specified in the following 2) to the Pharmaceutical Evaluation Division. In addition, the documents must be submitted in an electronic file in principle.	4. Procedure for designation of SAKIGAKE pharmaceutical products 1) Application for designation as eligible product Those who intend to apply for designation of SAKIGAKE pharmaceutical products shall submit the application form using Form 107-2 specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961, hereinafter referred to as "Regulation") revised by the "Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020)" and attachment specified in the following 2) to the Pharmaceutical Evaluation Division. In addition, documents must be submitted in hard copies (one original copy and 2 duplicate copies) and electronic format by mail or in person. Mail to: 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916 Japan Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Attention: Personnel in charge of designation

PSEHB/PED Notification
No. 0831-6
August 31, 2020
[Partially revised] December 22, 2023

To: Commissioners of Prefectural Health Departments (Bureaus)

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

Handling of designation of Innovative Pharmaceutical Products under the SAKIGAKE system

With the aim of promoting the development of innovative pharmaceutical products, medical devices, and regenerative medical products for their early practical use in Japan ahead of the rest of the world, SAKIGAKE product designation system has been implemented as a pilot system since FY 2015 as provided in “Pilot operation of SAKIGAKE product designation system” (PFSB/ELD Notification No. 0401-6, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (herein after referred to as “MHLW”, dated April 1, 2015).

Since the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019, hereinafter referred to as “Amendment Act”) gave SAKIGAKE product designation system legal force, we have compiled handling principles on designation of innovative pharmaceutical products under the SAKIGAKE system (hereinafter referred to as “SAKIGAKE pharmaceutical products”) stipulated in Article 77-2, Paragraph 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as “Act”) revised by the Amendment Act. We ask you to understand this compilation and inform related parties under your jurisdiction of this matter.

In addition, pharmaceutical products designated by the following previous notifications shall be handled as done before irrespective of this notification: “Pilot operation of SAKIGAKE

product designation system" (PFSB/ELD Notification No. 0401-6 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 1, 2015); "Pilot operation of SAKIGAKE product designation system for drugs (2nd)" (PSEHB/PED Notification No. 1003-1, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated October 3, 2016); "Pilot operation of SAKIGAKE product designation system for drugs (3rd)" (PSEHB/PED Notification No. 1005-1, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated October 5, 2017); "Pilot operation of SAKIGAKE product designation system for drugs (4th)" (PSEHB/PED Notification No. 0907-1, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated September 7, 2018); and "Pilot operation of SAKIGAKE product designation system for drugs (5th)" (PSEHB/PED Notification No. 0906-1, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated September 6, 2019).

Note

1. Requirements for designation of SAKIGAKE pharmaceutical products

SAKIGAKE pharmaceutical products shall meet all of the following 4 requirements.

Even if all of the 4 requirements are met, the following cases will not be designated in principle:

- Cases in which an additional indication is intended to be designated for a certain product previously designated as SAKIGAKE pharmaceutical products and the mechanism of action is the same for both the previously designated indication and additional indication.
- Cases in which the proposed indication has been already designated under the SAKIGAKE system for other pharmaceutical products with the same mechanism of action.

1) Requirement 1: Innovativeness of therapeutic pharmaceutical products

In principle, the therapeutic pharmaceutical product has any of the following features: The mechanism of action is novel and distinct from that of the approved drugs; the therapeutic pharmaceutical product has the same mechanism of action as that of the approved drugs but is planned to be indicated for the target disease for the first time; or the therapeutic pharmaceutical product employs an innovative drug delivery system. The approved drugs include those approved only in foreign countries.

2) Requirement 2: Seriousness of target diseases

The target diseases shall meet any of the following conditions.

- Serious life-threatening disease
- Disease with persistent symptoms (giving difficulty in living in society) without any radical treatment available

3) Requirement 3: Prominent efficacy in treatment of the target disease

No approved drugs available; or significantly improved efficacy or safety is expected compared with the existing therapeutic drugs/therapies. For drugs expected to have significantly improved efficacy, at least the efficacy in humans shall be suggested by exploratory clinical trials irrespective of location of the trial (in or outside Japan).

4) Requirement 4: Intent and organizational capacity for development and application earlier in Japan ahead of the rest of the world

In recognition of the priority placed on early-stage development within Japan, the applicant is required to demonstrate plans to submit the approval application in Japan either earlier than anywhere in the world (countries with the approval system equivalent to that in Japan) or in Japan and the other countries at the same time (submission within 3 months from the date of the world-first submission, which is used as the initial date in reckoning, shall be regarded as simultaneous submission.). In addition, the applicant is required to have organizations that can achieve the approval application and respond to inquiries and requests from the expedited approval review, by utilizing the “SAKIGAKE comprehensive assessment consultation” (hereinafter referred to as “SAKIGAKE consultation”) provided by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”). It is desirable for therapeutic pharmaceutical products applied for designation to meet both of the following conditions that ensure that progress of development in Japan can be tracked.

- First In Human (FIH) study has been conducted in Japan
- Proof Of Concept (POC) study has been conducted in Japan.

The applicant of a drug requiring companion diagnostics for its use, if applicable, is required to have the organizations that can achieve the approval application of the concerned companion diagnostics in parallel (including a collaborative organization with the other companies).

2. Method of designation of SAKIGAKE pharmaceutical products

Designation of SAKIGAKE pharmaceutical products shall be made on the opinion of the Pharmaceutical Affairs and Food Sanitation Council. For the time being, designation shall be conducted approximately twice a year (around April and October), and the frequency is subject to change depending on the situation of review system. Ad hoc designation may be conducted if required from a viewpoint of public health. For the designated SAKIGAKE pharmaceutical products, the following information shall be posted on the MHLW website: Date of designation, name of the pharmaceutical product, target disease as well as name and address of the applicant.

3. Consultation for designation of SAKIGAKE pharmaceutical products

Those who intend to apply for designation of SAKIGAKE pharmaceutical products shall consult personnel in charge of designation in the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (hereinafter referred to as “Pharmaceutical Evaluation Division”) beforehand.

4. Procedure for designation of SAKIGAKE pharmaceutical products

1) Application for designation as eligible product

Those who intend to apply for designation of SAKIGAKE pharmaceutical products shall submit the application form using Form 107-2 specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961, hereinafter referred to as “Regulation”) and attachment specified in the following 2) to the Pharmaceutical Evaluation Division. In addition, the documents must be submitted in an electronic file in principle.

2) Attachment for the application form

Documents attached to the application form are specified in the provisions in Article 251-2, Paragraph 2 of the Regulation, and the specific contents are as follows: In addition, submission of the other document may be requested where necessary.

A Documents on the mechanism of action or principle

B Documents on medical needs, including

(a) Information on the target disease such as disease pathogenesis and symptoms

(b) Information on current status of medical care such as availability of similar drugs and therapies

C Summary of study results on toxicity and pharmacological effects

D Summary of clinical trial results

E Overview of development plan in Japan and foreign countries

F Summary of the drug applied for designation

Summary prepared in accordance with Annex Form as a document for explanation at the Committee and for announcement

5. Priority handling of designated SAKIGAKE pharmaceutical products and points to consider

1) Priority consultation

Because the designated SAKIGAKE pharmaceutical products can be given priority over those of the other drugs in consultations at the PMDA, the person who has received designation for the concerned product in accordance with provisions in Article 77-2, Paragraph 2 of the Act (hereinafter referred to as “designation holder”) shall consult the PMDA for the schedule.

2) Enhancement with prior assessment

The SAKIGAKE consultation at the PMDA is available for the designated SAKIGAKE pharmaceutical products. To complete the regulatory process from approval application to approval within 6 months, the concerned consultation service should be actively utilized even before the application. In principle, the SAKIGAKE consultation in all the consultation categories shall be utilized from receipt of the designation to the approval application by consulting the concierge in 4).

- Especially, for the quality issues, the designation holder shall actively utilize the consultation service such as the SAKIGAKE consultation and quality consultation for drugs to ensure that GMP inspection can be conducted immediately after the approval application. In addition, the designation holder shall obtain information on timing of submission of validation data at a commercial scale and available dates for GMP inspection by the approval application.
- Furthermore, for GLP/GCP/GPSP inspections, the designation holder shall actively utilize the consultation service such as the SAKIGAKE consultation and obtain information necessary for such an assessment at an early stage to ensure prompt scheduling and implementation of on-site inspection.

Although the process from approval application to approval is targeted to be completed within 6 months, if the prior assessment by the above SAKIGAKE consultation is not adequate, the period of the process may be individually set according to the assessment status of the pharmaceutical product.

3) Priority review

As specified in Article 14, Paragraph 8 of the Act, the designated SAKIGAKE pharmaceutical product is subject to priority review.

4) Concierge

PMDA personnel designated as a person appropriate for liaison and coordination between the MHLW and the PMDA (hereinafter referred to as “concierge”) shall be engaged in a consultation for development progress management of the concerned product and coordination with the applicant and department/ divisions related to approval review. Soon after designation, the concierge in charge of the concerned product shall communicate with the designation holder.

6. Discontinuation of studies/researches, etc.

If the designation holder intends to discontinue studies/researches, marketing, or manufacturing of the designated SAKIGAKE pharmaceutical product, the designated holder shall promptly submit an appropriate notification to the Minister of Health, Labour and Welfare based on provisions in Article 77-5 of the Act.

In addition, the notification of discontinuation shall be submitted in Form 108 of the Regulation.

7. Rescindment of designation

When receiving the notification of discontinuation pursuant to the provisions of Article 77-5 of the Act, the Minister of Health, Labour and Welfare rescinds the designation based on provisions in Article 77-6, Paragraph 1 of the Act.

In accordance with Paragraph 2 of the same article, the designation may be rescinded in any of the following cases.

When revoking the designation, Pharmaceutical Evaluation Division shall report to the Pharmaceutical Affairs and Food Sanitation Council and post it on the website of the Ministry of Health, Labour and Welfare as done in the above 2.

1) The requirement 1 or 2 for designation is no longer met because another drug, etc. has been approved in Japan earlier than the designated SAKIGAKE pharmaceutical product.
2) Prominent efficacy is not expected based on results, etc. of confirmatory clinical trials, and it is considered that the requirement 3 for designation is no longer met.

3) For the designated SAKIGAKE pharmaceutical product, the designation requirement 4 is deemed to be no longer met because of either of the following cases:
   - An approval application is not submitted in Japan ahead of other countries or at the same time.
   - Early development in Japan is unlikely to be achieved because an approval application is submitted without undergoing adequate prior assessment or the submitted documents are found considerably defective.

4) When the designated SAKIGAKE pharmaceutical product has been approved outside Japan before approval in Japan.

5) When unlawfulness such as false descriptions in the application for designation is found.

6) When studies/researches or marketing of the designated SAKIGAKE pharmaceutical product is not conducted without any legitimate grounds.

7) When the designation holder has violated the Act or other pharmaceutical laws and regulations specified by Cabinet Order, or any of the dispositions thereupon.

8. Succession

If the designated holder transfers the development right in Japan to others (hereinafter referred to as “successor”), the designated holder shall submit the notification of discontinuation of studies/researches in accordance with 6, and the successor shall submit the application form in 4 (1) and document in (2) F. However, if the contents of the documents have been changed since the time when the designation holder receives the designation, data that show that the changes satisfy the requirements at the time of succession shall also be submitted. Succession is approved with the letter of designation that is separately issued.

Designation holders who consider succession shall consult the Pharmaceutical Evaluation Division in advance. In so doing, the designation holders shall also submit a copy of the contract for succession and document that explain the background of succession.

9. Others

If it becomes necessary to consider the development of companion diagnostics (in vitro diagnostics or medical devices) to improve the efficacy or safety of the SAKIGAKE pharmaceutical products, the designation holder shall consult the concierge promptly about this matter because necessary actions may be taken on the concerned diagnostics (including designation as SAKIGAKE pharmaceutical products) as well to prevent delay of development and approval of the designated product.

10. Date of enforcement

This notification shall take effect on September 1, 2020.

(Annex)

Summary of applicability of designation requirements of Innovative Pharmaceutical products under the SAKIGAKE system

<table>
<tr><td colspan="2">Applicant name</td><td colspan="2">Enter in both Japanese and English.</td></tr>
<tr><td rowspan="2">Name</td><td>Non-proprietary name*1</td><td colspan="2">Enter both Japanese and English name such as INN.</td></tr>
<tr><td>Brand name*2</td><td colspan="2">Enter in both Japanese and English.</td></tr>
<tr><td colspan="2">Target indication</td><td colspan="2">Enter in both Japanese and English.</td></tr>
<tr><td rowspan="2">Designation requirement 1</td><td>Innovativeness of therapeutic pharmaceutical products*3</td><td colspan="2">☐Distinct mechanism of action from that of the approved drugs
☐Having the same mechanism of action as that of the approved drugs but being planned to be indicated for the target disease for the first time
☐Employing an innovative drug delivery system
☐Others (　　)*4</td></tr>
<tr><td colspan="3">(Reason for judging that the above requirement is met)</td></tr>
<tr><td rowspan="2">Designation requirement 2</td><td>Seriousness of target diseases*3</td><td colspan="2">☐ Serious life-threatening disease
☐ Disease with persistent symptoms (giving difficulty in living in society) without any radical treatment available</td></tr>
<tr><td colspan="3">(Outline of the target disease)</td></tr>
<tr><td rowspan="2">Designation requirement 3</td><td>Prominent efficacy in treatment of the target disease*3</td><td colspan="2">☐ No approved drugs available
☐ Expecting significantly improved efficacy or safety in comparison with the existing therapeutic drugs/therapies.</td></tr>
<tr><td colspan="3">(Current therapies for the target disease, summary of clinical trial results suggesting the efficacy)</td></tr>
<tr><td rowspan="3">Designation requirement 4</td><td>Intent and organizational capacity for development and application earlier in Japan ahead of the rest of the world*3</td><td colspan="2">☐ Plan of approval application earlier (only) in Japan than anywhere in the world
☐ Plan of world-first approval application in multiple countries and regions including Japan
☐ Having a system that can achieve the approval application</td></tr>
<tr><td>Planned timing of approval application</td><td colspan="2"></td></tr>
<tr><td colspan="3">(Outline of progress and schedule of development*5*6)</td></tr>
</table>

*1: If a non-proprietary name is not determined, enter “Code name.”
*2: Enter the determined name, if applicable. Enter the Japanese name if the drug is approved in Japan. Enter the English name otherwise. Enter “-” if the drug is not commercially available anywhere.
*3: Fill in appropriate boxes
*4: If this item is chosen, briefly describe the reason for expecting significantly improved efficacy.

*5: Describe the outline including planned schedule for SAKIGAKE comprehensive assessment consultation.
*6: For a drug requiring companion diagnostics for its use, describe the outline including collaborative organization with the concerned diagnostics companies and progress of the development.