PSB/PED Notification No. 1009-1
October 9, 2024

To: Director Generals 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 "Points to Consider for Approval Applications for Drugs"

For the handling, etc. of details related to applications for marketing approval of drugs, "Points to Consider for Approval Applications for Drugs" (PFSB/ELD Notification No. 1121-12 of the Evaluation and Licensing Division dated November 21, 2014, hereinafter referred to as "Division Notification") have been followed. Please be aware that the Division Notification has recently been partially revised as follows, and give guidance to the related businesses under your jurisdiction.

This notification applies to approval applications for drugs filed on October 9, 2024 or later.

Note

At the end of A of "(6) Attached Table 2-(2) Guidance/OTC drugs of Director-General Notification" in "1 Handling of data to be attached to marketing application," "In this regard, attention should be paid to bioequivalence with approved prescription drugs." is added.

(Reference: Whole text after revision)

1 Handling of data to be attached to marketing application

The data that should be attached to marketing application (hereinafter referred to as "submission data") are as shown in Attached Tables 1 and 2 of Director-General Notification. Details shall be handled as follows.

(1) B2 of Attached Table 1 of Director-General Notification

For the time being, (8-2), (9-2), and (10-3) in the left column of Attached Table 2-(1) Prescription drugs and (1), (2), (3), (3)-[1], (3)-[2], and (3)-[3] in the left column of Attached Table 2-(2) Guidance/OTC drugs of Director-General Notification shall be prepared with reference to Appendix 3 of the "Guidelines for Preparation of Data to Be Attached to Marketing Application for Manufacturing or Import Approval Application for New Drugs" (PMSB/ELD Notification No. 899 dated June 21, 2001).

(2) D of Attached Table 1 of Director-General Notification

A Secondary pharmacology data refer to the data on the action or mechanism of the effect of the test substance that are not related to the expected therapeutic target.

B Safety pharmacology data refer to data on undesirable pharmacological actions in the physiological functions of the body that are related to exposure to a drug.

C Other data on pharmacology include those on pharmacodynamic drug interactions.

(3) F7 of Attached Table 1 of Director-General Notification

Data on other toxicities include those on antigenicity and dependence.

(4) G of Attached Table 1 of Director-General Notification

Regarding clinical data, the study results in a sufficient number of cases to evaluate the efficacy and safety of the proposed drug should be submitted with reference to the guidelines, etc. established based on 3 in Section 2 of the note of Director-General Notification. For orphan drugs, the study results that can confirm the efficacy and safety in a feasible number of patients are acceptable in view of the small number of patients with the target disease.

(5) Attached Table 2-(1) Prescription drugs of Director-General Notification

A The data submitted at the time of approval application for approved drugs, etc. may be used as the data in D1 and E1 to 4 of drugs corresponding to (6).

B If an application for a drug corresponding to (8-2) that has the same dosage form as that of an approved drug, etc. is filed after the re-examination period of the approved drug, etc. (limited to re-examination period added due to active ingredient or its combination ratio, or route of administration different from those of approved drugs, etc.), "Guidelines for Handling of Stability Study Data of Drugs with New Routes of Administration" (PAB/ELD Notification No. 425 dated May 28, 1997) do not apply, and it is not necessary to attach data of C1 and 2.

C When collecting and preparing the data in E5 for drugs corresponding to (8) and (8-2), refer to "Guidelines for Bioequivalence Testing of Generic Drugs"(PMSB/ELD Notification No. 487 dated December 22, 1997) and "Guidelines for Bioequivalence Testing for Addition of Drug Products with Different Dosage Forms" (PMSB/ELD Notification No. 783 dated May 31, 2001).

D Data of drugs corresponding to (10) to (10-4) may need to be attached depending on individual drugs even if they are not required to be attached.

E For radiopharmaceuticals, attachment of some of the data in D and F may be skipped if scientifically justified. Drugs containing new substances as ingredients for non-radioactive labels are also classified into (1).

F For biological products, etc., attachment of some of the data in D, E and F can be skipped if scientifically justified.

G The scope of submission data for the drugs that are intended solely for use for diagnosis of diseases and are applied to the human skin (drugs for patch tests) is, in principle, the data listed in the right column of Attached Table 1-(1) of this notification. Refer also to PAB Notification No. 471 dated April 17, 1991, "Handling of Drugs for

Patch Tests" and PAB/ELD Notification No. 195 dated the same day, "Handling of Drugs for Patch Tests."

(6) Attached Table 2-(2) Guidance/OTC drugs of Director-General Notification

A For drugs corresponding to (4), data on the efficacy and safety of the active ingredient shall be included. In this regard, attention should be paid to bioequivalence with approved prescription drugs.

B A guidance/OTC drug that is equivalent or considered equivalent to the guidance/OTC drug concerned, the application of which is made during the survey period for the safety at the time of use designated by the Minister of Health, Labour and Welfare at the time of approval of the guidance/OTC drug concerned falls into the same application category as the guidance/OTC drug concerned, and requires equivalent or more data.

C A drug for which application is made after completion of the survey on the safety of a guidance/OTC drug at the time of use and which has the same active ingredient and its content, dosage and administration, indication, and dosage form as those of the guidance/OTC drug concerned or a minor difference in dosage form corresponds to (8). However, for minoxidil, nicotine, and other substances for which similar risks are considered, data on bioequivalence are required for the time being.

D (7)-[1] OTC combination drugs with similar prescription for which it is difficult to show in existing data or nonclinical studies that the combination of related ingredients does not enhance pharmacological actions, or in which vitamins, etc. are combined with Chinese herbal formulation require clinical study data.

(7) Insecticides and disinfectants

A For insecticides or disinfectants that are not used directly on the human body, the scope of submission data shall be those listed in the right column of Attached Table 1-(2) of this notification, in principle.

B For the data of D2 of the insecticides or disinfectants corresponding to (1), it is acceptable to use the "Guidelines for General Pharmacology Studies" (Attachment to PAB/NDD Notification No. 4 of New Drugs Division, Pharmaceutical Affairs Bureau dated January 29, 1991) as the guidelines for preparing data. The data in D1 of insecticides or disinfectants corresponding to (2) should be the data on basic and on-site primary pharmacodynamics studies. The data in F6 should be the data on skin/mucosa irritation tests and skin allergy tests.

C The data in D1 of insecticides corresponding to (1) should be the data on the test using each target pest at 2 or more sites. However, if there are results of the tests of the efficacy for killing flies, data on the results of tests of the efficacy for killing mosquitos may be omitted, and if there are results of the tests of the efficacy for killing cockroaches, data on the results of tests of the efficacy for killing bedbugs, fleas, and house dust mites may be omitted. In addition, for insecticides intended for the effect of long-term natural transpiration of their main agents, the provision in PAB/PD Notification No. 227 dated June 9, 1969, "Handling of transpirant" shall be applied.

D For disinfectants corresponding to (2), include data on the persistence of the drug concerned in the target of disinfection.

(8) Drugs containing new excipients

A When applying for drugs containing new excipients corresponding to 10 in Section 2 of the note of Director-General Notification, attach the data on origin or history of discovery and usage conditions in foreign countries etc., the data on manufacturing process, specifications, test methods, etc., the data on stability, and the data on toxicity, of the new excipients concerned.

B Data showing the stability of the excipient concerned in the drug product can replace the data on stability if there is a rational reason.

C For data on toxicity, published literature may be used if it is on reliable experiments.

2 Handling of omission of submission data

In the following cases, some of the submission data can be omitted.

(1) Salts and esters

For a drug that has the same chemical basic structure of the active (effective or toxic) body of the active ingredient as that of an approved drug, etc. (i.e., acid or metal salt with different acid or metal, ester that differs in alcohol or acid group that is not the active body) and the indications, dosage and administration, toxicity, adverse reactions, pharmacological actions, etc. of which are assumed to be almost equivalent to those of the approved drug, etc., the following submission data can be omitted in principle, depending on the degree of similarity of disposition (particularly absorption) between the active ingredient and the approved drug, etc. In this case, supporting data that justify the omission should also be submitted.

A Toxicity

Data on repeated-dose toxicity (long-term), reproductive and developmental toxicity, and carcinogenicity

B Pharmacological actions

Data on primary pharmacodynamics, secondary pharmacodynamics/safety pharmacology

C Absorption, distribution, metabolism, and excretion

Data on distribution, metabolism, and excretion

(2) Change in route of administration

A Toxicity

If the change in the route of administration does not increase the systemic exposure to the drug compared to the route before the change, the data on repeated-dose toxicity (long-term), reproductive and developmental toxicity, and carcinogenicity can be omitted in principle. In this case, supporting data that justify the omission should also be submitted.

When the concerned drug is to be used for a long period in association with the change of the administration route, data on repeated-dose toxicity for a corresponding period and data on carcinogenicity (where necessary) need to be submitted.

B Absorption, distribution, metabolism, and excretion

In principle, data on distribution, metabolism, and excretion after the drug enters systemic circulation can be omitted. In this case, supporting data that justify the omission should also be submitted.

3 Study guidelines

For the guidelines for studies stipulated in 3 of Section 2 of the note of Director-General Notification, refer to the guidelines separately shown in notifications of the Evaluation and Licensing Division, etc.

It is not always necessary to strictly adhere to the methods shown in these guidelines if studies are based on rational grounds reflecting academic advances, etc. These guidelines will be reviewed or new guidelines will be established as necessary in the future.

4 Handling of combination drugs

(1) Scope of combination drugs

A Combination drugs refer to drugs containing two or more active ingredients as specified in 2 (10) of Section 1 of the note of Director-General Notification, but the active ingredients mentioned here do not include pharmaceutical excipients. However, if the content is close to the therapeutic dose, even the ingredient added as an excipient should be handled as an active ingredient, in principle.

B In principle, the following items are handled as combination drugs.

[1] Extracts from two or more kinds of plants (including Chinese herbal preparations)

C The following items should be handled as single-ingredient drug products, in principle.

[1] Synthetic products each ingredient of which is difficult to separate and purify and which do not require such operation

[2] Extracts from a single plant. However, extracts using the plants that have markedly different active ingredients in each part (roots, stems, leaves, etc.) are excluded.

(2) Combination drugs must fulfill one of the following conditions.

[1] Drugs difficult to prepare before use such as infusion solution

[2] Drugs that reduce adverse reactions (toxicity) or have synergistic effects

[3] Drugs that clearly contribute to improvement of convenience for patients

[4] Other drugs for which the significance of combination is scientifically reasonable

(3) When applying for new combination drugs, data showing the rationale for the reason for combining the active ingredients should be submitted. These data should be based on clinical studies and animal studies, in principle. However, for drugs judged to be almost equivalent to approved drugs, etc. for which the significance of combination is considered to have been established academically, the attachment of such data can be omitted. For Chinese herbal preparations, citations describing the relevant formulation from appropriate books may be used as the data showing the rationale for the reason for combining the ingredients.

(4) Infusion solutions, artificial kidney perfusion solutions, etc. that have the active ingredients, combination ratios, etc. not considered to be similar to those of approved drugs, etc. based on comprehensive evaluation, such as those containing new active ingredients or newly targeting patients with special pathological conditions with changed combination ratios, do not fall under the category of combination prescription drugs with similar formulations.

5 Handling of submission data, etc. in joint development

(1) When a drug is jointly developed by more than one party and all or some of the members of the group consisting of these multiple parties (hereinafter referred to as "joint development group") apply for approval of the drug concerned, the data prepared by other members may be used if the following conditions A and B are satisfied.

A A contract that includes the following has been concluded between the parties concerned prior to all applications by the joint development group: Each member of the joint development group can use all data (including the data that serve as rationale for the data concerned) prepared by the members other than the member concerned; the cooperation of members other than the member concerned for fulfillment of storage responsibility for the above data has been secured.

B A copy of the contract specified in A is submitted at the time of approval application.

(2) When multiple members of the joint development group file the application for approval of a drug related to the joint development, the submission data shall be handled as follows.

A Specifications, etc.

[1] When individual applicants file the approval application for a drug with the same manufacturing process (including the cases of minor changes) and the same formulation (including the content of active ingredients and excipients and dosage form, the same applies hereinafter), it is acceptable that a member of the joint development group prepares data and, after they are submitted, other individual applicants store a copy of the data. When the manufacturing process is different, it is acceptable that each applicant confirms on its own responsibility that the quality of the drug related to its approval application is the same as that of the drug of the member who submitted the data, and stores the record.

[2] When individual applicants file the approval application for a drug with the same content of the active ingredient and the same dosage form, it is acceptable

that a member of the joint development group prepares the data on the rationale for specifications and test methods and, after they are submitted, other individual applicants store a copy of the data, if the test methods are the same. The data on the test results (measured values) that confirm the conformance with the specifications established based on the established test methods shall be prepared and submitted for each drug related to the approval application by each applicant.

B Stability

[1] When individual applicants file the approval application for a drug with the same manufacturing process, the same formulation, and also the same packaging material and form, it is acceptable that a member of the joint development group prepares data and, after they are submitted, other individual applicants confirm the stability or the drug related to their own approval applications on their own responsibility and store the record.

[2] When there are multiple packaging materials or forms, or there are multiple drug products with different formulations or dosage forms, depending on individual applicants, it is acceptable that the joint development group collect and prepare the stability data that are necessary at the time of application for these multiple drug products by a single applicant and, after they are submitted, other individual applicants store a copy.

C Toxicity, pharmacological actions, absorption/distribution/metabolism/excretion (excluding bioequivalence)

It is acceptable that a member of the joint development group prepares the data and, after they are submitted, other individual applicants store a copy.

D Bioequivalence

[1] When individual applicants file the approval application for a drug with the same manufacturing process and the same formulation, it is acceptable that a member of the joint development group prepares data and, after they are submitted, each of other applicants confirms that the drug related to its own approval application is bioequivalent by appropriate studies and stores the record.

[2] When individual applicants file the approval application for a drug with a different manufacturing process, formulation, or dosage form, each applicant shall confirm that the drug is bioequivalent by appropriate studies and submit the data.

E Clinical data

It is acceptable that a member of the joint development group prepares the data and, after they are submitted, other individual applicants store a copy.

(3) Even if some members of the joint development group have not filed any approval application for the drugs related to the joint development, these members that have not filed any application are subject to the on-site inspection of conformity to standards based on the latter part of Article 14, Paragraph 5 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 “Pharmaceuticals and Medical Devices Act”).

6 Matters to be described in marketing application form

In addition to separately specified information, the following information shall be described in individual columns of the marketing application form.

(1) Name column

A The generic name shall be entered only for single crude drugs and drug products listed in the Minimum Requirements for Biological Products. Procedures should also be taken for naming of those for which no Japanese accepted name (JAN) has been established in Japan.

B A brand name should not cause any health hazard and should maintain the dignity as a drug. In principle, brand names of prescription drugs should include information on dosage forms and contents (or concentrations, etc.) of active ingredients.

(2) Column for ingredients and contents, or nature

Specifications shall be established for ingredients or nature, and the purpose of combining the ingredients or nature other than active ingredients or active nature shall be described.

(3) Column for manufacturing process

Manufacturing process should be described with reference to "Guidelines for Items Required To Be Entered on Marketing Application Form for Drugs, etc. under the Revised Pharmaceutical Affairs Act" (PFSB/ELD Notification No. 0210001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated February 10, 2005).

(4) Column for storage method and shelf life

The retest period of the drug substance can be set in the approved product information of a drug product.

(5) Column for specifications and test methods

Necessary items should be established with reference to the guidelines, etc. established based on 3 of Section 2 of the note of Director-General Notification.

For the ingredients described in the official compendial such as the Japanese Pharmacopoeia, the specifications in the official compendial shall be used instead of the specifications in the appendix unless there is a special reason.

(6) Remarks column

A Enter the applicable category among those shown in the left column of Attached Table 2 or the left column of Attached Table 1 of the note of Director-General Notification, including whether the drug is a prescription drug or a guidance/OTC drug, following the example.

[1] For prescription drugs that are drugs with new indications
(Example of description) Application category Prescription drugs (4)

[2] When specifications and test methods of prescription drugs are changed
(Example of description) Application category Prescription drugs (10)

[3] For generic drugs
(Example of description) Application category Prescription drugs (10-3) (the same as ××× marketed by ○○ Pharmaceuticals)

[4] For drugs with new active ingredients requiring guidance (over-the-counter)
(Example of description) Application category Guidance/OTC drugs (4)

[5] For insecticides that are new drug products of insecticides
(Example of description) Application category OTC drugs/insecticides, etc. (2)

B When applying for drugs containing new excipients, enter "Containing new excipients."

C In addition, when applying for products listed in the Japanese Pharmacopoeia, items intended to receive priority review, items with ongoing stability studies, or kit products, or when also applying for companion diagnostics, etc., state to that effect. When multiple parties file the application in joint development, enter the names of the other co-applicants.

D In the approval application for partial changes in approved product information based on Article 14, Paragraph 8 of the Pharmaceuticals and Medical Devices Act, provide the summary of changes (a comparison table before and after the change and reason for the change).

E If a retest period is set in the column for storage method and shelf life, describe to that effect.

F In the case of OTC drugs, enter "as per the marketing approval standards for ○○○" if an application is made according to the separately specified approval standards, and concisely specify the reason for the application if the application is made to the Minister of Health, Labour and Welfare.

7 How to edit application data, etc.

(1) The application data for drugs corresponding to (1) to (8), (9), (10), (10-2), and (10-4) of Attached Table 2-(1) Prescription drugs of Director-General Notification should be complied in accordance with PMSB/ELD Notification No. 899 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, dated June 13, 2001, "Guidelines for Preparation of Data To Be Attached to Marketing Application Form for Manufacturing or Import Approval Application for New Drugs." The application data for other prescription drugs and the guidance/OTC drugs in Attached Table 2-(2) of Director-General Notification shall be compiled in the following manner, in principle.

[1] Outline table (see the attached form)
[2] Marketing application form (copy)
[3] Package insert (draft)
[4] Certificates (statement of the responsible person supervising collection and preparation of application data, documents related to GLP and GCP, contract [copy] related to joint development, etc.)
[5] Marketing application submission data "Summary of data" (including separate volumes such as a list of patients and a list of patients with adverse reactions)
[6] List of submission data
[7] Submission data (data specified in Attached Table 2 of Director-General Notification)
[8] Other reference data

(2) When editing the data, pay attention to the following points.

A If photographs of TLC, etc. in the data, etc. on specifications and test methods, tissue photographs in the data, etc. on toxicity, etc. are unclear, submit the photographs concerned separately in an album.

B To the clinical study reports submitted as clinical data, attach the protocol and sample case report form among the appendices. Other appendices usually do not need to be included in the submission data, but should be ready for prompt submission upon request from the reviewing authority.

C As other reference data, the data at the time of approval (a copy of approval document, review report at the time of approval, outline of data, list of submission data, etc.) shall be attached in the case of applications for additional indications, change in dosage and administration, etc. of approved drugs, etc., and the data on the record of the clinical trial consultation provided by Pharmaceuticals and Medical Devices Agency shall be attached if such consultation has been provided.

D For prescription drugs corresponding to Attached Table 2-(1) of Director-General Notification and guidance/OTC drugs corresponding to (1) to (7)-[2] in Attached Table 2-(2) of Director-General Notification, a draft of the package insert shall be submitted as the data concerning descriptions in package inserts, etc. specified in Article 52, Paragraph 1 of the Act specified in H in Attached Table 1 of Director-General Notification.

It is stated in Note 2 for Attached Table 2-(1) of Director-General Notification that "in principle, it is not necessary to attach the data in H only for the application for the content that does not cause changes in the descriptions in the package insert" in the application for the drugs corresponding to (10) to (10-4). Even for changes in manufacturing process, etc., the draft package insert should be submitted if the description in the package insert is to be changed by, for example, adding the statement that bovine-derived materials are used.

For drugs corresponding to (1) to (6) in Attached Table 2-(2) of Director-General Notification, a draft check sheet, a draft information provision materials necessary for marketing, and data on presence or absence of possible abuse, etc. should be submitted, depending on individual drugs.

8 Other

(1) The number of copies of application data to be submitted to the Ministry of Health, Labour and Welfare shall be 2 (original and copy) for the Ministry of Health, Labour and Welfare and 1 (copy) for Pharmaceuticals and Medical Devices Agency, 3 in total, for new drugs, and 1 for other drugs.

(2) For imported drugs, attach the import contract for the drug concerned or equivalent data to the marketing application form.

Attached Form

Overview table

Brand name			
Non-proprietary name			
Name of applicant			
Date of application	Month DD, YYYY		
Application category	(Example of description) Prescription drugs (1)		
Contents of submission data			Submitted data (○)
A Origin or history of discovery and usage conditions in foreign countries etc.		1 Origin or history of discovery 2 Usage conditions in foreign countries 3 Characteristics and comparison with other drugs, etc.	
B Manufacturing process, specifications, etc.		1 Structural determination and physicochemical properties, etc. 2 Manufacturing process 3 Specifications	
C Stability		1 Long-term storage test 2 Stress test 3 Accelerated test	
D Pharmacological actions		1 Primary pharmacodynamics 2 Secondary pharmacology/safety pharmacology 3 Other pharmacology	
E Absorption, distribution, metabolism, and excretion		1 Absorption 2 Distribution 3 Metabolism 4 Excretion 5 Bioequivalence 6 Other pharmacokinetics	
F Acute toxicity, subacute toxicity, chronic toxicity, teratogenicity, and other toxicities		1 Single-dose toxicity 2 Repeated-dose toxicity 3 Genotoxicity 4 Carcinogenicity 5 Reproductive and developmental toxicity 6 Local tolerance 7 Other toxicities	
G Clinical data		Clinical data	
H Descriptions in package inserts, etc. specified in Article 52, Paragraph 1 of the Act		Descriptions in package inserts, etc.	
Other			

Attached Table 1-(1) Drugs for patch test

Left column	Right column							
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(1) Drugs with different test items from those of approved drugs, etc.	○ ○ ○	× × ○	× × ○	× × ×	× × × × × ×	× × × × × × ×	○	○
(2) Other drugs	× × ×	× × ○	× × ○	× × ×	× × × × × ×	× × × × × × ×	×	○ 1)

Note 1) The symbols and numbers in the right column indicate the symbols and numbers of the data specified in Attached Table 1 of Director-General Notification. In principle, ○ means that the data should be attached, × means that it is unnecessary to attach the data, and △ means that the necessity shall be judged for each drug. The same applies to Attached Table 1-(2) shown below.

Note 2) The note, 1), in the right column shall be as follows.

1) In principle, it is not necessary to attach the data in H only for the application for the content that does not cause changes in the descriptions in the package insert such as changes in the manufacturing process or test method.

Attached Table 1-(2) Insecticides and disinfectants

Left column	Right column							
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(1) New insecticide/disinfectant main agents (drugs containing new active ingredients)	○ ○ ○	○ ○ ○	○ ○ △	○ ○ ×	○ ○ ○ ○ × ×	○ ○ ○ × ○ ○ △	×	○
(2) New insecticide/disinfectant main agents (drugs with different ingredient composition [active ingredients and their concentrations], dosage and administration, indications, or dosage forms from those of approved drugs, etc. that are insecticides/disinfectants)	○ ○ ○	× × ○	△ △ △	○ × ×	× × × × × ×	○ △ × × × △ △	×	○
(3) Other drugs	× × ×	× × ○	× × ○	× × ×	× × × × × ×	× × × × × × ×	×	△ 1)