
Translated by PhRMA Japan (Pharmaceutical Research and Manufacturers of America Japan) and EFPIA Japan (European Federation of Pharmaceutical Industries and Associations Japan) with consultation to MHLW (Ministry of Health, Labour and Welfare) and PMDA (Pharmaceuticals and Medical Devices Agency).

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

PSEHB Notification No.0608-1

June 8, 2017

To: Prefectural Governors

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

Instructions for Package Inserts of Prescription Drugs

The above-mentioned matter has been properly operated in accordance with the “Instructions for Package Inserts of Prescription Drugs” (PAB Notification No. 606 from the Director-General of the Pharmaceutical Affairs Bureau [PAB], Ministry of Health and Welfare [MHW] dated April 25, 1997) and “Instructions for Precautions for Use of Prescription Drugs” (PAB Notification No. 607 from the Director-General of the PAB, MHW dated April 25, 1997) (Hereinafter, these are referred to as the “Former Director-General’s Notifications”). However, the circumstances surrounding medical care have been drastically changed. These include the advancement of medicine, aging of society, and development of IT technology; hence, the Instructions for Package Inserts of Prescription Drugs is stipulated as presented in the Appendix to make the package inserts and other relevant matters easier to understand and use. Please, therefore, make the Instructions thoroughly known to all relevant industries and organizations under your supervision with attention being paid to the below-mentioned points, and also make the necessary arrangements for appropriate instructions to be given with regard to the package inserts of prescription drugs.

Please be advised that copies of this notification will be sent to the head of each separately listed organization.

1. Main points of the Instructions

- (1) The sections and structure of the package insert and other relevant documents were reviewed, such as repealing the Sections “Relative Contraindications” and “Careful Administration” contained in the Former Director-General’s Notifications and establishing a new section, “PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS.”
- (2) Sequential numbers will be appointed to the sections: Numbers will be assigned to each section from “WARNINGS,” and if there is no applicable information in a section, the number of that section will be left vacant.
- (3) Information to be described in the package inserts was reorganized, totally.

2. Scope of application

The Instructions shall be applied to package inserts for prescription drugs. However, they will not be applicable to in vitro diagnostics, vaccines, antitoxins, or biological preparations for tests.

For biological products and specified biological products, information shall be described in accordance with this notification as well as based on the “Information to be Described in the Package Inserts of Biological Products” (PMSB Notification No. 0515005 from the Director-General of the Pharmaceutical and Medical Safety Bureau [PMSB], Ministry of Health, Labour and Welfare [MHLW] dated May 15, 2003).

3. Date of implementation

The Instructions shall be applicable from April 1, 2019. However, revisions in compliance with the Instructions shall be made as early as possible by March 31, 2024, for the package inserts of drugs that have been approved and the package inserts (draft) of drugs submitted for approval as of April 1, 2019.

4. Revision and repeal of existing notifications

(1) Repeal

The Former Director-General’s Notifications will be repealed and replaced with the contents herein.

(2) Revision

Consequent to the repeal of the Former Director-General’s Notifications and the issuance of this notification, “‘Instructions for Package Inserts of Prescription Drugs’ (PAB Notification No. 606 dated April 25, 1997) and ‘Instructions for Precautions for Use of Prescription Drugs’ (PAB Notification No. 607, April 25, 1997)” mentioned in Appendix 1 of the “Instructions for Package Inserts of Biological Products” (PMSB/SD Notification No. 0520004 from the Director of the Safety Division, PMSB, MHLW dated May 20, 2003) will be amended to “‘Instructions for Package Inserts of Prescription Drugs’ (PSEHB Notification No.0608-1 dated June 8, 2017,

from the Director-General, Pharmaceutical Safety and Environmental Health Bureau, MHLW),” and the phrase “after the Section ‘5. Name of Product’ and before the Section ‘6. WARNINGS’” in Section II, Item (3) of Appendix 1 will be modified to a phrase “after the section ‘G. Name of Product’ and before the Section ‘1. WARNINGS.’”

Instructions for Package Inserts of Prescription Drugs

I. Basic Rules for Compilation of Package Inserts

1. Package inserts and other relevant documents for prescription drugs shall be prepared by the marketing authorization holders of the drugs in accordance with the provisions set forth in each item of Article 52, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 in 1960; hereinafter referred to as the “PMD Act”) so that the necessary information is provided to healthcare professionals such as physicians, dentists, and pharmacists to ensure the safety of patients taking the drugs and to promote their proper use of drugs.
2. Information to be included in package inserts shall be that required for use of the drugs within the scope of approval, as a rule. However, other information that is considered to be important and particularly necessary shall be provided.
3. Information shall be described in the order specified in Section II “Sections and their Order” with its section number concerned. When there is no information to be provided in a section, the information may be omitted, but the section number shall not be moved up. However, for A and E to G listed in Section II, it is not necessary to indicate the section numbers and section names of A and E to G, and the section numbers of B to D
4. The “PRECAUTIONS” shall include the sections from “1. WARNINGS” to “15. OTHER PRECAUTIONS” excluding “3. COMPOSITION AND PRODUCT DESCRIPTION,” “4. INDICATIONS” and “6. DOSAGE AND ADMINISTRATION” among those listed in Section II “Sections and their Order.”
5. Even if drugs contain the same ingredient, if their routes of administration vary, the package inserts shall be separately prepared to avoid misunderstanding by users.
6. When precautions and adverse reactions markedly differ according to indications or dosage and administration, they shall be separately described.
7. Information to be described in the Sections “PRECAUTIONS” and “PRECAUTIONS FOR HANDLING” of generic drugs and bio-similar products shall be, in principle, the same as that of their reference drugs and reference biological drugs. However, this is not applicable to the case where different information needs to be described according to the differences of each product.
8. Deletion or changing of information currently included shall only be done on the basis of sufficient rationale.
9. Information shall not be repeated in two or more different sections.
10. Related sections should be mutually referred to.

11. Description in the sections belonging to “PRECAUTIONS,” can be not quantitative but comprehensive (e.g., carefully, periodically, frequently, or as appropriate) if data is lacking or insufficient.

II. Sections and their Order

- A. Date of Preparation or Revision
- B. Standard Commodity Classification Number of Japan
- C. Approval Number, Date of Initial Marketing in Japan
- D. Storage, Shelf Life
- E. Therapeutic Category
- F. Regulatory Classification
- G. Name of Product

1. WARNINGS
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
3. COMPOSITION AND PRODUCT DESCRIPTION
 - 3.1 Composition
 - 3.2 Product Description
4. INDICATIONS
5. PRECAUTIONS CONCERNING INDICATIONS
6. DOSAGE AND ADMINISTRATION
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION
8. IMPORTANT PRECAUTIONS
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
 - 9.1 Patients with Complication or History of Diseases, etc.
 - 9.2 Patients with Renal Impairment
 - 9.3 Patients with Hepatic Impairment
 - 9.4 Persons with Reproductive Potential
 - 9.5 Pregnant Women
 - 9.6 Breast-feeding Women
 - 9.7 Pediatric Use
 - 9.8 Geriatric Use
10. INTERACTIONS
 - 10.1 Contraindications for Co-administration (Do not co-administer with the following.)
 - 10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)
11. ADVERSE REACTIONS
 - 11.1 Clinically Significant Adverse Reactions

- 11.2 Other Adverse Reactions
- 12. INFLUENCE ON LABORATORY TESTS
- 13. OVERDOSAGE
- 14. PRECAUTIONS CONCERNING USE
- 15. OTHER PRECAUTIONS
 - 15.1 Information Based on Clinical Uses
 - 15.2 Information Based on Nonclinical Studies
- 16. PHARMACOKINETICS
 - 16.1 Blood Level
 - 16.2 Absorption
 - 16.3 Distribution
 - 16.4 Metabolism
 - 16.5 Excretion
 - 16.6 Patients with Specific Backgrounds
 - 16.7 Drug-Drug Interactions
 - 16.8 Others
- 17. CLINICAL STUDIES
 - 17.1 Clinical Studies for Efficacy and Safety
 - 17.2 Post-marketing Surveillance, etc.
 - 17.3 Others
- 18. PHARMACOLOGY
 - 18.1 Mechanism of Action
- 19. PHYSICOCHEMICAL PROPERTIES
- 20. PRECAUTIONS FOR HANDLING
- 21. APPROVAL CONDITIONS
- 22. PACKAGING
- 23. REFERENCES
- 24. REFERENCE REQUEST AND CONTACT INFORMATION
- 25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS
- 26. MARKETING AUTHORIZATION HOLDER, etc.

III. Instructions

A. Date of Preparation or Revision

- (1) The date of preparation or revision and the version number shall be included.
- (2) When a revision is made because of the release of reexamination or reevaluation results or a change in the indications or in the dosage and administration, such a fact shall be stated.

B. Standard Commodity Classification Number of Japan

The Standard Commodity Classification Number of Japan shall be provided from the middle

classification down to the detailed classification on the basis of the Standard Commodity Classification of Japan.

C. Approval Number, Date of Initial Marketing in Japan

- (1) The Approval Number shall be included. For drugs exempt from approval, the license number shall be entered in place of the Approval Number.
- (2) The Date of Initial Marketing in Japan shall be included.

D. Storage, Shelf Life

- (1) Storage and Shelf life while unopened shall be included in accordance with the marketing approval document.
- (2) Regarding drugs for which a shelf life is specified according to the Japanese Pharmacopoeia (JP) or standards pursuant to the provisions of Article 42, Paragraph 1 of the PMD Act (hereinafter referred to as the “legal standards”), that shelf life shall be included.

E. Therapeutic Category

A therapeutic category that can correctly represents the efficacy or property of the drug concerned shall be included. Any expression that might be misleading to users shall be avoided.

F. Regulatory Classification

The classification of poisonous drug, powerful drug, narcotic, psychotropic, stimulant, raw material for stimulant, habit-forming drug, specially approved pharmaceutical, or prescription-only drug, shall be indicated.

G. Name of Product

- (1) For non-JP drugs, the approved brand name shall be included.
If the brand name in alphabet is available, it shall also be included.
- (2) Regarding drugs for which legal standards are stipulated, the standard name shall be included.
For other drugs, if the non-proprietary name is available, it shall be included as well.
- (3) For drugs listed in the JP, the JP-specified names shall be mentioned, and brand names shall also be included, if they are available.

1. WARNINGS

This section shall be filled out when alert is particularly needed because fatal or extremely serious and irreversible adverse reactions can occur or such adverse reactions can result in serious accidents.

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

- (1) Patients to whom the drug should not be administered shall be listed on the basis of their symptoms, underlying diseases, complications, past history, family history, physical constitution, concomitant medications, and other relevant factors. Different types of patients shall be listed separately if they have different reasons for contraindication.
- (2) For contraindications other than hypersensitivity, the rationale shall be noted concisely in [], in principle.

3. COMPOSITION AND PRODUCT DESCRIPTION

(1) "3.1 Composition"

- [1] The name (s) of the active ingredient (s) (non-proprietary names, if available) and the quantity (ies) (if the active ingredient is unknown, its nature and a summary of the manufacturing method) shall be included, in principle, in accordance with the column for "Ingredients and quantity or nature" of the marketing approval document.
- [2] Excipients shall mean, in principle, ingredients other than the active ingredient (s) listed in the column for "Ingredients and quantity or nature" of the marketing approval document. For injections (including body fluid agents, artificial perfusion liquids, and powders for injection), the names and quantities of ingredients shall be included, and for other drug products, the name of each ingredient, shall be included.
- [3] For drugs containing peptides or proteins manufactured using cell culture technology or recombinant DNA technology as active ingredients, the names of productive cells shall be included.

(2) "3.2 Product Description"

- [1] The color and form (powder, granules, etc.), identification code, and other relevant information necessary for identification shall be provided.
- [2] For drug products for which release rates are adjusted, the function shall be described in accordance with the "Dosage form classification" in the marketing approval document.
- [3] For aqueous solution for injections, the pH and osmotic pressure shall be included. For sterile drugs (excluding injections), such a fact shall be stated.

4. INDICATIONS

- (1) The approved indications shall be described accurately.
- (2) For drugs exempt from approval, indications that are within a range recognized medically and pharmacologically and that are notified to the agency, shall be accurately listed.
- (3) For drugs that have already completed reexamination or reevaluation, the indications shall be described on the basis of the results of the reexamination or reevaluation.

5. PRECAUTIONS CONCERNING INDICATIONS

Precautions for the selection of patients and treatment within the scope of approved indications shall be included. In principle, information falling under Section "2. CONTRAINDICATIONS" shall not be necessary in this section.

6. DOSAGE AND ADMINISTRATION

- (1) The approved dosage and administration shall be accurately described.
- (2) For drugs exempt from approval, the dosage and administration that are within a range recognized medically and pharmacologically and that are notified to the agency, shall be accurately included.

- (3) For drugs that have already completed reexamination or reevaluation, the dosage and administration shall be provided on the basis of the results of the reexamination or reevaluation.
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION
Precautions that are particularly necessary for dosage and administration under specific conditions as well as when they are adjusted shall be described within the scope of approved dosage and administration.
8. IMPORTANT PRECAUTIONS
Important precautions for performing tests necessary upon treatment with the concerned drug, duration of treatment, and other relevant matters to prevent clinically significant adverse reactions or accidents shall be concisely described.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
 - (1) Precautions concerning patients with specific backgrounds shall be provided when clinical use in such patients is anticipated on the basis of indications and other relevant matters and more special attention is required for them compared with other patients when using the concerned drug and when there is information on appropriate use.
 - (2) When the concerned drug shall not be administered to the said patients, such a fact shall be stated in the Section “2. CONTRAINDICATIONS” as well.
 - (3) In addition to the precautions concerning patients with specific backgrounds, objective data obtained from clinical studies, nonclinical studies, post-marketing surveillance, epidemiological studies, and other relevant matters shall be provided so that prescribers can judge risks.
 - (4) “9.1 Patients with Complication or History of Diseases, etc.”
This section shall be filled out for patients requiring more special attention than other patients based on their complications, past history, family history, genetic predispositions, and other relevant factors if they do not fall under the Sections from “9.2 Patients with Renal Impairment” to “9.8 Geriatric Use.”
 - (5) “9.2 Patients with Renal Impairment”
 - [1] When it is necessary to adjust dosage and administration or to pay special attention on the basis of pharmacokinetics and the occurrence of adverse reactions, such facts shall be stated while considering the severity of renal impairment.
 - [2] The details of information on dialysis patients and removal by dialysis, if any, shall be briefly described.
 - (6) “9.3 Patients with Hepatic Impairment”
When it is necessary to adjust dosage and administration or to pay special attention on the basis of pharmacokinetics and the occurrence of adverse reactions, such facts shall be stated while considering the severity of hepatic impairment.
 - (7) “9.4 Persons with Reproductive Potential”

- [1] When patients and their partners are required to practice contraception, such a fact shall be stated with the required period of contraception.
- [2] If pregnancy tests are necessary before and periodically during treatment with the concerned drug, such a fact shall be mentioned.
- [3] If it is necessary to pay attention to the effects on gonads, fertility, etc., such a fact shall be stated.

(8) “9.5 Pregnant Women”

- [1] Necessary information shall be included while considering not only placental transfer and teratogenicity but also the amount of fetal exposure, the duration of exposure during pregnancy, clinical use experience, the availability of alternative drugs, and other relevant matters.
- [2] Precautions shall be described using basically “this drug should not be administered,” “it is advisable not to administer this drug,” or “this drug should be administered only if the expected therapeutic benefits outweigh the possible risks associated with treatment.”

(9) “9.6 Breast-feeding Women”

- [1] Necessary information shall be provided while considering not only transfer to breast milk but also effects on breastfed babies anticipated from pharmacokinetics and pharmacological actions, clinical use experience, and other relevant matters.
- [2] Matters concerning the effects on breast milk secretion shall be included separately from the effects on breastfed babies.
- [3] Precautions shall be described using basically “Women should be instructed to avoid breastfeeding,” “it is advisable not to breastfeed” or “the continuation or discontinuation of breastfeeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding.”

(10) “9.7 Pediatric Use”

For drugs that may be used in low-birth-weight babies, newborns, nursing infants, infants, or children (hereinafter referred to as “children”), if they have special adverse effects on children or special precautions are found to be necessary on the basis of their pharmacokinetics, such facts shall be described while considering age categories.

(11) “9.8 Geriatric Use”

When it is necessary to adjust dosage and administration or to pay special attention on the basis of pharmacokinetics and the occurrence of adverse reactions, their details shall be concisely described.

10. INTERACTIONS

- (1) When co-administration with other drugs causes the enhancement or reduction of the pharmacological actions of the drug concerned or the concomitant medication or causes the augmentation of adverse reactions, occurrence of new adverse reactions, or aggravation of underlying diseases, etc., the drug combinations requiring precaution in clinical practice shall

be listed. This shall include important interactions with physical therapy, food, and beverages, etc.

- (2) In case an interaction is associated with changes in blood concentrations, if information is available on metabolic enzymes responsible for the mechanism of onset, this information shall be included in a preceding paragraph.
- (3) Information provided in the Section “10.1 Contraindications for Co-administration” shall also be included in the Section “2. CONTRAINDICATIONS.” Contraindications for co-administration should keep consistency so that drugs causing interactions are mutually contraindicated.
- (4) The names and therapeutic categories of drugs causing interaction shall be included first, and then the details (clinical symptoms and measures, mechanism and risk factors, etc.) shall be given briefly. Drugs or Therapeutic Categories with different types of interaction (in light of mechanisms of action etc.) shall be described in different paragraphs.
- (5) In the Section “10.1 Contraindications for Co-administration,” non-proprietary names and representative brand names shall be provided as the names of drugs.
- (6) In the Section “10.2 Precautions for Co-administration,” non-proprietary names or the names of therapeutic categories shall be indicated as the names of drugs. If the names of therapeutic categories are listed, in principle, representative non-proprietary names shall also be listed.

11. ADVERSE REACTIONS

- (1) Adverse reactions occurring in association with use of the drug shall be listed.
- (2) The frequency of adverse reactions shall be included on the basis of the results of clinical studies, etc. that were accurately and objectively conducted.
- (3) The Section “11.1 Clinically Significant Adverse Reactions” shall be described with attention being paid to the following points:
 - [1] Information requiring special precaution shall be described while considering the outcome and seriousness of adverse reactions.
 - [2] Event names of adverse reactions shall be used as section names. If initial symptoms (including abnormal laboratory values), the onset mechanism, time to onset, risk factors, preventive measures, special measures, and other relevant matters are known, such data shall be described under relevant sections as necessary.
 - [3] Clinically significant adverse reactions that have only occurred overseas shall also be provided as necessary.
 - [4] Clinically significant adverse reactions known to occur with similar drugs shall be included only when the same precautions are found to be necessary.
- (4) The Section “11.2 Other Adverse Reactions” shall be included with attention being paid to the following points:

[1] Other adverse reactions shall be classified by the site of occurrence, administration method, pharmacological mechanism, or onset mechanism and included with respective frequency category.

[2] Other adverse reactions that have only occurred overseas shall also be included as necessary.

12. INFLUENCE ON LABORATORY TESTS

This section shall be included when the use of a drug causes apparent changes in laboratory data that are clearly not associated with disorder in organs or functional impairment of patients.

13. OVERDOSAGE

Symptoms of intoxication that occur on overdosage (including suicide attempts, misuse, and accidental exposure to children) shall be described. Items to be monitored and measures (including specific antagonists and the usefulness of dialysis) shall also be indicated, if known.

14. PRECAUTIONS CONCERNING USE

- (1) Precautions necessary for use such as the administration route, dosage form, injection rate, administration site, method of preparation, and instructions to patients shall be included.
- (2) Information shall be concretely described by adding appropriate sections such as "Precautions Concerning the Preparation of the Drug," "Precautions Concerning Administration of the Drug," and "Precautions Concerning the Dispensing of the Drug," or others.

15. OTHER PRECAUTIONS

- (1) "15.1 Information Based on Clinical Uses"
Particularly important information such as safety concerns and the lack of efficacy, if any, shall be accurately summarized and included even if the evaluation has not been established in the report.
- (2) "15.2 Information Based on Nonclinical Studies"
Particularly important findings of toxicity that are observed in animals shall be briefly described even if it is unclear whether or not they can be extrapolated to humans.

16. PHARMACOKINETICS

- (1) In principle, data from humans shall be included. When data in humans are not available, the results of nonclinical studies shall be included in this section as supplementary data.
- (2) When nonclinical study results are included, the animal species shall be stated, and when the results of in vitro studies are provided, such a fact shall be stated.
- (3) "16.1 Blood Level"
 - [1] Blood drug concentrations and main pharmacokinetic parameters in healthy subjects or patients shall be included (excluding those falling under the Section "16.6 Patients with Specific Backgrounds").
 - [2] Single or repeated administration, doses, route of administration, the number of subjects/patients, and other relevant information shall be specified.

(4) “16.2 Absorption”

Absorption data such as bioavailability in humans and the effect of meal shall be included.

(5) “16.3 Distribution”

Distribution data such as tissue distribution and protein-binding rate shall be described.

(6) “16.4 Metabolism”

Information on drug metabolism such as metabolic enzymes and their contribution shall be provided. If the major elimination pathway is metabolism, such a fact shall be described clearly.

(7) “16.5 Excretion”

Excretion data such as urinary or fecal excretion rates of the unchanged drug and metabolites shall be included. If the major elimination pathway is excretion, such a fact shall be described clearly.

(8) “16.6 Patients with Specific Backgrounds”

[1] Blood drug concentrations, main pharmacokinetic parameters, and other relevant data in patients with specific backgrounds shall be provided.

[2] Categories of patients such as renal impairment, hepatic impairment, children, and the elderly shall be indicated.

(9) “16.7 Drug-Drug Interactions”

[1] In principle, the results of clinical drug interaction studies shall be provided for the drug interactions to which attention is called in the Section “10. INTERACTIONS”. As necessary, data such as in vitro studies using human biological specimens shall be supplemented with respect to the mechanisms and risk factors for drug interactions.

[2] When presenting the results of clinical drug interaction studies, the degree of changes in blood concentrations and pharmacokinetic parameters shall be numerically described so that the degree of drug interactions can be quantitatively judged.

[3] Drug interactions to which no attention is called in the Section “10. INTERACTIONS” shall be summarized only when they are particularly important, such as drugs being highly likely to be co-administered.

(10) “16.8 Others”

Although the data does not fall under the Sections from “16.1 Blood Level” to “16.7 Drug-Drug Interactions,” when drugs require therapeutic drug monitoring (TDM), pharmacokinetic data such as effective blood concentrations, a range of toxic concentrations, and the relationship between pharmacokinetics (PK) and pharmacodynamics (PD) shall be described.

17. CLINICAL STUDIES

(1) “17.1 Clinical Studies for Efficacy and Safety”

[1] The results of pivotal clinical studies, which were accurately and objectively conducted, of which reliability was ensured, which were intended to investigate efficacy and safety, and

which can be used as rationales for approved indications and for dosage and approved administration, shall be included.

[2] Study designs (including dosage, duration of treatment, and sample size) and main efficacy and safety results shall be briefly provided in accordance with the approved dosage and administration.

[3] The results of secondary endpoints may be briefly included only when they are particularly important.

(2) “17.2 Post-marketing Surveillance, etc.”

[1] This section shall be filled out only when pre-approval clinical study data are extremely limited and the results are particularly important for supplementing data in the Section “17.1 Clinical Studies for Efficacy and Safety such as in the case of orphan drugs.”

[2] In principle, the results of studies implemented in accordance with the Ministerial Ordinance on the Good Post-marketing Study Practice (Ordinance No. 171 of the Ministry of Health, Labour and Welfare in 2004) shall be included.

(3) “17.3 Others”

[1] The results of particularly important clinical pharmacology studies (e.g., QT/QTc evaluation study) that do not fall under the Section “17.1 Clinical Studies for Efficacy and Safety” or “17.2 Post-marketing Surveillance, etc.” but that were accurately and objectively performed and used endpoints for the central nervous system, cardiovascular system, respiratory system, etc. other than efficacy endpoints, shall be included.

[2] The dosage, a sample size, and subject category (healthy individuals or patients, males or females, and adults or children) shall be indicated.

18. PHARMACOLOGY

(1) Pharmacological actions and mechanisms of actions supporting indications shall be described within the scope of approved indications.

(2) A summary of the mechanism of action shall be concisely stated under a section “18.1 Mechanism of Action.” If the mechanism of action is unclear, it is acceptable to state such a fact.

(3) Under sections from “18.2” onward, pharmacological actions supporting indications shall be included with appropriate section names.

(4) When the results of pharmacology studies in humans are described, the difference of subjects (healthy individuals or patients, males or females, and adults or children) shall be clearly described.

(5) When the results of nonclinical studies are entered, the species of animal used shall be stated, and when the results are from in vitro studies, this fact shall be stated.

(6) For combination drugs, synergistic effects shall be included only when data with sufficient objectivity are available.

19. PHYSICOCHEMICAL PROPERTIES

The non-proprietary name, chemical name, molecular formula, structural formula, nuclear physical characteristics (only for radioactive substances), etc. shall be indicated. However, the information may be omitted for drugs combining numerous active ingredients, such as infusion, except for the main active ingredient.

20. PRECAUTIONS FOR HANDLING

- (1) Management, storage, or precautions for handling other than those specified in the Item “D. Storage, Shelf Life” such as storage conditions and expiration period after opening the package and precautions for checking quality before use shall be described.
- (2) For drugs that are listed in the JP or for which legal standards are specified and precautions for handling are stipulated, such precautions shall be included.

21. APPROVAL CONDITIONS

Approval conditions shall be included in accordance with the marketing approval document. However, this is not applicable to early post-marketing phase vigilance.

22. PACKAGING

A packaging form and unit shall be indicated for each brand name. The names of equipment, solutions, and other relevant items composing the product, if any, shall be listed.

23. REFERENCES

This section shall present the main literature that provides evidence to support information provided in each section.

24. REFERENCE REQUEST AND CONTACT INFORMATION

The name, address, and contact information (e.g., telephone or fax number) for literature requests and for making inquiries shall be included.

25. PRECAUTION CONCERNING HEALTH INSURANCE BENEFITS

- (1) When health insurance benefits are not applicable to drugs or are only applicable to part of their indications, such facts shall be stated.
- (2) This section shall be filled out if the drugs which are included in the National Health Insurance reimbursement price list, are subject to the restriction of treatment duration or any precautions concerning health insurance benefits are required.

26. MARKETING AUTHORIZATION HOLDER, etc.

The name and address of the marketing authorization holder shall be indicated.

IV. Handling of data

1. Nonclinical study data

Domestic and overseas data from nonclinical studies shall be weighed equally. Details of the abnormalities as well as information on the administration method (such as dosage, duration of administration, route of administration, and dosing frequency) and animal species can be included in parentheses, if they are extremely important.

2. Epidemiological data

Important epidemiological data shall be included, if any, and the methods of the study shall also be included.

3. Data on comparison with other drugs

Data on comparison with other drugs (including bioequivalence studies) shall be provided only if they are sufficiently objective and important.

(Appended list)

President of the Japan Medical Association

President of the Japan Dental Association

President of the Japan Pharmaceutical Association

President of the Japanese Society of Hospital Pharmacists

President of the Federation of the Pharmaceutical Manufacturers' Association of Japan

President of the Japan Pharmaceutical Manufacturers Association

Chairman of the Japan-Based Executive Committee, Pharmaceutical Research and Manufacturers of America

Chairman of the European Federation of Pharmaceutical Industries and Associations

President of the Japan Generic Medicines Association

Chairman of the Japan Kampo Medicines Manufacturers Association

President of the Japan Medicinal Plant Federation

Chairman of the Japan CRO Association

Chief Executive of the Pharmaceuticals and Medical Devices Agency

Version:

1.0 (23-January-2018)

1.1(1-May-2019)

Document History

Version	Release Date	Sections revised	Brief Summary of Changes
1.1	1-May-2019	II.2 II.10.1 II.10.2 II.16.7 III.F. III.2. III.14. (2) III.16. (9) III.16. (10)	Updated for consistency with the English translation guidance (PSEHB/SD Notification No. 0329-8 dated March 29, 2019)

Reference:

Instructions for Package Inserts of Prescription Drugs

<http://www.pmda.go.jp/files/000218446.pdf>

(Japanese original text)