CHAPTER 5

SUPPLY AND DISSEMINATION OF DRUG SAFETY MANAGEMENT INFORMATION

Manufacturing/marketing authorization holders of drugs must collect and examine information on proper use of drugs such as information on drug efficacy, safety and quality, and supply this information to medical institutions as specified in the Law. For this purpose, drug marketing authorization holders should prepare standard operating procedures based on the provisions in the GVP ordinance and endeavor to establish a comprehensive system for the supply and dissemination of information on proper and safe use of drugs.

1. PACKAGE INSERTS

The most basic tool for supplying information on drugs to health professionals is package inserts, and the contents of package inserts for prescription drugs have been specified by the Pharmaceutical Affairs Law. These package inserts are public documents that pharmaceutical marketing authorization holders are obliged to prepare for the purpose of supplying to health professionals including physicians, dentists and pharmacists the information necessary to assure the safety of patients administered the drug and to promote the proper use of the drug concerned based on the provisions of the Law. The Law specifies items which must be included in package inserts or containers/wrappers (package insert information), points to consider in preparing package inserts and items which are not allowed to be included in package inserts. The revised Law enacted on November 25, 2014 included the provisions that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. and that brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication. It also specifies penalties for not complying with these provisions and for including false or exaggerated information in package inserts. The MHLW has also issued notifications that provide guidelines on the actual items to be included, order of their inclusion, and preparation of package inserts, as well as guidelines on the preparation of Precautions for package inserts. Important information on adverse reactions, etc. obtained and evaluated in post-marketing surveillance on product safety must be reflected in package inserts. Because of the limitations on space and the amount of information that can be presented in package inserts, manufacturers and marketing authorization holders may prepare various types of information to supplement the package inserts.

Concerning the format and the contents of the package inserts and precautions for use, the necessity of a complete reconsideration of package inserts was pointed out in the final report of the Council on 21st Century Pharmaceuticals entitled "Proper Use of Drugs in Future Health Care and the Role of the Regulatory Authorities" in May 1993, and in the interim report of the Study Committee on Measures to Promote Appropriate Use of Drugs in July 1995. At about the same time, the Sorivudine incident involving a very severe adverse reaction caused by the interaction of this antiviral agent and an anticancer drug occurred, and the MHW (currently MHLW), health professionals and pharmaceutical companies considered emergency measures to assure proper supply of information on drug safety, mainly related to interactions (Notification No. 999 of PAB dated November 24, 1993 and Notice No. 1445 of the Japan Pharmaceutical Manufacturers Association dated November 21, 1994).

To cope with this problem, the MHW (currently

MHLW) established three special committees on the revision of pharmaceutical package inserts, which completed their work and submitted reports in May 1996. Based on these reports, guidelines for package inserts and for Precautions were completely revised (Notification No. 606 of PAB dated April 25, 1997, Notification No. 59 of the Safety Division, PAB dated April 25, 1997, and Notification No. 607 of PAB dated April 25, 1997).

Two notifications concerning package inserts for biological products were issued in May 2003: “Entries in Package Inserts for Biological Products” (Notification No. 0515005 of the PMSB dated May 15, 2003) and “the Guidelines for Entries in Package Inserts of Biological Products” (Notification No. 0520004 of the Safety Division, PMSB dated May 20, 2003). These notifications came into effect from July 2003.

After that, the guidelines on preparation of package inserts were revised and the following notifications were issued to make the package inserts easier to understand and easier to use reflecting the dramatic changes in the situation surrounding medicine, including advancement of medical care, aging of the society, and advancement of IT technology, and proposal of "Review of the Drug Administration for Preventing Recurrence of Drug-induced Sufferings (Final Proposal)" in 2010, and proposals made in Health and Labour Sciences Research from 2008 to 2013 and subsequent examination.

(1) Guidelines on Preparation of Package Inserts for Prescription Drugs (Notification No. 0608-(1) of the PSEHB dated June 8, 2017)

(2) Points to Consider Regarding Guidelines on Preparation of Package Inserts for Prescription Drugs (Notification No. 0608-(1) of the Safety Division, PSEHB dated June 8, 2017)

The major points of improvement are reconsideration of the items and structure, including abolishment of the sections of “Relative contraindications” and “Careful administration,” and addition of a section of “Use in patients with special backgrounds," and overall improvement of the information to be entered. The guidelines were applied from April 2019 (the transitional measure period for approved products will be 5 years). Subsequently, Questions and Answers for the Guidelines on Preparation of Package Inserts for Prescription Drugs (Office Communication of the Pharmaceutical Safety Division of MHLW dated January 17, 2019, and Office Communication of Office of Pharmacovigilance I and Office of Pharmacovigilance II of PMDA dated January 17, 2019) were issued.

For generic drugs, "Improvement of Provision of Information in Package Inserts, etc. of Generic Products" (Notification No. 0413-(2) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0413-(1) of the Safety Division, PSEHB dated April 13, 2018) was issued to improve provision of information, and the notification requires that the same information as that provided in the package inserts, etc. of the branded products should be provided in the sections of "Pharmacokinetics," "Clinical Studies" and "Pharmacology."

The notification entitled “Enforcement of The Law for Partial Amendment of the Pharmaceutical Affairs Law”(Notification No. 0806-(3) of PFSB dated August 6, 2014) specified that precautions for usage and handling based on the latest scientific knowledge and information should be prepared to promptly reflect essential cautions, etc. based on outcome from evaluation of safety information including adverse drug reactions collected according to the provisions in the Law and the MHLW Ordinance on GVP. Package inserts must include the package insert information based on latest findings, nonetheless package inserts prior to amendment may be attached in the following exceptional amendment case:

(1) When the products had already been manufactured and distributed prior to amendment of package insert information (post-

marketing products),

(2) When the package insert includes all of the information before amendment (that is, old package insert printed at the time of amendment), and all of the following requirements are met:

i. The products are manufactured and distributed within 6 months after the amendment date (within 1 year in cases of amendment of package insert information of products requiring testing or multiple products, which cannot be manufactured and marketed promptly with the amended package insert information),

ii. The amended package insert information are published on the PMDA homepage, and

iii. The manufacturing/marketing authorization holder of the product may promptly notify users including physicians or pharmacists of information on amendment of package insert information.

For submission of notifications, it was specified in the "Points to consider for notification of package insert information" (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014) that notifications should be submitted on the web page for notification via the PMDA homepage before initiation of manufacturing/marketing in cases of notifications for products to be newly manufactured/marketed including new drugs (nonetheless, when information provision to medical institutions, etc. is started prior to initiation of manufacturing/marketing, the notification should be submitted in advance preferably), or before the initiation date of information provision of the amendment or the initiation date of manufacturing/marketing of products with the amended package insert, whichever is earlier, in cases of amendment of package insert information. It was also specified that package insert information should be published on the PMDA homepage promptly upon submission of the notification to the PMDA. Nonetheless, when there is a certain time between the notification date and the amendment date of package insert information, publication may be made in line with the scheduled amendment date.

Of note, it is possible that information provision of the amended package insert information may be initiated upon submission of the notification to the PMDA, however it is recommended that such information is provided upon confirmation of PMDA's acceptance, because some modification may be needed when any inadequacy was found at confirmation from the PMDA (Office Communication of the Safety Division, PFSB dated September 1, 2014).

1.1 New Guidance on the Style and Format of Package Inserts

1) 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 Pharmaceutical and Medical Device 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 "Sections and their Order" with its section number concerned. When there is no information to be provided in a section, the section

may be omitted, but the section number shall not be moved up.

(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 “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 original drugs and original 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.

1.2 Headings and Their Sequence in Package Inserts

The layout of a package insert (image) after revision of the guidelines for preparation are shown below. Refer to **Fig. 18** Layout of Package Insert Based on Revised Guidelines for Preparation (Image) for the layout. Information for all sections from "Warning" shall be described with its section number concerned. When there is no information to be provided in a section, the section may be omitted, but the section number shall not be moved up.

* Headings and Their Sequence in Package Inserts

A. Date of preparation and/or revision(s) of the package insert
B. Standard Commodity Classification No. of Japan, etc.
C. Approval Number, Date of Initial Marketing in Japan
D. Storage, Shelf Life
E. Therapeutic Category
F. Regulatory Classification (specified biological product, biological product, poisonous substance, deleterious substance, habit-forming drug, prescription drug, etc.)
G. Name of Product [brand name, non-proprietary name, Japanese Accepted Name (JAN), etc.]
1. WARNINGS
2. CONTRAINDICATIONS (This drug should not be administered 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 (This drug should not be co-administered with the following drugs.)
   - 10.2 Precautions for Co-administration (This drug should be co-administered with caution.)
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 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.

1.3 Precautions

The Precautions are prepared voluntarily by the manufacturer of the drug concerned or under the guidance of the MHLW based on the guidelines in the MHLW notifications listed previously. Information obtained from post-marketing drug use results (clinical experience) surveys, and foreign and domestic case reports and research reports is collected and evaluated, and the Precautions are revised to incorporate the latest data as required. Revisions based on the results of reexaminations and/or reevaluations are undertaken as required.

The headings* used in the Precautions are as follows. Refer to No. 606 of PAB, Notification No. 0608-(1) of the PSEHB, Notification No. 0608-(1) of the Safety Division, PSEHB, and notifications related to biological products (Notification No. 0515005 of the PMSB and Notification No. 0520004 of the Safety Division, PMSB) for details concerning the contents of Precautions.

* Headings used with precautions

1) Warning (in red letters and encased in red at the beginning of "Precautions")
2) Contraindications (This drug should not be administered to the following patients.) (in black letters and encased in red.)
3) Precautions related to indications (In the event of such precautions, they are entered

under the heading "Precautions" following "Indications" in the package insert.)

4) Precautions related to dosage and administration (In the event of such precautions, they are entered under the heading "Precautions" following "Dosage and Administration" in the package insert.)
5) Important precautions
6) Precautions concerning patients with specific backgrounds
7) Drug interactions (Use the formats which are easy to understand, such as tables. Enter non-proprietary name or drug indication classification as drug name.)
   - See MHLW Notification (Notification No. 0723-(4) of the Pharmaceutical Evaluation Division, PSEHB dated July 23, 2018) and the Q&As (Office Communication dated July 23, 2018) for basic way of thinking about provision of information and precautions related to drug interactions.
   (1) Contraindications for coadministration ("This product should not be coadministered with the following drugs.") (in black letters and encased in red, with simple explanation provided under "Contraindications" above.)
   (2) Precautions for coadministration
8) Adverse reactions (Describe adverse reactions which occur in association with the use of the drug. Describe the incidence based on the results of clinical trials, etc. conducted accurately and objectively.)
   (1) Clinically significant adverse reactions
   (2) Other adverse reactions
9) Effects on laboratory tests
10) Overdosage
11) Precautions concerning use
12) Other precautions (toxicity obtained in animal studies requiring particular caution, etc.)

Reference: Age classification for pediatric use (basic standards)

Children: under 15 years of age
Small children: under 7 years of age
Infants: under 1 year of age
Newborns (neonates): under 4 weeks of age
Low birth weight infants (premature infants): body weight of less than 2,500 g (according to the WHO recommendation)

1.4 Labeling of Excipients

When excipients such as stabilizers, preservatives, and vehicles are used in products listed in the Japan Pharmacopoeia (JP), in the Minimum Requirements for Biological Products or in the Radiopharmaceutical Standards, the names and quantities of these excipients must be included in the relevant package inserts or on the containers or wrappers.

Since safety problems considered to be caused by excipients have appeared, the names and quantities of excipients specified in Notification No. 853 of the PAB dated October 1, 1988 must be included in the relevant package inserts or, if necessary, on the containers or wrappers of all prescription drugs since October 1988.

All ingredients as a rule, except for the ingredients stipulated in the MHLW Notification (Notification No. 0608-(1) of the Safety Division, PSEHB dated June 8, 2017) shall be included in the package insert because of the social responsibility to disclose as much information as possible related to drugs as life-related products. A voluntary agreement of the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) (FPMAJ Notification No. 170 dated March 13, 2002) should be referred to.

1.5 Entries for Biological Products

Specified biological products

1) Regulatory classification
   Specified biological products

2) Name
For genetic recombinants, “recombinant” is included immediately after the non-proprietary name
3) Beginning of the package insert (before the “Warning”)
(1) Risk of spread of infections derived from raw materials can not be completely eliminated.
(2) Summary of safety measures undertaken to prevent spread of infection.
(3) Use must be kept to a minimum after careful investigation of necessity in treatment of disease.
4) Composition and description
(1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
(2) Names of parts of humans or other organisms among raw materials
(3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)
5) Precautions, Important Precautions
Health professionals such as physicians must explain to persons using the drug the efficacy and safety and other measures required for proper use of the drug concerned.
6) Precautions for handling
Health professionals such as physicians must record the names and addresses of persons using the drug and preserve such records in medical institutions, etc.
7) Other items required for proper use

Biological products (excluding specified biological products)

1) Regulatory classification
Biological product
2) Name
For genetic recombinants, “recombinant” is included immediately after the non-proprietary name
3) Composition and description
(1) Names of ingredients among raw materials and packaging materials derived from humans or other organisms
(2) Names of parts of humans or other organisms among raw materials
(3) Name of country where blood was collected as a raw material and collection methods (donor blood or non-donor blood)
4) Other items required for proper use

1.6 Brand Names of Prescriptions Drugs

For prevention of medication accidents related to prescription drugs, Notification No. 935 of the PMSB was issued on September 19, 2000 to specify that brand name should include information of the dosage form and specification or content in addition to brand name (example, XXXX Capsules 25 mg) in principle. By Notification No. 0602009 of the PFSB dated June 2, 2004, relevant companies were requested to take active measures. The notifications issued jointly by directors of the Evaluation and Licensing Division and the Safety Division, PFSB specified handling of brand names of prescription combination drugs and heparin preparations (injection) and labeling of solutions attached to injection (Notification No. 0922002 of the Evaluation and Licensing Division, PFSB and No. 0922002 of the Safety Division, PFSB dated September 22, 2008) and handling of brand names of insulin preparations (Notification No. 0331001 of the Evaluation and Licensing Division, PFSB and No. 0331001 of the Safety Division, PFSB dated March 31, 2012). Handling of brand names of prescription combination drugs and insulin preparations was partially amended in Notification No. 0710-(7) of the

Evaluation and Licensing Division, PFSB and No. 0710-(5) of the Safety Division, PFSB dated July 10, 2014). The brand name of generic drugs is required to be a name based on the Japanese Accepted Name as directed in Notification No. 0922001 of the Evaluation and Licensing Division, PFSB dated September 22, 2005 and the brand name of biosimilar products as directed in Notification No. 0214-(1) of the Evaluation and Licensing Division, PFSB dated February 14, 2013.

For generic drugs of combination drugs, unified brand names had been discussed, and since August 2013, these have been managed in accordance with voluntary consensus that unified brand names may be retained by Japanese Society of Generic and Biosimilar Medicines as trade names and used by companies on a license basis.

The application fee for revising brand name was lowered in April 2005. The timing of brand name revision for prevention of medical accident is the time for NHI price listing twice a year. As a result, measures have been completed for a total of about 5,400 products as of the NHI price listing in September 2009.

1.7 Consultation Works Related to Revision of Package Insert

Package inserts are updated whenever necessary based on collection and evaluation of the information obtained from post-marketing use-results surveys of drugs, case reports in Japan and abroad, and literature reports.

In the meantime, PMDA newly established three consultations regarding package inserts of drugs on December 25, 2017 to improve consultation works for those who desire revision based on the results of post-marketing clinical studies, etc.: "Consultation for preliminary confirmation of revision of drug package insert" and "Consultation for drug package insert revision" in which appropriateness of the revision of the package insert is evaluated based on evaluation including efficacy, and "Consultation for investigating conformance to evidence data for drug package insert revision" in which reliability of the data on clinical studies which serve as the rationale for the package insert revision is verified.

1.8 Information about English Package Insert

For the purpose of further promotion of harmonization of international regulations and international cooperation in the area of pharmaceutical products and medical devices, it is required to proactively send information regarding pharmaceutical regulations in Japan to the international society. Concerning package inserts, “Guidance on English Translantation of Package Inserts for Prescription Drugs” targeting the package inserts prepared based on the new instructions was compiled to facilitate English translation and provision of information (Notification No. 0329-(8) of the Safety Division, PSEHB dated March 29, 2019). This Guidance lists “drugs approved in Japan for the first time in the world,” “drugs with a new mechanism of action,” “drugs approved based on multi-regional joint study data,” “drugs for which English translation of the review report is disclosed on the website of PMDA,” “drugs for which English translation of review reports is publicized,” and “other drugs for which provision of information to foreign countries is useful” as the drugs for which English translanation of package inserts is recommended.

2. INFORMATION TO SUPPLEMENT PACKAGE INSERTS

Because of space limitations in Japanese package inserts, the following main media are also of use to provide more detailed information about pharmaceutical products.

- Outline of Prescription Pharmaceutical Product Information

- Pharmaceutical Interview Forms
- Commentaries on "Precautions" in package inserts of new drugs

New drugs that are approved after October 2001 are marked with a logo commonly adopted by the pharmaceutical industry indicating that the drug is subject to early post-marketing phase vigilance for such a period of time as specified in labeling (6 months after the start of marketing).

2.1 Outline of Prescription Pharmaceutical Product Information

The Outline of Prescription Pharmaceutical Product Information is prepared by the manufacturing/marketing authorization holders with the objective of providing accurate and appropriate information to health professionals to promote proper use of their drugs. The material is available in two types: the general outline version showing the entire description of the product containing information under all headings of package insert and property-specific version containing information under certain headings of package insert such as clinical studies and clinical pharmacology.

The Outline of Prescription Pharmaceutical Product Information is prepared on the basis of the “Guidelines for Preparation of Outlines of Prescription Pharmaceutical Product Information” (prepared by the Japan Pharmaceutical Manufacturers Association [JPMA], developed in September 2015). To ensure consistency of the content with that of the package insert, attention should be paid to the JPMA Code of Practice.

In addition, the Outline of Prescription Pharmaceutical Product Information is internally reviewed by the pharmaceutical company and voluntarily reviewed by JPMA. Because administrative disciplinary actions were taken in 2014 and 2015 against the advertisement violating the law (Article 66) that prohibits false or exaggerated advertisements, the system to strengthen the internal review system of pharmaceutical companies was introduced in 2016, such as placement of the responsible organization of the internal review outside of the sales division and involvement of a third party in the internal review in principle. For the voluntarily review of JPMA, expansion of the scope and introduction of the electronic review system were conducted in 2017.

2.2 Pharmaceutical Interview Forms (IF)

In medical settings, physicians and pharmacists, etc. collect detailed information about drugs through interviews with medical representatives (MR) of pharmaceutical companies and utilize such information in daily works. Pharmaceutical Interview Forms (IFs) used to specify questions to be asked for such purposes, but in order to reduce the burden on pharmacists and MRs, the replies (detailed information) to the questions are already entered, and the IF are supplied to health professionals from pharmaceutical company as academic material to be used in explanations and discussions concerning the product.

The Japanese Association of Hospital Pharmacists published new preparation guidelines in November 2018, and IFs are being prepared in the new format for new drugs approved from April 2019.

"Guidelines for preparation of interview forms for generic products" was issued by the Japan Generic medicines Association for generic products. The guidelines mainly introduce the examples of the sections describing the data which are deemed to be unique to generic products, such as the results of bioequivalence studies, elution studies, and stability studies, as well as the procedures for describing these issues. The guidelines are used as the standards for preparation of IF together with the guidelines of the Japanese Association of Hospital Pharmacists.

Basically, IFs are provided in electronic media of PDF files. However, they can be searched on the

website of PMDA together with the package inserts.

2.3 Commentaries on "Precautions" in Package Inserts of New Drugs

Commentaries are prepared by marketing authorization holders of drugs for detailed explanation of "Precaution " when a new drug is launched.

Reflecting the notification of revision of the instructions for package inserts and precautions in April 1997, a guide to preparation of the commentaries was published (Notification No. 88 of the Safety Division, PAB dated June 27, 1997) and commentaries have been prepared for the new drugs launched after that.

3. SUPPLY AND DISSEMINATION OF SAFETY MANAGEMENT INFORMATION

For the proper use of drugs, it is important that the necessary information be supplied and disseminated in an appropriate and timely manner to health professionals.

Safety management information reported to the MHLW, etc. is evaluated by the PMDA after hearing opinions of experts. After the Committee on Safety of Drugs of the Council on Drugs and Food Sanitation approves the results, the necessary administrative measures based on the evaluation results are taken. These administrative measures include the following:

- Discontinuation of manufacturing or marketing of drugs, and instructions for recall of products
- Cancellation of approval
- Partial changes in approved items related to indications, dosage and administration, etc.
- Instructions for distribution of emergency safety information
- Instructions for distribution of safety flash reports (so-called blue letters)
- Instructions for revision of Precautions
- Changes in designation as controlled substances such as poisons, narcotics, or prescription drugs, or changes of regulatory category
- Instructions to companies to perform surveillance or research

Among these measures, extremely urgent and important safety-related information to warn the public and healthcare professionals of safety concerns or to restrict the use of products will be distributed as emergency safety information, and information necessary for improving their precautions on safety concerns earlier than the conventional approach through package inserts revision will be distributed as safety flash reports.

In addition to emergency safety information and safety flash reports, other information including notices of revision of Precautions is also distributed, but these are the most frequently used administrative measure.

In order to facilitate efficient revision of package inserts of drugs, revision of precautions for use, etc., a “Flowchart of standard procedures related to work on package inserts of drugs” has been specified in Office Communication of the Safety Division, PFSB dated November 25, 2014. This flowchart is posted on the PMDA homepage "Consultation regarding examination/implementation of safety measures (for companies)."
http://www.pmda.go.jp/safety/consultation-for-mah/0007.html
http://www.pmda.go.jp/files/000144200.pdf

When the PMDA considers that an investigation of safety measures is necessary as a result of screening (primary and secondary) of data collected by the PMDA, a basic time schedule in weekly units is prepared in which the PMDA first sends an inquiry to the company, the company submits its opinions, an interview advice meeting is held, a meeting of experts is convened (convened about every 5 weeks), and measures (issuing of notifications, etc.) are taken. When the company considers that it is necessary to investigate safety measures, the same type of

schedule is shown starting with a revision consultation from the company, holding an interview (face-to-face) advice meeting, convening a meeting of experts, and taking measures (refer to **Fig. 19** and **Fig. 20**).

The PMDA receives applications for consultation from companies for not only revision of package inserts of individual drugs but also for promotion of proper use to prevent serious adverse drug reactions, treatment safety, and other measures to improve safety of drugs. Accurate advice and guidance are given to the companies, and this contributes not only to the improvement of the safety of individual drugs but also to improvement of the system for safety measures of the company.

Refer to the following PMDA homepage for consultations on revision, etc. of package inserts applied for by companies and procedures for applications for other consultations.
http://www.pmda.go.jp/safety/consultation-for-mah/0001.html

Media and procedures for provision and dissemination of safety management information include the obligation to prepare SOPs by drug marketing authorization holders based on the specifications in the GVP Ordinance, and provision and dissemination of information based on these SOPs.

The main information media and information dissemination procedures are described below.

3.1 Distribution of Emergency Safety Information (Yellow Letters)

1) Preparation criteria

Emergency safety information ("yellow letter") is prepared by the marketing authorization holder on the basis of discussion with the MHLW and PMDA following an order or instruction of the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures (2) below in for drawing people (patients) or physician's emergent and specialized attention to safety-related matters and drug-use restriction in situations (1) as listed below. Practices for disseminating such information are specified in Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

(1) Situations
- Situations where cases of deaths, disabilities, events that may lead to death or disability, and difficult-to-treat conditions are reported by ADR reporting systems
- New safety-related problems such as the occurrence of unknown serious ADRs that apparently outweigh expected therapeutic benefits
- Regulatory measures taken overseas to resolve and prevent emergency and significant safety issues
- Safety issues considered to remain unresolved despite the dissemination of urgent safety information ("yellow letter") or safety flash reports ("blue letter")

(2) Measures to be implemented
- Creation of "warning" box or addition of "warning notice"
- Creation or addition of contraindications
- Revision of precautions accompanying the implementation of new safety measures (e.g., laboratory tests)
- Changes in indications, dosage, method of administration, or method of use, etc. for safety-related reasons
- Regulatory measures (discontinuation or suspension of marketing or cancellation of approval) for safety-related reasons, accompanying a recall of a drug
- Other measures for the prevention or early detection of ADRs concerned

2) Format and content

Emergency safety information must be prepared in the style and format specified in the guidelines, using yellow paper, etc. for easy identification of

important information by the public (patients) and medical personnel.

3) Methods of information dissemination

(1) The staff (MRs) in charge of drug information of the marketing authorization holder directly distributes the information to physicians, pharmacists, and other health professionals in medical institutions. The dissemination is required to be efficiently carried out by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns. PMDA distributes urgent safety information, revisions to package inserts, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.

(2) The marketing authorization holder must transfer safety information to medical or pharmaceutical organizations and requests them to cooperate in collecting and disseminating information through efficient communication tools such as their homepages. If the marketing authorization holder knows patient groups that use the products concerned, the safety information should be distributed to such groups.

The information will also be placed in the homepage of the PMDA together with the safety flash report (blue letters) in the following section.

Japanese:
https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/esc-rsc/0001.html

English:
https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the homepage of companies or the like.

4) Distribution

The distribution of emergency safety information to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Pharmaceutical Safety Division of Pharmaceutical Safety and Environmental Health Bureau when distribution has been completed as specified by the office.

3.2 Safety Flash Report (Blue Letters)

1) Preparation criteria

The safety flash report (“blue letter”) is prepared by the marketing authorization holder on the basis of discussion with the MHLW and PMDA following an order or instruction from the MHLW, voluntary decision by the marketing authorization holder, or other requirements in cases where it is judged necessary to take the measures specified in Section 3.1: 1-(2) above for drawing physician’s urgent and specialized attention to safety-related matters and measures necessary for optimal drug use (e.g., efficient method of notification, laboratory tests, etc.) similarly to the procedures for handling important safety information as noted above but more promptly than routine revisions of “precautions for use” with an intent to prevent the recurrence and spread of health-related harm or injury to the public. Practices for disseminating such information are specified in Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014.

2) Format and content

Safety flash reports must be prepared in the style and format specified in the guidelines, using blue paper, etc. Information contained in the reports may be required to be arranged for the public (patients) depending on the usage in practice.

3) Methods of information dissemination

(1) The staff (MRs) in charge of the drug information of the marketing authorization holder are to efficiently distribute the information to physicians, pharmacists, and other health professionals in medical institutions by using multiple communication tools such as direct handout, direct mail, fax, and e-mail to achieve prompt and widespread alert for safety concerns. PMDA distributes safety flash reports, revisions of package inserts, etc. to medical personnel who have registered their e-mail address with the Agency via PMDA medi-navi.

(2) The marketing authorization holder must transfer safety information to medical or pharmaceutical organizations, as appropriate, and requests them to cooperate in collecting and disseminating information through efficient communication tools such as their homepages. If the marketing authorization holder knows patient groups that use products concerned, safety information should be distributed to such groups, as appropriate.

Of note, for drugs of which package insert information are subjected to be notified, manufacturing/marketing authorization holders must notify the PMDA of details of amendment in package inserts prior to publication on the homepage of companies or the like.

4) Distribution

The distribution of emergency safety information to medical institutions must be completed within 1 month of receipt of the government order, according to the plan and method of distribution. The marketing authorization holder must submit a safety information dissemination report to the Director of the Pharmaceutical Safety Division of Pharmaceutical Safety and Environmental Health Bureau when distribution has been completed as specified by the office.

3.3 Commentaries on "Precautions" in Package Inserts of New Drugs

As a rule, MRs distribute the commentaries to medical institutions before new drugs are used in medical practice in order to assure proper use of new drugs.

3.4 Distribution of Information by 'Notices of Revision of Precautions'

The marketing authorization holder must prepare Notices of Revision of Precautions specifying the contents of revision after any revision of the precautions for use, and distribute it to medical institutions (Notification No. 1031-(1) of the Safety Division, PFSB dated October 31, 2014, and Notification No. 129 of the JPMA dated February 26, 2015).

1) Preparation criteria

(1) Cases where the Director of the Safety Division of PFSB orders or recommends revision of the Precautions or other sections of package insert based on the results of an investigation by the PMDA.

(2) Cases where the manufacturer and marketing authorization holder voluntarily revises the Precautions (revisions are to be notified to the PMDA beforehand).

2) Format and content

The paper must be not yellow or blue.

3) Methods of information dissemination

In the case of 1)-(1) above, MRs of the marketing authorization holder are to promptly distribute the notices to physicians, pharmacists, and other health professionals. PMDA distributes the notices of the Director of the Safety Division, PFSB, etc. to medical personnel who have registered their e-mail address

with the Agency via PMDA medi-navi.

In the case of 1)-(2) above, the notices are to be distributed to health professionals, as required, as directed in 1)-(1) above.

4) Distribution

The dissemination of the notices to medical institutions must be completed as soon as possible after receipt of the notification of the Director of the Safety Division of PFSB or the decision to make a voluntary revision.

3.5 Dissemination of Information for Drugs That Have Completed Reexamination or Reevaluation

Once the reevaluation results and reexamination results are available, the marketing authorization holder of the drug concerned disseminated information by preparing a “Notice of Reevaluation Results” and “Notice of Reexamination Results” as required, which they distribute to medical institutions. The FPMAJ compiles all of the reevaluation results and publishes a “Notice of Prescription Drug Reevaluation Results” in the journals of the Japan Medical Association, Japan Dental Association, and Japan Pharmaceutical Association.

3.6 Dissemination of ADR Information by the Pharmaceuticals and Medical Devices Safety Information (Information on Adverse Reactions to Drugs)

Among the case reports and scientific reports on adverse reactions collected from the manufacturer/marketing authorization holder, and ADR reports collected from or submitted by health professionals, the MHLW compiles commentaries and Notices of Revisions of Precautions concerning important ADRs. They are supplied in digest form as "Pharmaceuticals and Medical Devices Safety Information" to health professionals who submitted ADR reports, and also published in the media, on the PMDA homepage for information on drugs , and in various publications such as the Journal of the Japan Medical Association and the Journal of the Japanese Association of Hospital Pharmacists. An English version is sent to WHO.

The digest has been published since June 1973 and is available and regularly updated at the following PMDA homepage.

Japanese:
http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/safety-info/0043.html

English:
https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html

3.7 Dissemination of Information by Drug Safety Update

Drug Safety Update (DSU) is published for prescription drugs and the DSU of the OTC version (Information of revisions of precautions for use for OTC drugs) is published for non-prescription drugs under the supervision of the Ministry of Health, Labour and Welfare as the information journals which summarize and comprehensively and promptly convey information on revisions of the Precautions evaluated by the Ministry of Health, Labour and Welfare.

The Society of Japanese Pharmacopoeia and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) have been jointly editing and publishing the DSU, since September 1992 (10 times per year) (published by the FPMAJ since Issue No. 128 dated April 2004). The journal is distributed by mail to medical institutions nationwide including approximately 10,000 hospitals, 90,000 clinics and 60,000 dental clinics, as well as about and 50,000 pharmacies and dispensing facilities within one month after printing.

The DSU of the OTC version has been edited and published by the Japan Federation of Self-Medication Industries since November 2015.

These journals are available immediately after publication at the following the PMDA homepage.
http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/dsu/0001.html
http://www.pmda.go.jp/safety/info-services/drugs/calling-attention/otc-dsu/0001.html

3.8 Medical Guides for Patients

Marketing authorization holders for drugs will prepare medical guides for patients for obtaining marketing approvals, etc. of drugs if considered necessary by the Ministry of Health, Labour and Welfare. To promote the accurate understanding of patients, etc. regarding prescription drugs to help early detection of serious adverse reactions, the documents explain the matters that are particularly important to know when using drugs based on the package insert with simple expressions (Notification No. 0630001 of PFSB dated June 30, 2005, Notification No. 0331-(1) of the Safety Division, PFSB dated March 31, 2014, and Notification No. 0331-(8) of the Compliance and Narcotics Division, PFSB).

3.9 Manual for Handling Disorders due to Adverse Drug Reactions

The Ministry of Health, Labour and Welfare started the “Project to Take Comprehensive Measures for Serious Adverse Reactions” in 2005 with the aim of making the transition from the reactive safety measures to predictive and preventive safety measures. A manual for handling disorders due to adverse drug reactions, which comprehensively cover the methods of treatment and discrimination to be utinized by patients as well as physicians, pharmacists, nurses, etc. in clinical settings for adverse reactions that need to be given high priority judging from the seriousness has been created in cooperation with exerts, etc. in related academic associations. The revisions and updates reflecting the latest findings will be made by the end of FY2020. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html.

4. ELECTRONIC INFORMATION DISSEMINATION

The MHLW received a report from its special committee on policies to supply drug information to health professionals, etc. using the Internet, which was established in 1997, and started operation of a "Drug Information System” to supply such information via the Internet at the end of May 1999.

The information supplied includes information regarding the proper use of drugs, information on package inserts of prescription drugs, safety information disseminated by the MHLW, cases of suspected adverse reactions collected by the MHLW, as well as risk management plan (RMP), information on Yellow Letters (formally-called Dear Doctor Letters)/Blue Letters, drug guide for patients, the manual for handling disorders due to adverse drug reactions, drug approval applications, drug recalls, etc.

The marketing authorization holder is required to discuss the necessity for issuance and publication of “PMDA requests on the proper use of drugs” among official notices on the proper use of drugs, if ADRs due to drug use or those due to improper drug use do not decrease despite major revisions to labeling such as an issue or revisions of warnings and precautions. The marketing authorization holder is also required to determine the necessity of disseminating such information through print media, as appropriate.

Standard Generalized Markup Language (SGML) was adopted as the basic format for information about package inserts of prescription drugs, but was changed to Extensible Markup Language (XML) from April 2019 to cope with the revised instructions for package inserts and to improve the convenience of the package insert search system of PMDA's HP.

The supply of package insert information for non-prescription drugs was started from March 2007 and

supply of information on drug interview forms from May 2009.

The PMDA is providing services free (via PMDA medi-navi) to distribute safety-related information such as revisions to precautions in use of drugs, which has been placed on the Agency's homepage for information on drugs, to medical personnel who have registered their e-mail address with the Agency. http://www.pmda.go.jp/safety/info-services/medi-navi/0006.html

5. PACKAGE INSERTS OF NON-PRESCRIPTION DRUGS

The MHW established a special committee to improve package inserts of non-prescriptions drugs in August 1996 following the revision of the guidelines for package inserts of prescription drugs, and this group issued its report in September 1998.

The PMSB of the MHLW issued notifications on August 12, 1999 on the type and format for non-prescriptions drugs to define items of information to be included in the package insert, entry methods for Precautions, and information that should be included on the outer containers. The style and format of the description on the outer containers or wrappers were revised to assist the purchase of suitable drugs based on labeling and issued as a notification of PFSB on October 14, 2011. The old notification of PMSB dated August 12, 1999 was abolished accordingly. For non-prescription Chinese herbal preparations with the established approval criteria, items to be included in Precautions in package inserts, etc. were presented in Notification No. 1014-(7) of the Safety Division, PFSB and No. 1014-(8) of the Evaluation and Licensing Division, PFSB dated October 14, 2011, and partially amended in Notification No. 0327-(1) of the Safety Division, PFSB and No. 0327-(1) of the Evaluation and Licensing Division, PFSB dated March 27, 2013.

Labeling requirements of excipients of non-prescription drugs are the same as those for prescription drugs according to a voluntary agreement of the JPMA (Notification No. 165 of the JPMA dated March 27, 1991) and Office Communication of the Safety Division, PAB dated June 3, 1991. Based on a voluntary agreement of the JPMA (Notification No. 170 of the JPMA dated March 13, 2002), all ingredients must be included in package inserts by March 31, 2004 and the names of excipients including voluntarily designated ingredients must be included on the outer container (or its equivalent).

Based on this voluntary agreement, Notification No. 165 of the JPMA was canceled and the Office Communication of the Safety Division, PAB dated June 3, 1991 was canceled by Notification No. 0409001 of the Safety Division, PMSB dated April 9, 2002.

For the background of labeling of excipients for prescription drugs, refer to Section 1.4 on excipients.

The revised Law enacted on November 25, 2014 specified that package insert information should be based on scientific knowledge and information obtained in latest literatures, etc. as is the case for prescription drugs. Nonetheless, the exceptions for package insert information to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).

6. PACKAGE INSERTS OF GUIDANCE-MANDATORY DRUGS

For guidance-mandatory drugs (refer to CHAPTER 2, 3.2 Classification of Drugs), as is the case for prescription drugs, package inserts should be based on scientific knowledge and information obtained in latest literatures, etc., and brand names and precautions for usage and handling should be noticed prior to initiation of manufacturing/marketing or amendment followed by prompt publication on the PMDA homepage (Notification No. 0806-(3) of PFSB dated August 6, 2014).

For notification, the specified notification format

should be submitted to the PMDA with package insert information (copy) attached (Notification No. 0901-(1) of the Safety Division, PFSB dated September 1, 2014).

Nonetheless, the exceptions for package inserts to be attached to products may be applicable also as is the case in prescription drugs (refer to 1. PACKAGE INSERTS).

Fig. 18 Layout of Package Insert Based on Revised Guidelines for Preparation (Image)

**Revised: Month, 20XX (Version XX, ○○)

Standard Commodity Classification No. of Japan

Name of therapeutic category

Storage:
Expiration date:

Nonproprietary name, standard name, or name designated on Japanese Pharmacopoeia

	●mg	▲mg
Approval No.		
Date of initial marketing in Japan	XX, 20XX	XX, 20XX

Regulatory classification

Prescription drug Note)

Brand Name

Name of Product

Note) Caution : Use under prescription from a physician, etc.

1. Warning

2. Contraindications (This product is contraindicated in the following patients.)

3. Composition and description
 3.1 Composition
  <Table format >
 3.2 Description of drug product
  <Table format >

4. Indications

5. Precautions related to indications

6. Dosage and administration

7. Precautions related to dosage and administration

8. Important precautions

9. Precautions related to patients with special backgrounds
 9.1 Patients with complications or disease history

 9.2 Patients with renal dysfunction

 9.3 Patients with hepatic dysfunction

 9.4 Persons with reproductive ability

 9.5 Pregnant women

 9.6 Lactating women

 9.7 Pediatric use

 9.8 Elderly use

10. Drug interactions
 10.1 Contraindications for coadministration (This product should not be coadministered with the following drugs.)

Drug name	Signs, symptoms and treatment	Mechanism and risk factors

 10.2 Precautions for coadministration (XX should be administered with care when coadministered with the following drugs.)

Drug name	Signs, symptoms and treatment	Mechanism and risk factors

11. Adverse reactions
 11.1 Clinically significant adverse reactions
 11.1.1○○

 11.2 Other adverse reactions

	≥○%	0.1 to ≤○%	≤ 0.1%	Unknown frequency

12. Effects on laboratory tests

13. Overdosage

14. Precautions concerning use

15. Other precautions
 15.1 Information based on clinical use

 15.2 Information based on nonclinical studies

16. Pharmacokinetics
 16.1 Blood concentration

 16.2 Absorption

 16.3 Distribution

 16.4 Metabolism

 16.5 Excretion

16.6 Patients with special backgrounds

16.7 Drug interactions

16.8 Others

17. Clinical studies

17.1 Studies on efficacy and safety

17.2 Post-marketing surveillance, etc.

17.3 Others

18. Pharmacology

18.1 Mechanism of action

18.2 ○○ action

19. Physicochemistry

20. Precautions in handling

21. Approval conditions

22. Packaging

23. References

24. Request for literature should be made to:

25. Precautions related to insurance benefits

26. Manufactured and distributed by:

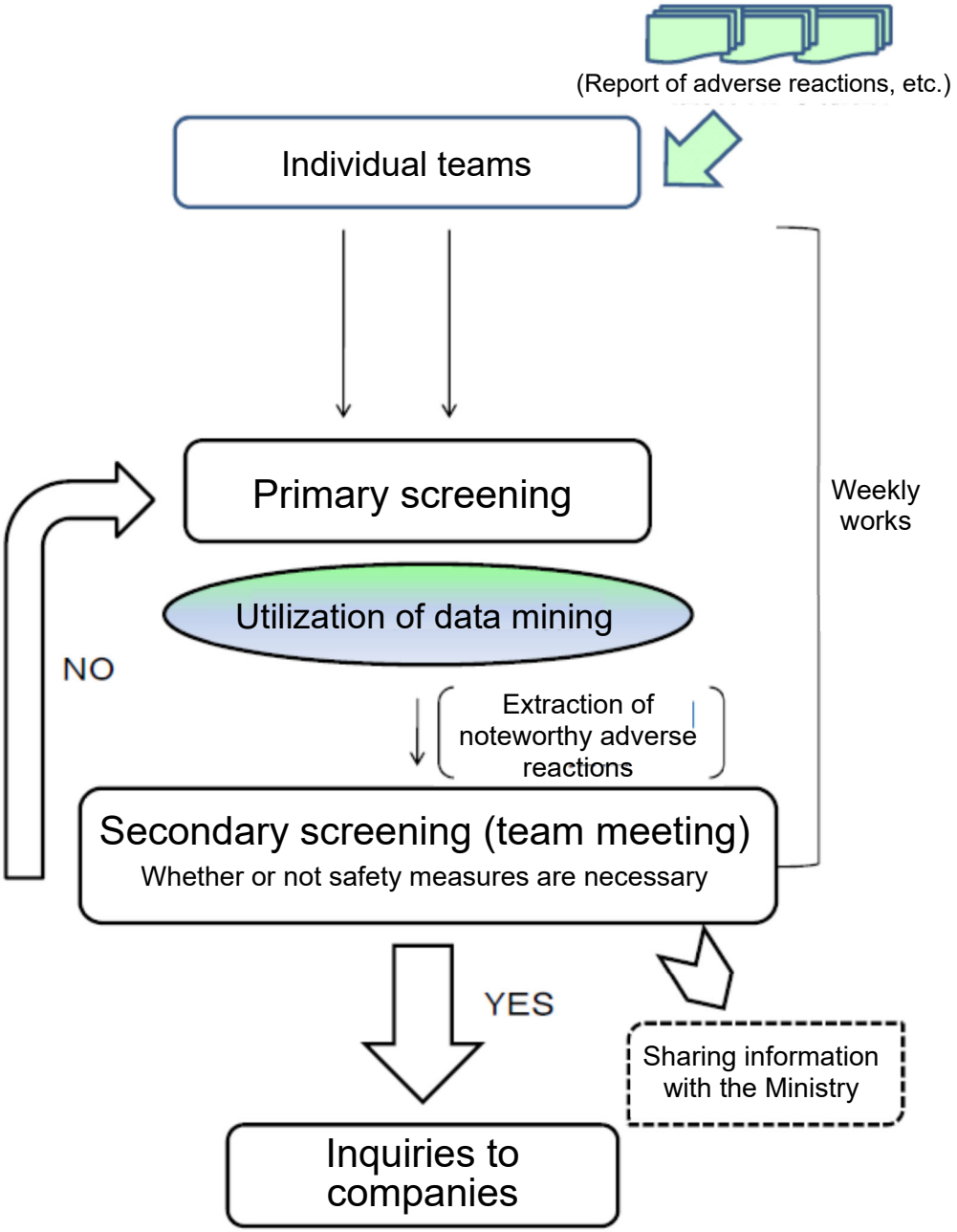

Fig. 19 Standard Procedures for Revision of Package Insert at PMDA (1)

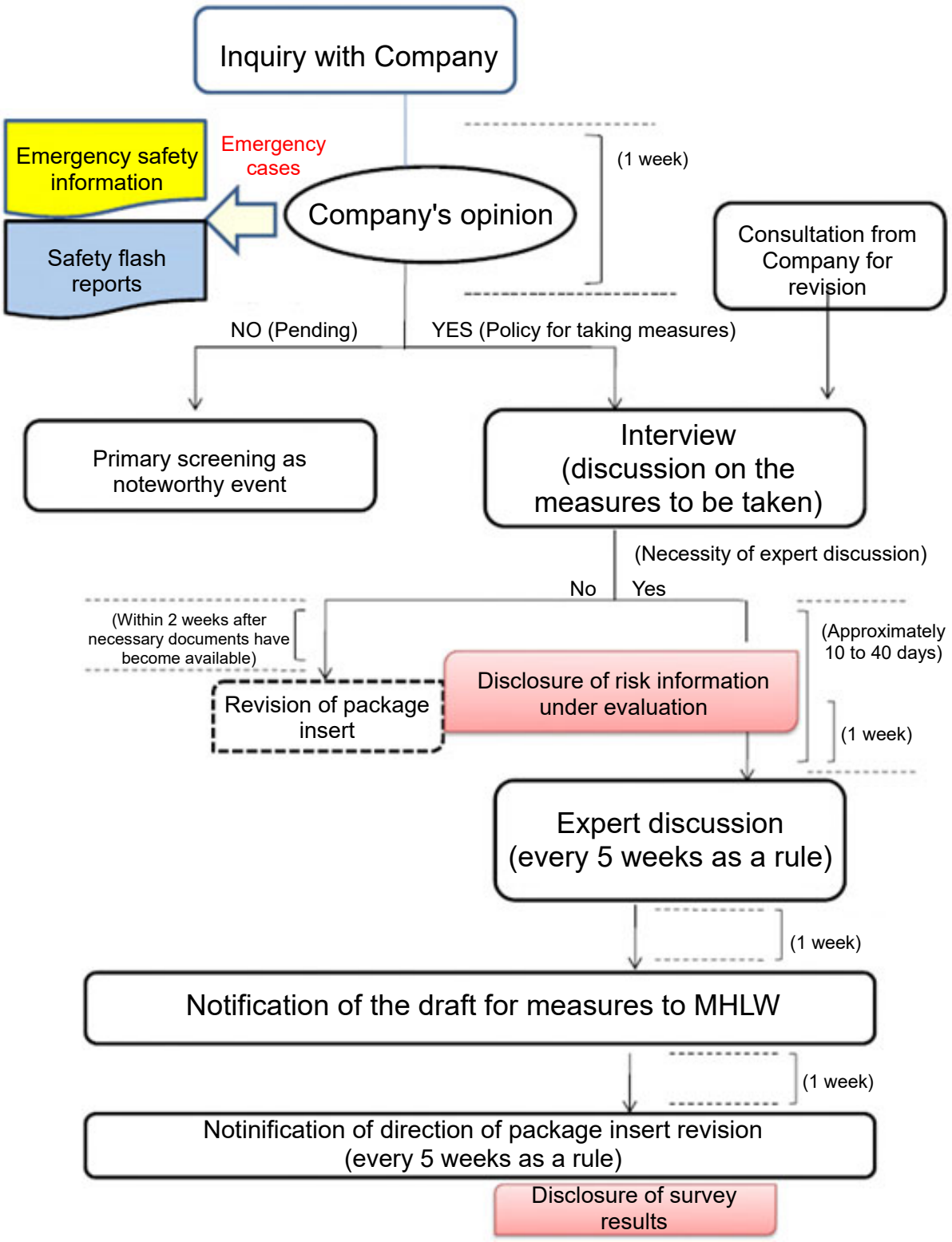

Fig. 20 Standard Procedures for Revision of Package Insert at PMDA (2)