September 29, 2014

# Notification

PFSB/SD Notification No. 0929-2

To: Commissioner of Prefectural Health Department (Bureau)

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

## Guideline on Revision of Precautions and other information

The *Act for Ensuring the Quality, Efficacy, and Safety of Drugs, Medical Devices, and other products* (Act No. 145, 1960. Hereinafter referred to as "the Act") after revision by the *Act for Partial Amendment of the Pharmaceutical Affairs Act etc.* (Act No. 84, 2013) requires marketing authorization holders of drugs, medical devices, and cellular and tissue-based products to notify and make public of information specified in the Items in Article 52-1, Article 63-2-1, and Article 65-3-1 of the Act (hereinafter referred to as "package insert and other information"). This regulation stipulates that the details of the package insert and other information must be based on the latest literature and other evidence.

Package insert and other information of each drug had been revised accordingly via the Obligation to Prevent Harm specified in Article 77-4 of the Act and via the safety management operations of the marketing authorization holders based on the *Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices* (Ministerial Ordinance No. 135 of the Ministry of Health, Labour and Welfare, 2004. Hereinafter referred to as the "GVP Ordinance"). With the recent revision of the *Pharmaceutical Affairs Act*, the points to be considered have been compiled as attached guideline regarding the safety management operations of the marketing authorization holders, in order for the latest package insert and other information to be available at all times. We ask that you inform marketing authorization holders and relevant organizations placed under your administration to utilize this for their business operations.

Although this guideline was prepared for Precautions and other information of prescription drugs (excluding in vitro diagnostics), post-marketing safety management of other drugs, medical devices, and cellular and tissue-based products shall be conducted in accordance with this guideline.

# Attachment

## Guideline on the Revision of Precautions and other information for Prescription Drugs

In order for drug marketing authorization holders to develop appropriate safety-ensuring measures, including revision of package insert and other information, based on the latest safety management information, safety management information must be collected appropriately and scientifically considered, and based on those results, procedures must be stipulated to enable development of safety-ensuring measures, and operations must be steadily conducted according to that procedure. The following are the points to be considered for this.

### 1. Principles

#### (1) Basic approach

- All relevant persons in the company shall approach their work with intensity since the post-marketing safety management of drugs is a drug risk management operation. They shall act with caution, collect detailed safety management information, and provide information to the safety management division or the division for safety-ensuring operations (hereinafter referred to as the “safety management and other divisions”).

- The optimum safety-ensuring measures based on the latest safety management information shall be regarded as the highest priority in order to provide healthcare professionals and patients with drugs with the optimum risk/benefit balance.

- The marketing supervisor-general shall decide the safety-ensuring measure with the upmost respect to the measures that the safety management supervisor compiled.

- The marketing authorization holder shall make efforts to establish an in-house system, such as for personnel and organizations, in order to enable the marketing supervisor-general, safety management supervisor, and the safety management and other divisions to collect information promptly and appropriately; to take safety-ensuring measures based on the latest evidence; and to allow proactive approaches for introducing the latest evaluation methods/safety-ensuring measures.

- Attention shall be paid to information including diseases (e.g., clinical guidelines), the experience of drug use in clinical settings, and clinical positioning of the drug, which shall all be utilized in considering safety-ensuring information and developing safety-ensuring measures.

(2) In-house operational procedures and organization/system

- Operational procedures and organization/system shall be established to enable the safety management and other divisions to promptly and comprehensively collect safety management information.

- Operational procedures and organization/system shall be established to enable relevant divisions (e.g., development, manufacturing/quality assurance, sales, pharmaceutical affairs, call center) within the company to promptly provide the safety management and other divisions with necessary information (e.g., adverse drug reaction/infection information [including adverse events], information related to drug development such as development safety update report [DSUR], company core data sheet [CCDS], company core safety information [CCSI], periodic benefit-risk evaluation report [PBRER], information on defects etc., safety information from healthcare professionals etc.).

- Operational procedures and organization/system shall be established to enable the safety management and other divisions to centrally evaluate/analyze safety management information and to develop safety-ensuring measures appropriately.

- The safety management and other divisions shall be proactively involved in the development of risk management plans (RMP) from the stages of drug development and application reviews.

(3) Relationship with foreign and domestic relevant companies

- A system shall be established for information to be promptly obtained from foreign and domestic relevant companies (including headquarters of foreign companies) and to enable adequate communication.

- When preparing CCDS, CCSI, and PBRER with foreign companies, a system shall be established to enable use of Japanese safety management information in consideration of safety-ensuring operations.

- Marketing authorization holders that market products also distributed in a foreign country shall make agreements in advance on methods of obtaining safety management information, communication methods, and deadlines for providing information with relevant groups or foreign corporations in which contracts have been concluded on marketing of products, and shall collect safety management information specified in Article 7 of the GVP Ordinance in accordance with “Procedures for Collecting Safety Management

Information" specified in Article 5-1-1 of the GVP Ordinance.

2. Collection of Safety Management Information

In obtaining safety management information ([1] information from healthcare professionals, [2] information from academic conference reports/literature etc., [3] information from Ministry of Health, Labour and Welfare, prefectures, PMDA, etc., [4] information from foreign governments, foreign companies, etc., [5] information from other marketing authorization holders etc., [6] other information) specified in Article 7 of GVP Ordinance, the following matters are required to be considered.

(1) Collecting information from healthcare professionals

- Collect information on adverse drugs reactions etc. from the medical institutions to which products are supplied, and explain at every opportunity the importance of safety management operation, especially of providing information on adverse drug reactions/infections (including adverse events) etc. to the marketing authorization holders.

(2) Collecting literature/academic conference information, foreign regulation information and other information

- Select literature/academic conferences etc. according to the area of the study that the drug handles in order to obtain information.

- Steadily collect regulatory information from regulatory agencies of Japan, the United States, and Europe as well as from the World Health Organization etc.

- Be careful so that the area of information collection (e.g., literature/academic conference subject to information collection, search keyword) is appropriate when using medical information outsourcing services in collecting literature/academic conference information and foreign regulation information.

- If evaluation of the causal relationship between the adverse event and the drug is necessary, collect information from epidemiological surveys regarding the disease and consider conducting appropriate epidemiological surveys.

- Collect information on the efficacy of the drug as well, which shall be used in considering safety

management information and developing safety-ensuring measures.

- Promptly collect information from Ministry of Health, Labour and Welfare and PMDA by registering on the PMDA Medinavi website etc.

- In addition to the above, marketing authorization holders of generic drugs must be regularly checked for any package insert information that has been updated within one month in order to promptly obtain knowledge of any revision to the Precautions in brand name products.

3. Considering Safety Management Information

Because consideration of the collected safety management information will be the premise of developing safety-ensuring measures, the following points shall be put into account when considering safety management information.

- Evaluation of the causal relationship shall be discreet and be based on objective information to the extent possible. If information is insufficient for evaluating, continue detailed investigations etc. at medical institutions and re-evaluate upon collection of information.

- Pay attention to the accumulated status of domestic and foreign adverse drug reactions (including adverse events) and to similar adverse drug reactions (e.g., whether there is any related adverse drug reaction or reporting via other names of adverse drug reactions). Pay attention to cases of adverse reactions of the drug of interest or adverse reactions of drugs in the same category reported by other marketing authorization holders by utilizing the PMDA website regarding information about case reports on suspected adverse drug reactions.

- Examine the relationship of safety management information with clinical trial data and non-clinical trial results.

- Regarding cases with adverse drug reactions, examine whether there is any characteristic patient background (e.g., complications, coadministered drugs, clinical laboratory values); whether there is any tendency of adverse drug reactions in specific areas or medical institutions; whether there is any relationship with a specific lot etc.; or whether there is any suspected factor in changes of frequency etc.

4. Development of Safety-ensuring Measures

The following points shall be considered when developing safety-ensuring measures based on the consideration of safety management information (e.g., recalls, Dear Healthcare Professional Letters of Emergent Safety Communications, Dear Healthcare Professional Letters of Rapid Safety Communications, revision of package insert, conduct of new surveillance), and it is important to advance the development via consultations with PMDA and MHLW, if necessary.

- Detect early signals using analytical methods such as data mining.

- Determine safety-ensuring measures based on the factors including seriousness/severity, causal relationship, accumulated status, and necessity of emergency measures of the adverse drug reactions.

- If there is an established RMP, develop safety-ensuring measures based on the latest risk management plan and risk minimizing plan.

- Develop optimum safety-ensuring measures to minimize any risk. Develop additional measures especially if there are many non-complying cases for proper use of product.

- When establishing safety-ensuring measures, confirm the present description in the package insert used in Europe and the United States, CCDS, CCSI, and package inserts of similar products.

- When establishing safety-ensuring measures based on foreign regulatory information (including revision of CCDS, CCSI), confirm the rationale of the foreign regulation and consider whether safety-ensuring measures are necessary at medical practices in Japan.

5. Periodic Review of the Package Insert

Adverse drug reaction reporting system, GVP, and other systems have been gradually established based on the *Pharmaceutical Affairs Act*, and if these are complied, there will be no major problem regarding important matters of the current package insert.

However, for drugs (including generic drugs) in which much time has elapsed since their initiation of marketing and little recent safety information has been obtained, it is important to periodically review those current package inserts from the perspective of whether they are reflecting the latest evidence.

In such cases, it is desirable to compare with the following information and periodically confirm whether the current Precautions, the handling precautions, and other information are appropriate.

- Information such as CCDS, CCSI

- Current status of foreign measures

- Accumulated status of literature information

- For similar products and generic drugs, the present description of Precautions and other information in the brand name product.

-The present description regarding newly observed interactions with other products