December 2, 2013

Notification

PFSB/SD Notification No.1202-1

Director of Safety Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Good Vigilance Practice Ordinance to be complied by Marketing Authorization Holders

The *Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices* (MHLW Ministerial Ordinance No.135 of 2004; hereinafter referred to as "*GVP Ordinance*") is stipulated as requirements for licensing marketing authorization holders under Article 12-2-2 of *Pharmaceutical Affairs Law* (Act No. 145, 1960; hereinafter referred to as "*PAL*"). Caveats of the GVP Ordinance are presented in notifications including the *Notification on Enforcement of the Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices and the Ministerial Ordinance on Partial amendment of Pharmaceutical Affairs Law Enforcement Regulations* (PFSB Notification No. 0992005, dated September 22, 2004), *Notification on Enforcement of the Ministerial Ordinance and other rules on Partial amendment of the Pharmaceutical Affairs Law Enforcement Regulations (regarding Adverse Drug Reaction Reports or Other Case Reports)*（PFSB Notification No. 0317006, dated March 17, 2005; hereinafter referred to as "*ADR Notification*"）.

The Pharmaceuticals and Medical Devices Agency (PMDA) recently conducted assessment of compliance of re-examination application with the *Ministerial Ordinance on Good Post-marketing Study Practice for drugs* (MHLW Ministerial Ordinance No.171 of 2004), and identified cases that might be conflict with the *GVP ordinance*. Further, the PMDA has noticed some cases that needed to be improved in post-marketing safety measures regarding compliance with the *GVP ordinance*. Caveats for post-marketing pharmacovigilance practices under the *GVP Ordinance*, therefore, are presented below. You are encouraged to be aware of the following descriptions, and fully inform and instruct relevant companies and organizations under your jurisdiction.

If the MHLW/PMDA finds cases described in 'Notes' 1-4 or cases where reporting of adverse reactions was delayed, the information on reporting delay will be provided to relevant municipalities in order to promote appropriate post-marketing pharmacovigilance practices.

Notes

1. Collecting research reports suggesting that drugs do not demonstrate effectiveness for approved indications

Research reports suggesting that drugs do not demonstrate effectiveness for approved indications, which are required under Article 253-1-2-ロ of the *Pharmaceutical Affairs Law Enforcement Regulations* (hereinafter referred to as "*Enforcement Regulations*") based on PAL Article 77-4-2, include clinical trials or preclinical studies suggesting that drugs or active

ingredients do not demonstrate effectiveness for approved indications; However, some *Protocols on Collection of Safety Management Information* stipulated in Article 5-1-1 of the *GVP ordinance* were considered to have flaws to collect research reports suggesting lack of effectiveness. There also have been some *Protocols on Collection of Safety Management Information* that include reports of only clinical trials and do not include reports of preclinical studies.

MAHs are required to appropriately collect safety management information stipulated by Article 7 of the *GVP Ordinance* by setting up the *Protocols on Collection of Safety Management Information* that provide how to collect literature or other articles suggesting that marketed drugs or active ingredients do not demonstrate effectiveness for approved indications in clinical trials, preclinical trials, and other findings.

2. Prompt collection of information from overseas companies

MAHs should collect safety management information from overseas companies, if there are drugs that are used overseas and ascribed to contain the same ingredients as the drugs manufactured by the MAHs (hereinafter referred to as "*overseas drug*"). However, there have been cases where information was not collected appropriately (e.g., cases where information collection was too fragmentary to take an appropriate safety measure, or where it took too long time to obtain information from overseas companies).

MAHs manufacturing drugs that has *overseas drugs* should appropriately collect safety management information stipulated by Article 7 of the *GVP Ordinance* by determining with overseas companies in advance about ways of obtaining and transmitting of safety management information and time deadlines for providing information, and including these procedures in the *Protocols on Collection of Safety Management Information* under Article 5-1-1 of the *GVP Ordinance*.

If MAHs learn that a new additional safety measure (e.g., revision of labeling of *overseas drug*, or revision of company core safety information [CCSI] of drugs used internationally) is under review, the MAHs should promptly submit the information to the PMDA. MAHs are also required to review necessity of an additional safety measure including revision of package inserts in Japan concurrently before a safety measure including labeling revision is finalized overseas.

3. Consideration of necessity for reporting Adverse Drug Reactions (ADRs)

When MAHs consider safety management information based on Article 8-1-1 of the *GVP Ordinance* regarding adverse drug reaction reports obtained from medical facilities and determine whether the ADRs fall under any of (1) through (5) of 253-1-1-ノ of the *Enforcement Regulations* (i.e., determination of seriousness of the ADRs), some MAHs appeared to determine based on only opinions of reporting doctors or healthcare professionals and fail to report to the PMDA about the ADRs that should have fallen under any of (1) through (5) of 253-1-1-ノ of Enforcement Regulations.

MAHs are responsible to determine seriousness of ADRs conclusively, even if the reporting doctors considered that the ADRs were non-serious. MAHs should comprehensively determine seriousness of reported ADRs, considering symptoms and overall status, underlying and concomitant diseases, and outcomes of patients.

4. Management when upgrading of data-processing systems

In the case where MAHs outsourced data-processing of ADR reports, there have been some cases where information on ADRs that should have been submitted under *PAL* were not appropriately processed and failed to be reported, because data-processing was affected by updated programs after upgrading of data-processing systems in outsourcing contractors.

MAHs should ensure that updated programs following upgrading do not affect data-processing not only in their own companies but also in outsourcing contractors, in order to process information on ADRs appropriately.