March 24, 2006

Notification

Administrative Notice

To: Federation of Pharmaceutical Manufacturers' Associations of JAPAN

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

Q&A on Early Post-marketing Phase Vigilance for Prescription Drugs

The implementation method, etc. of the early post-marketing phase vigilance for prescription drugs has been specified in PFSB/SD Notification No. 0324001 by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated March 24, 2006, "Implementation Method, etc. of Early Post-marketing Phase Vigilance for Prescription Drugs." This time, in relation to this notification, "Q&A on Early Post-marketing Phase Vigilance for Prescription Drugs" has been summarized as shown in the Appendix. This notification asks for your cooperation in making these widely known to affiliated vendors.

Q&A 1 to 23 in Administrative Notice by Safety Division and Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare, dated February 23, 2001, "Q&A on Enforcement of Ministerial Ordinance to Partially Revise the Ministerial Ordinance on Good Post-marketing Surveillance Practices and Revision of Early Post-marketing Phase Vigilance in Relation to Reexamination of Drugs" shall be deleted, associated with the issuance of this administrative notice.

A copy of this administrative notice will be sent to each division of the Pharmaceutical Affairs, Prefectural Health Department (Bureau).

(Appendix)

Q&A on Early Post-marketing Phase Vigilance for Prescription Drugs

[Abbreviations]

Act: Pharmaceutical Affairs Act (Act No. 145 of 1960)

Enforcement Ordinance:
Ministerial Ordinance for Enforcement of Pharmaceutical Affairs Act (Ordinance of the Ministry of Health and Welfare No. 1, 1961)

GVP Ordinance:
Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (Ordinance of the Ministry of Health, Labour and Welfare No. 135, 2004)

MR: Medical Representative

PMDA: Pharmaceuticals and Medical Devices Agency

MHLW: Ministry of Health, Labour and Welfare

EPPV: Early post-marketing phase vigilance

MAH: Marketing authorization holder

Q1: What kind of survey is the early post-marketing phase vigilance? What types of drugs are subject to the vigilance?

A1: “Early post-marketing phase vigilance” (hereinafter referred to as “EPPV”) is a survey of which the major purpose is to ensure that healthcare professionals understand the correct use of drugs by providing accurate information, precautions, etc. to medical institutions and to minimize the damage caused by adverse drug reaction, etc. during the 6-month period from the time when the marketing authorization holders (hereinafter referred to as “MAHs”) of drugs launch their products as well as by promptly collecting information on the occurrence of cases, etc. listed in Article 253, Paragraph 1, Item 1-(a), 1-(c)-(i) to -(v), and 1-(g) as well as Paragraph 1, Item 2-(a) of the Enforcement Ordinance and taking necessary safety measures.

Drugs subject to EPPV are new drugs that fall under Article 14-4, Paragraph 1, Item 1 of the Act, provided that such drugs may be excluded from EPPV if there is a rational reason not to conduct EPPV.

(Reference) Enforcement Ordinance (Excerpt)
Article 253 When MAHs or foreign exceptional approval holders for drugs learn of any of the following events concerning the drugs which they market or have obtained approval for, they shall report this fact to the Minister within the period specified for the event that occurred.

(1) The following events: 15 days
  (a) Deaths suspected of being caused by an adverse reaction of the drug concerned.
  (Omitted)

(c) Any of the following events when it is suspected that they have been caused by an adverse drug reaction of the drug concerned or an overseas drug and such events could not have been predicted from the Precautions etc. of the drug concerned or when it could have been predicted from the Precautions, etc. of the drug concerned but the conditions for onset could not have been predicted or changes in the conditions for onset may cause or spread hazards to public health and hygiene [excluding cases in (d) and (e)].
  (i) Disability
  (ii) Cases for which there is a risk of death or disability
  (iii) Cases that require admission or prolongation of the period of admission to a hospital or clinic for treatment [excluding cases in (ii)]
  (iv) Deaths or severe cases corresponding to those in (i) to (iii)
  (v) Congenital diseases or anomalies in the next generation

(d) Adverse reaction suspected to be caused by the drug concerned occurring in the cases in (c) (i) to (v) when 2 years have not passed from the date of approval for drugs approved under Article 14, Paragraph 1 of the Act as a drug which has different active ingredients from those in approved drugs provided in Article 7, Paragraph 1, Item (1) (a) (i) of the Fee Ordinance related to the Pharmaceutical Affairs Act (Cabinet Order No. 91, 2005)

(e) Onset of cases in (c) (i) to (v) suspected to be caused by an adverse reaction of the drug concerned when the drug was undergoing EPPV pursuant to the provisions of Article 2, Paragraph 3 of the Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices (MHLW Ordinance No. 135, 2004) [excluding cases in (d)]

(f) Onset of infection suspected to be caused by the use of the drug concerned that could not have been predicted from the Precautions, etc. of the drug concerned.

(g) Deaths or onset of events in (c) (i) to (v) caused by infection suspected to be due to the use of the drug or overseas drug concerned [excluding cases in (f)]
(Omitted)

(2) The following events: 30 days
  (a) Onset of events in (c) (i) to (v) of the preceding item suspected to be caused by adverse reaction of the drug concerned [excluding cases in (c), (d), and (e) in the preceding item]
  (Omitted hereafter)

Q2: Explain the relationship between EPPV and the system of reporting adverse drug reaction/infection based on the provision of Article 77-4-2, Paragraph 1 of the Act.

A2: The purpose of EPPV is to promote immediate reporting of information on serious adverse drug reaction or infection when they occur, and to avoid such information remaining unreported or hidden, by periodically and repeatedly asking and alerting doctors, etc. who use MAH's drugs;

(1) To make efforts to appropriately use the drug because it is a new drug.
(2) To utilize the given information on safety management in order to ensure appropriate use.
(3) To immediately report when serious adverse drug reaction or infection occur.

Therefore, when MAHs, etc. obtain information on the occurrence of serious adverse drug reaction or infection from medical institutions during EPPV, they are required to report to PMDA based on the provision of Article 77-4-2, Paragraph 1 of the Act.

Note that, based on the provision of Article 253, Paragraph 1, Item 1-(e) of the Enforcement Ordinance, a serious case, etc. that occurs during EPPV and is suspected to be caused by an adverse reaction to a drug should be reported to PMDA within 15 days, regardless of its predictability from Precautions.

(Reference) Pharmaceutical Affairs Act (Excerpt)
Article 77-4-2 MAHs or foreign exceptional approval holders of drugs, quasi-drugs, cosmetics, or medical devices must report to the Minister as specified by MHLW Ordinance when they learn of diseases, disabilities, or deaths suspected to be caused by adverse drug reaction or for other reasons and when infectious diseases are suspected to be caused by use of drugs, quasi-drugs, cosmetics, or medical devices or any other matter specified by MHLW Ordinance related to the efficacy and safety of drugs, quasi-drugs, cosmetics, or medical devices that they market or have received approval to market.

Q3: What should an MAH do when it believes that there is a rational reason not to conduct EPPV at the stage of review for approval of the new drug?

A3: MAHs are requested to prepare documentation on the rationale for not conducting EPPV and to consult Office of Safety II, PMDA. This consultation should be done as soon as possible after it is found that the case is an issue[Note)] requiring deliberation by Drug Committee I or Drug Committee II of Pharmaceutical Affairs and Food Sanitation Council, or by the time before the Committee convenes at the latest.

Note: If the case is determined to be an issue to be reported, not an issue to be deliberated, no re-examination period will be newly added to the case.

Q4: Regarding drugs with Conditions for Approval to conduct EPPV provided in Article 10 of GVP Ordinance, is it necessary to describe these Conditions for Approval in the package insert of the drug?

A4: No, it is not necessary.

Q5: Explain how to show that the new drug is subject to EPPV.

A5: That should be clearly shown in the “Ethical Drug Product Information Brochure,” “Explanation of ‘Precautions’ of the New Drugs,” etc. for 6 months after the launch of its sale. It is acceptable to use a mark standardized by the pharmaceutical industry or its sticker, if it can clearly show that the drug is subject to EPPV.

Q6: What exactly is meant by the date of the “launch of sale” provided in Article 2, Paragraph 3 of GVP Ordinance?

A6: In principle, it is the date of launch determined by MAHs.

Q7: What exactly is meant by the date of “launch of sale” in cases of additional Indications or additional Dosage and Administration (products subject to re-examination)?

A7: In principle, it is the approval date of the partial change to the Indications or Dosage and Administration. In this case, it is acceptable that an explanation and request for cooperation on EPPV is performed before supplying a drug within approximately 2 weeks after the approval of the partial change to the approved product information.

If an MAH newly supplies a drug to a medical institution where the MAH has no previous history of supplying the drug, the MAH should make efforts to provide an explanation and make a request for cooperation before supplying the drug.

Q8: Is it necessary to submit an EPPV plan before the start of EPPV?

A8: Currently, MHLW and PMDA do not uniformly require submission of the plan in advance. However, if there is an issue requiring consultation in relation to preparing an EPPV plan, consult the Drug Safety Division,Office of Safety[1].

Q9: Are dispensing pharmacies subject to EPPV?

A9: Principally, hospitals and clinics are subject to EPPV but dispensing pharmacies are not. However, MAHs should provide necessary information, etc. to dispensing pharmacies.

Q10: Is it necessary to conclude a contract on EPPV with medical institutions before starting EPPV?

A10: No, it is not necessary.

EPPV is different from use-results surveys, specified use-results surveys, etc. EPPV is not a survey for individual cases but part of collecting and providing information on safety management and reporting activities that have been conventionally conducted based on the provisions of Article 77-3, Paragraph 1 and Article 77-4-2, Paragraph 1 of the Act[2].

Q11: Is it necessary to provide medical institutions with information on safety management obtained from EPPV?

A11: Regarding information on safety management obtained from EPPV, such information should be provided to medical institutions, etc. at appropriate intervals. For example, when many cases of serious adverse drug reaction are reported, such information should be compiled every month and provided to medical institutions with measures to ensure safety.

Q12: What are the implications of the time of supply for medical institutions adopting external prescription?

A12: In medical institutions adopting external prescription, EPPV should, in principle, be conducted taking the date of supply as the date when the drug began to be prescribed (when it was discovered that prescription of the drug had begun) or the date when the medical institutions adopted the drug, whichever is earlier. When MAHs become aware that the drug is being prescribed through spontaneous reports on adverse drug reaction, information from dispensing

[1] An EPPV plan shall be submitted to the Office of Safety 2 due to organizational restructuring after the issue of this notice

[2] The provision fall into Article 68-2, Paragraph 1 due to amendment of the Act in 2014 November.

pharmacies, or other sources, MRs, etc. should explain and request cooperation within approximately 2 weeks from the time of these facts became known.

Q13: The drug was previously supplied to a medical institution but was not used, and all of the supplied drugs were returned. In this case, if the drug was supplied to the medical institution again, how should EPPV be conducted?

A13: EPPV should be conducted based on the date when the drug was supplied again as the starting date. In this case, if the explanation and request for cooperation before supply were already done at the time of initial supply, such explanation, etc. may be omitted the second time. However, the periodic request for cooperation, etc. should be made on the date when the drug was supplied again as the starting date, even if the periodic request for cooperation and alerting had been done after the initial supply.

Q14: When MRs cannot explain and make a request for cooperation before supplying the drug, what kind of document on explanation and request for cooperation should be prepared? How should this be carried out specifically?

A14: For example, it is a written request prepared by MAHs which describes the purpose of EPPV and the request for cooperation. “Ethical Drug Product Information Brochure” or “Explanation of ‘Precautions’ of the New Drugs” may not be replaced with the document on explanation.

Regarding the method of contact, it is acceptable to provide the document by mail, facsimile, e-mail, or utilizing wholesaler, etc.

In this case, MRs shall explain and make a request for cooperation within approximately 2 weeks after the start of supply.

Q15: Can the drug be supplied to the medical institutions that will not cooperate despite the provision of an explanation and request for cooperation before supplying the drug?

A15: EPPV does not restrict the supply of the drug to medical institutions. However, making requests for cooperation should be continued by explaining the purpose of this system even after the start of supply.

Q16: How should the explanation and request for cooperation be carried out when it is discovered that the drug is being supplied to medical institutions where the explanation and request for cooperation should have been done before supply but have not in fact been done?

A16: Efforts should be made to ascertain which medical institutions are being supplied. However, if such a case is discovered after supply has begun, MRs, etc. shall explain and make a request

for cooperation within approximately 2 weeks from the time when MAHs became aware of the fact that the drug was being supplied.

Q17: When a drug of one product with one name is marketed by more than one company, should each company request cooperation, etc. on EPPV?

A17: This should be done by MAHs at their own responsibility and are not to be done by individual distributors. Outsourcing within a specified scope is acceptable.

Q18: Is it necessary to keep a record about the explanation and request for cooperation before (or after) supply of the drug, and periodic request for cooperation and alerting after supply?

A18: In order to conduct EPPV appropriately, it is necessary to retain the explanatory document before and after supply of the drug and the written request asking for cooperation. In addition, it is also necessary to prepare a procedure to ascertain the status of a visit, etc. by the MRs, etc. and to keep a record of the status, etc. The record on the conduct of EPPV shall be prepared in each medical institution and appropriately managed as shown in Part 2-2, (8)-d of PFSD Notification No. 0922005 by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, dated September 22, 2004, “Enforcement of Ministerial Ordinance to Partially Revise the Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices and Ordinance for Enforcement of the Pharmaceutical Affairs Act.”

(Reference) Part 2-2, (8) of PFSD Notification No. 0922005 by the Secretary-General of Pharmaceutical and Food Safety Bureau, MHLW, dated September 22, 2004; Early Post-marketing Phase Vigilance (in relation to Article 10)

(a) to (c) (Omitted)

(d) The first-class MAHs shall collect information on safety management related to EPPV, examine it, and take necessary measures based on the results of the examination, according to the provisions of Article 7, 8, and 9, respectively, of the GVP Ordinance. Records on the implementation of EPPV shall be prepared and appropriately managed in each medical institution.

Q19: Specifically, how should the periodic request for cooperation and alerting after supply be done?

A19: Preferably, this should be done by the MRs, but it is also acceptable that they are done by mail, facsimile, e-mail, or contact by the wholesalers, etc. However, when serious adverse drug reaction or infection occur, it is necessary to collect information, etc. according to the post-marketing safety management operating procedure manuals of each MAH. For example, MRs visit the medical institutions.

Q20: Is it necessary to conclude a contract with a wholesaler when they are requested to perform the information provision service such as periodic alerting to medical institutions?

A20: When the service provided in Article 97 (Range of Activities for Post-marketing Safety Management that May Be Subcontracted) of Enforcement Ordinance is to be outsourced, it is necessary to conclude the contract with the wholesaler based on the provision of Article 98-2 (Methods for Subcontracting Post-marketing Safety Management Activities for Prescription Drugs or Highly Controlled Medical Devices) or Article 98-3 (Methods for Subcontracting Post-marketing Safety Management Activities for Non-Prescription Drugs or Controlled Medical Devices) of Enforcement Ordinance.

Q21: What are the "safety measures" that are to be described in the EPPV report?

A21: This refers to, for example, measures such as the revision of the package insert and information provision activities to ensure safety, which are taken when MAHs obtain information on "occurrence of serious adverse drug reaction or infection" from medical institutions.

Q22: If consultation to PMDA is necessary regarding the enforcement of safety measures such as revision of Precautions, is it the Drug Safety Division, Office of Safety[3], PMDA, which is responsible for the consultation services?

A22: Yes, it is acceptable.

Q23: How is the end date of EPPV determined?

A23: In principle, the date of the "end of the EPPV period" is the date when 6 months has elapsed after the start of EPPV. However, it is acceptable to set the date as the last day of the month in which EPPV is scheduled to end. In this case, the EPPV report shall be submitted within 2 months from the date that is regarded as the end date of EPPV.

Q24: Should the EPPV report and the periodic safety report be submitted separately?

A24: Yes, they are to be submitted separately.

[3] Now the Office of Safety 2 is responsible for the consultation service due to organizational restructuring after the issue of this notice.