Provisional Translation (as of October 26, 2009) *

Administrative Notice
September 7, 2009

To: Federation of Pharmaceutical Manufacturers' Association of Japan

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau (PFSB),
Ministry of Health, Labour and Welfare (MHLW),
Safety Division, PFSB, MHLW

Re: Q & A on use-results surveys conducted as All-Case Surveillance and Early Post-Marketing Phase Vigilance (EPPV) for Prescription Drugs

Regarding implementation procedures, etc. of drug use-results surveys that are conducted as All-Case Surveillance (hereinafter referred to as the All-Case Surveillance) and EPPV for prescription drugs, guidance is respectively shown by PFSB *(Yakusyoku-shinsa)* Notification No. 1027001 by the Director of the Evaluation and Licensing Division, PFSB, MHLW, dated October 27, 2005, "Guideline on the Implementation Procedures of Post-Marketing Surveillance, etc. for Prescription Drugs".

PFSB *(Yakusyoku-an)* Notification No. 0324001 by the Director of the Safety Division, PFSB, MHLW, dated March 24, 2006, "Implementation Procedures, etc. of EPPV for Prescription Drugs" and the Office Communication of Safety Division, PFSB, MHLW, dated March 24, 2006, "Q & A regarding EPPV for Prescription Drugs". Recently we reviewed the guidelines to make post-marketing surveillance and safety measures required for approving drugs more practical and effective and compiled our conclusions in "Q & A regarding All-Case Surveillance and EPPV for Prescription Drugs" as shown in the attachment. Please acknowledge and disseminate the information contained in this document to your member companies.

* This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the Japanese text shall prevail.

(Attachment)

Q & A for All-Case Surveillance and EPPV for Prescription Drugs

<All-Case Surveillance>

Q1: For what kind of pharmaceutical products are required the All-Case Surveillance by a regulatory agency as an approval condition?

A1: The All-Case Surveillance means a use-results survey that is conducted to collect information on all patients who have used the product since its launch until a data from certain number of cases have been accumulated. The All-Case Surveillance is required for products that needs the background information of patients treated with the product as well as safety and efficacy issues related to the product for reaffirming approval details and collecting information which is essential for proper use at the earliest possible stage , thoroughly.

For example, the regulatory agency may require the implementation of the All-Case Surveillance for a pharmaceutical product as an approval condition when there are only a small number, or even no cases existing in clinical trials in Japan and when there are any concerns about the pharmaceutical product regarding the occurrence of serious adverse drug reactions. Necessity for the All-Case Surveillance is determined by the following steps: review in PMDA[1)], subsequent discussion by the Pharmaceutical Affairs and Food Sanitation Council, and the final decision by MHLW.

Q2: Should use-result survey protocols for the All-Case Surveillance indicate contents of safety management[2)] programs and procedures of promoting proper use etc.?

A2: A Marketing Authorization Holder (MAH) can consult with PMDA[1)] individually if the sections of contents of the safety management programs and the methods of promoting proper use can be prepared separately from the use-result survey protocol.

The All-Case Surveillance is essentially aimed to keep track of information for proper use. The MAH should clearly set out and indicate the purpose, the number of subjects, and the study period, etc. in "basic protocol for post-marketing surveillance, etc." and "protocol for use-results survey".

Q3: A MAH usually conducts an All-Case Surveillance required prospectively as a conditional approval. Is it possible for the MAH to conduct it retrospectively, when the MAH has information on all cases who received the product?

A3: An All-Case Surveillance should be conducted prospectively as a rule. However, the MAH may replace the prospective surveillance with a retrospective one when there is a compelling reason

Q4: Is it possible that the regulatory authorities issue a notification requesting cooperation on All-Case Surveillance of the product in order to gain the understanding and cooperation more easily?

A4: Regulatory authorities are facilitating the understanding of those who are concerned by explicitly defining that the product is subject to the all –cases surveillance etc. in the package insert and the other official documents. However, regulatory authorities may consider the appropriate measures on a case-by-case basis. If applicants need the consultation, they should consult PMDA[1)] at their earliest possible convenience.

Q5: Are there cases in which the regulatory authorities require the collected results of adverse drug reaction occurrence and the status of treated cases (the registry status of the all-cases surveillance, etc.), periodically , at frequencies higher than periodic safety reports?

A5: Yes, there are.

But, as a rule , when regulatory authorities make such a request, they will issue a written document on the frequency and limit of the time for reporting, including the reasons at an early stage before the relevant committee meeting of the Pharmaceutical Affairs and Food Sanitation Council,.

Q6: For All-Case Surveillance can the MAH stop the patient registration for surveillance and requests made to medical institutions for new enrollment on

survey forms as soon as the target number of cases has been reached as stated in the protocol?

A6: The MAH can stop the requests to medical institutions for new enrollment on survey forms once the target patient number of the all-case survey stated in the protocol is reached. However, the MAH should continue the patient registration and keep the framework to collect survey forms and obtain proper information on an as-need basis, until the acknowledgement of the report at a committee meeting, at which time the approval condition is removed. Also, the MAH should consult PMDA[1)] regarding the handling of ongoing All-Case Surveillance in approval conditions.

Q7: What are the condition, procedure and timeline for the removal of an approval condition which imposes the All-Case Surveillance?

A7: If the MAH desires to remove the approval condition for the product which is ready for a certain degree of analysis and evaluation without waiting for an application for there-examination, the MAH can submit a written request for removal of the approval condition to the MHLW. After the receipt of the request, PMDA[1)] will evaluate and discuss the details of the surveillance, subsequently MHLW will decide whether or not to remove it with PFSB's agreement. The timeline for this differs depending on the product. PMDA[1)] will try to indicate the timeline to the MAH at an early stage after the written request is submitted. Before submitting the written request, contact PMDA[1)] with the details of the submission.

Q8: In some cases where All-Case Surveillance is required, MAHs are instructed to publish the progress of the surveillance and information collected on adverse drug reactions on their website. Are there any criteria for the contents, publication frequency, and publication period? When we want to change the way we publish the information, whom should we consult?

A8: Information to be made public is specified case-by-case at review based on the characteristics of the drug and patterns of adverse reactions. The protocol for conducting use-results surveys should include information on the method of publication. It is important to publish the information, focusing on the characteristics of each surveillance. Consult PMDA[1)] regarding any change to this publication.

Q9: Is it possible to use the materials, which support the status of visits to medical institution in the All-Case Surveillance, as a substitute for the visit record for early post-marketing surveillance, when the frequency of visits for All-Case Surveillance are planned higher than early post-marketing survey?

A9: It may be possible as long as those materials are developed that can feasibly substitute visit records for the early post-marketing surveillance. Consult PMDA[1)] for the acceptability of substitution.

<Early Post-Marketing Surveillance>

Q10: A1 of the office communication dated March 24, 2006 states that the EPPV may not be required, if there is a practical reason for not conducting the surveillance." Are there any specific examples of such cases?

A10: Yes, one example is that a supplemental approval for added indications for an approved pharmaceutical product where sufficient safety information on the product has been collected and where no change in its clinical usage is anticipated (e.g. there is no change in the indication, dosage and administration, precautions for use, or clinical department using the product)

Consult PMDA[1)] if the MAH considers that there is a practical reason for not conducting early post-marketing surveillance.

Q11: PFSB Notification No. 0324001 of the Safety Division, dated March 24, 2006, states that "appropriate procedure of conducting early post-marketing surveillance should be specified individually for each pharmaceutical product, though the following is suggested as a standard procedure," showing the standard procedure. However, what should the MAHs do when they will conduct specific surveillance, taking into account the characteristics of the product, its safety profile, etc. (i.e. changing the frequency of visits)?

A11: Consult PMDA[1)] when a draft of the EPPV protocol has been completed, if the MAHs will conduct specific surveillance on the basis of the characteristics of the product and its safety profile, etc.; for example changing visit frequency, so that it is appropriate for the product, product indications, the treatment population, and issues to be addressed.

Q12: When pharmaceutical products are expected to use in different diagnosis and treatment department from until due to additional drug indications, is it acceptable for the EPPV to only include those institutions with departments for diagnosis and treatment of those indications added?

A12: In principle yes, but consult PMDA[1)] in each case.

Q13: What kind of materials should be attached to the EPPV report?

A13: Attach the following materials so that the progress of the EPPV and appropriateness of the safety measures may be confirmed;

(1) The package insert at the time of submitting the EPPV

(2) Information Materials provided to medical institutions, etc. during and/or after the EPPV

(3) Materials relating to the progress of the EPPV conducted at medical institutions (the number of institutions at which explanations and requests for cooperation have been given before delivering the pharmaceutical product, the methods and frequencies of periodic requests for cooperation and drawing attention after delivery, etc.).

Q14: If the MAH provides the explanation on the EPPV and requests for cooperation with the EPPV at a product presentation targeting multiple medical institutions, can such a presentation be regarded that the MAH provided the explanation to all physicians who are at the presentation and requested for cooperation prior to delivery of the pharmaceutical product?

A14: Yes, as long as physicians who attended the presentation can be identified.

However, it must be described that aims of the presentation are explanation on the EPPV and request for cooperation with the EPPV.

Q15: What should be considered on the use of direct mails (DM), etc. as an alternative to MR visits during the EPPV?

A15: When using DMs, etc. as an alternative means, the way of thinking and reason regarding its use should be defined.

Note[1)] PMDA is an acronym of Pharmaceuticals and Medical Devices Agency. Office of New Drug is in charge of issues before marketing approval, and Office of Safety is in charge of issues after approval.

Note[2)] Safety management includes patient registration to ensure the safety of the pharmaceutical products and the management of distribution such as ensuring the delivery of the product to the correct institutions.