Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

February 22, 2013

FDA Circular
No. 2013-004

SUBJECT: Post Market Surveillance (PMS) of Authorized Drug Products

I. Rationale

This FDA Circular is issued in compliance to Section 5 of Republic Act No. 9711, otherwise known as the Food and Drug Administration (FDA) Act of 2009, which mandates the FDA to strengthen the post market surveillance (PMS) system in monitoring health products and incidents of adverse events, among others. The practice of monitoring the safety of a drug after it has been released in the market is an important aspect of Pharmacovigilance, as provided by Administrative Order (AO) No. 2011-009, the National Policy and Program of Pharmacovigilance.

On August 10, 2006, the BFAD, now the FDA, issued AO No. 2006-0021 to supplement AO No. 67 s. 1989, the Revised Rules and Regulation on Registration of Pharmaceutical Products and Bureau Circular No. 05 s. 1997, the Revised Checklist of Requirements and Guidelines for the Registration of Pharmaceutical Products. In the Annex of AO No. 2006-0021, new drugs, among others, were required PMS, i.e. to complete the clinical studies and to pass through a 3-year initial registration under monitored release before a market authorization or a Certificate of Product Registration (CPR) for general use may be granted.

Phase IV clinical trial was required for the following drug categories, as appropriate: newly introduced drugs, established drug with new indication, new route of administration or additional dosage or dosage strength, to gather more safety and efficacy data and information. A clinical trial protocol has to be submitted for approval before a Phase IV clinical trial can commence. The 3-year monitored or restricted release, however, is carried out on non-studied patients or patients of varying medical background and without interventions.

Based on the number of request for extension of marketing authorization under monitored release, the FDA observed that the studies conducted were at best seeding trials or marketing trials. One of the reasons cited for not completing the 3-year period studies was the failure to achieve the required number of around 3,000 patients. Based on the past reports submitted, PMS done through a monitored release were observational and non-experimental in nature.

The FDA pre-market approval process for market authorization is robust enough to ensure that only safe and effective drug products are released in the market. The FDA practices PMS and employs different approaches, such as sampling drug products in the market, inspecting drug establishments and drug outlets, testing drug samples, investigating

spontaneous adverse drug reaction (ADR) and adverse event (AE) reports, or maintaining ADR/AE databases, among others. However, The market authorization holder (MAH) is equally responsible for maintaining the safety and efficacy of a product while the product is in the market. The MAH plays a key role in PMS system.

II. Scope

This Circular shall cover all Market Authorization Holders of all authorized drug products, including established drugs, newly introduced drugs, drug products with new indication or route of administration, drug products with additional dosage or dosage strength, new dosage form, among others. It shall also cover generic and me-too drugs.

III. Objectives

The main objective for issuing this Circular is to set the standards and requirements on PMS system that defines the duties, responsibilities and obligations of the MAH and the Qualified Persons in Regulatory Affairs (QPIRA) in order to maintain the availability and accessibility of their products in the market.

IV. Definition of Terms

1. Adverse Drug Reaction (ADR) is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. An ADR in post-marketing situations usually refers to ADRs occurring at therapeutic doses, but for the purposes of reporting any dosage should be considered.

2. Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered the pharmaceutical product that does not necessarily have to have a causal relationship with the treatment for which the product is used. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. A pre-existing condition which, worsened in severity after administration of the product would also be considered as an adverse event. For clinical studies, the definition of an AE includes any untoward events occurring at any time after the subject's formal entry into the study (being after receipt of the signed informed consent) until the follow-up period as defined in the respective study protocol.

3. Company Core Data Sheet (CCDS) is a document is prepared by the Marketing Authorization Holder and contains, in addition to safety information, material relating to indications, dosing, pharmacology and other aspects of the product.

4. Expedited Reporting is a notification (submission) of an ICSR in a designated format to the appropriate NRA in compliance with the parameters and timelines specified by legislation and local regulatory guidelines. An expedited report would be an ICSR meeting the criteria for rapid transmission to the FDA.

5. Individual Case Safety Report (ICSR) is a report received by a company or agency which describes an adverse event.

6. International Birth Date (IBD) refers to the first market authorization granted by a National Competent Authority or National Drug Regulatory Authority in the world. The date when the CPR was approved by FDA shall be referred to as the National Birth Date (NBD).

7. Marketing Authorization (MA) is the approval granted by the National Regulatory Authority (NRA) to market a specific product in a particular country. The NRA in the Philippines is the FDA. A Certificate of Product Authorization is a MA issued by the FDA.

8. Marketing Authorization Holder (MAH) is the company named on the Marketing Authorization for a specific product in a particular country. The owner of the CPR issued by the FDA is the MAH.

9. Medicinal Product is a substance or combination of substances presented as having properties for treating or preventing disease in human beings; or a substance or combination which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. It also means a drug product.

10. Pharmacovigilance (PV) is the process of monitoring, assessing or evaluating and improving the safety of drug products carried out by pharmaceutical companies on their products and by government agencies on all drug products. It is also the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

11. Periodic Benefit Risk Evaluation Report (PBRER) refers to the benefit-risk evaluation report on marketed product submitted to the regulatory authority at regular intervals. The major aim of the report is to present a comprehensive and critical analysis of new or merging information on the risks to appraise the overall benefit risk profile of the product. PBRER may be prepared based on local data and information.

12. Periodic Safety Update Report (PSUR) refers to the document submitted at regular intervals by the MAH or product owner to regulatory authority which represents the worldwide safety experience of a medicinal product at a defined times of post-market authorization.. PSUR may be prepared using local data and information.

13. Post-Authorization Safety Study (PASS)/Post-Authorization Efficacy Study (PAES) refers to any non-interventional study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. A PASS or PAES is initiated, managed or financed by the MAH voluntarily or pursuant to obligations imposed by regulators and which involve the collection of data on suspected adverse reactions from patients or healthcare professionals. PAES may be required when the understanding of the disease or the clinical methodology indicates that previous efficacy evaluations might have to be modified significantly or PAES may be required when

some aspects of the efficacy of the product are identified and can be resolved only after the product has been marketed.

14. Risk Management Plan (RMP) means a set of health product vigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to health products, and the assessment of effectiveness of those interventions. The RMP is a requirement for the issuance of the appropriate authorization (Section 5 of RA No. 9711).

15. Spontaneous Report is an unsolicited communication by a regulatory authority, healthcare professional, consumer or other person that describes an ADR/AE in a patient administered the Product and which does not derive from a study or any organized data collection scheme.

V. General Standards and Requirements

1. All CPR- and PMS-related requirements, documents and reports shall be submitted, complied or completed by the QPIRA. A covering letter addressed to the FDA CDRR Director and signed by both the Medical Director and QPIRA and the Medical Director shall accompany all submitted documents and reports.

2. All MAH shall establish a PMS system for every product in the market, which shall be translated into a RMP to be submitted to FDA CDRR. A RMP is a requirement for the issuance of the appropriate authorization (Section 5 of RA 9711) and shall be one of the requirements when applying for a market authorization application. The RMP shall be proportionate to the risk as shown by clinical evidences and the risk profile of the product.

3. The FDA CDRR approval of market authorization under a monitored release shall be granted for a period of five (5) years without any extension.

4. After the issuance of the MA, the MAH shall submit a PSUR regularly to the FDA CDRR. When PBRER is part of the RMP, it shall also be submitted regularly to the FDA CDRR.

The frequency of submission of PSUR and PBRER shall left to the discretion of the MHA, Medical Director and QPIRA, taking into consideration the IBD, NBD, and knowledge on when the reports are available. In general a PSUR and/or PBRER shall be submitted at least once a year.

5. Prompt and regular or periodic submission of PSUR, PBRER, Individual Case Safety Report and Spontaneous ADR Reports shall constitute PMS activities. These reports shall replace the seeding trial or marketing trial and Phase IV clinical trial conducted in the past by drug companies under monitored release.

Phase IV may be conducted as deemed necessary by the MAH, provided that when it is going to be conducted in the country, a clinical trial protocol shall be submitted to the FDA CDRR for approval. When Phase IV clinical trial is to be conducted in other countries, a full report shall be submitted to the FDA CDRR.

6. PASS or PAES may be required as a condition for issuing a MA or may be required at any time after the issuance of authorization.

When a safety issue arise involving a drug product marketed by different MAHs, the MAHs shall collaborate in conducting the PASS or PAES. A PASS or PAES protocol shall be submitted to FDA CDRR for approval. Among other considerations, the FDA CDRR shall ensure that the PASS or PAES is non-interventional and that there will be no drug promotion during the course of the study.

Periodic and regular reporting shall be required while the post-authorization study is going on. The final report shall be prepared and submitted to the FDA after the data collection. When the submission of the final report will take more than 6 months, the MAH shall inform the FDA.

7. The MAH shall submit to the FDA CDRR all spontaneous ADR/AE reports and ICSR submitted to them within 5 days upon receipt. For serious ADR/AE, the MAH shall expedite the submission of report to the FDA CDRR.

8. The MAH shall inform the FDA CDRR when the product is no longer available in the market or if there is any plan to withdraw the product in the market. The MAH shall inform the FDA CDRR when the drug product is manufactured exclusively for government bidding.

VI. Other Considerations

1. As new or innovative drugs do not have any local pharmacoepidemiological data yet, the PSUR and PBRER prepared in other countries shall be submitted to FDA.

2. The general standards and requirements in this Circular are applicable to generic and me-too drugs.

3. There are instances when issues concerning GMP compliance, among others, may have impact or implication on the safety and efficacy of a drug product. Any new information which might influence the evaluation of the risk-benefit balance of the drug product shall be reported to FDA CDRR. Any change in product label or insert shall be reported immediately to the FDA CDRR. Any change in product labels and inserts needs prior FDA CDRR approval.

4. The FDA CDRR Director shall coordinate all review and evaluation of PMS reports, clinical studies, relevant literatures, and information among the Product Research and Standard Development Division, Product Registration and Licensing Division and Laboratory Support Division, as well as the ADR Unit and CTU Unit.

5. The FDA CDRR Director shall coordinate all its PMS-related activities with the National Pharmacological Center, Field Regulatory Operations Office, Legal Support Service Center and Policy and Planning Office, as appropriate.

6. The FDA CDRR Director through the FDA Academy shall conduct training for QPIRA and other stakeholders, as needed or appropriate.

VII. Penalty

The FDA may suspend or revoke the MA and/or QPIRA accreditation for any of the following reasons:

1. Failure to submit PMS requirements regularly or fulfill PMS obligations as required in this Circular, and

2. For submitting incomplete or incorrect data, information, reports and other documents that have bearing on the safety and efficacy of authorized product in the market.

VIII. Repealing Clause and Separability Clause

The pertinent sections and provisions of existing DOH administrative orders, bureau circulars, memoranda and operational manuals are hereby revised and modified accordingly. If any part, term or provisions of this Circular shall be declared invalid or unenforceable, the validity or enforceability of the remaining provisions shall not be affected and this Circular shall be construed as if it did not contain the particular invalid or unenforceable part, term, or provision.

IX. Effectivity

This Order shall take immediately upon approval and signature by the FDA Director.

KENNETH Y. HARTIGAN-GO, MD
Acting Director IV

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FDA Circular on Post Market Surveillance Signed by the FDA Director General

The FDA Circular on Post Market Surveillance (PMS) of Authorized Drug Products, which sets the standards and requirements on PMS system, was signed by the FDA Director General, Dr. Kenneth Y. Hartigan-Go.

Among others, the Circular defines the duties, responsibilities and obligations of Market Authorization Holders (MAH) and the FDA-accredited Qualified Persons in Regulatory Affairs (QPIRA). The Circular assures the public access to safe, effective and beneficial drug products that were approved by the FDA while monitoring for risks as the products are used by health professionals.

In effect, the MHA is no longer required to undertake Phase IV clinical trial and monitored release of new drugs or newly introduced drugs on around 3,000 patients for three (3) years. In lieu of the clinical trial and monitored release, periodic submission of post-authorization drug safety reports shall be required while product is on the market. On a case by case basis, however, non-interventional safety study may be required in order to confirm reports or information regarding the safety profile of the product or to measure the effectiveness of risk management system, among other reasons related to clinical findings.

The FDA and the Pharmaceutical Industry share the responsibilities of ensuring safety and efficacy through product stewardship and active monitoring of adverse drug reactions and adverse events in patients as well as the overall benefit or impact on public health.