



126 FEB 2020

FDA Circular
No. 2020-003

SUBJECT: Guidelines for Pharmaceutical Industry on Pharmacovigilance

I. BACKGROUND

Republic Act No. 9711, otherwise known as The Food and Drug Administration (FDA) Act of 2009 empowers the Food and Drug Administration to require all manufacturers, processors, traders, sellers, distributors, importers, exporters, and wholesalers of health products to report to FDA any incident that reasonably indicates that said product has caused or contributed to the death, serious illness or serious injury to a consumer, a patient, or any person.

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug related problems. Information obtained during clinical trials of new drugs is by design insufficient to provide a comprehensive overview of its safety and effectiveness in routine clinical practice. Thus, the long-term safety is only known when the drug is being used widely in a population through registration and authorization of its use. Monitoring is vital to prevent harm from adverse reactions arising from the use of registered drug products by providing timely information about safety of the products to patients, healthcare professionals and the public.

In order to monitor the safety and efficacy of drug products, Administrative Order No. 2011-0009 was issued establishing the National Policy and Program on Pharmacovigilance. Subsequently, pharmacovigilance related guidelines were issued including FDA Circular No. 2013-003 Post Market Surveillance and Periodic Safety Update Report, FDA Circular No. 2013-004 Post Market Surveillance of Authorized Drug Products, and FDA Circular No. 2018-012 Post marketing surveillance requirement for New Drugs under Monitored Release.

These issuances are necessary to fulfill the pharmacovigilance obligations of the pharmaceutical industries, in particular the market authorization holders (MAH). However, several issues were identified including but not limited to unclear guidelines on reporting mechanisms and timelines and redundancy on the requirement for MAH to conduct clinical trials in the local setting while safety concerns may also be addressed through post marketing studies conducted in other countries.

Thus, to provide updated and clear guidelines on pharmacovigilance obligations this Circular is hereby promulgated to serve as guide for MAHs.



II. OBJECTIVES

The main objective of this Circular is to provide clear guidelines for market authorization holders (MAH) on their pharmacovigilance requirements for all registered drugs and biological products for human use.

III. SCOPE AND COVERAGE

This Circular shall cover all MAH and drug establishments involved in the importation and distribution of registered drug and biological products for human use.

IV. DEFINITION OF TERMS

Adverse Drug Reaction (ADR) is a response to a drug 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 modification of physiological function.

For the purpose of this guideline it also refers to adverse event following immunization if the product involve is vaccine. It also refers to adverse reaction, suspected adverse (drug) reaction, side effect or undesirable effect.

Adverse events following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have causal relationship with the usage of vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory findings, symptoms or disease.

Serious adverse reaction is an adverse reaction which results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is associated with a congenital anomaly/birth defect.

Non-serious adverse reaction is an adverse reaction that does not meet the definition of a serious adverse reaction

Safety concern is an important identified risk, important potential risk or missing information.

Biological medicinal products refer to any product of biological origin, prepared with biological processes, derived from blood and plasma, or manufactured by biotechnology, consisting of substances of higher molecular weight whose purity, potency, and composition cannot readily and reliably be determined by chemical or physicochemical analysis. It also refers to biological products, biologics or biotherapeutic product.

New Drug Product (NDP) is defined as any pharmaceutical product with an active substance that has not been previously registered for any pharmaceutical use in the country, pharmaceutical or therapeutic innovation of a tried and tested or established drug with new mode of administration, new dosage strength, new dosage form and new fixed combination of two or more active ingredients, and/or new chemical or structural modification of a tried and tested or established drug. A new drug product is subject to additional monitoring after they are placed on the Philippine market.

V. GUIDELINES

A. THE QUALIFIED PERSON FOR PHARMACOVIGILANCE

The MAH must designate a pharmacovigilance officer which also refers to as Qualified Person for Pharmacovigilance (QPPV) who shall assume the following functions:

- maintain an effective Pharmacovigilance system of the MAH
- ensure conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with legal requirements
- have an overview of the safety profiles and any emerging safety concerns in relation to the products for which the MAH holds authorizations
- act as a single contact point during inspection and monitoring and respond promptly for any request/inquiry from FDA
- maintain and update company database of all adverse reactions involving their products and have on file all reported cases

The MAH must ensure the competence of their QPPV. The QPPV must be a holder of any baccalaureate degree in medically-related courses. The MAH shall assess the qualification of the QPPV prior to appointment.

The name of the designated QPPV shall be submitted and updated as part of the licensing requirements for distributors (MAH).

It is a must that the QPPV is residing within the Philippine territory.

B. PHARMACOVIGILANCE SYSTEM AND RECORDS OF PV ACTIVITIES

There should be system in place for pharmacovigilance activities and safety monitoring of pharmaceutical products including but not limited to, collection and management of all adverse reaction reports (serious and non-serious), signal detection and management, significant safety issues, medication errors, Risk Management Plans (RMP), Periodic Benefit Risk Evaluation Reports (PBRER), literature reviews, contracts with outsourced pharmacovigilance providers, direct healthcare communications, actions taken by other regulatory agencies. The MAHs must retain records pertaining to the reporting requirements and safety of the pharmaceutical product.

If the company has received no reports of adverse reaction, measures to encourage and facilitate reporting of healthcare professionals and consumers must be properly documented.

Records must be available and provided upon request during inspection by the FDA or as required for submission to the Pharmacovigilance Section, Product Research and Standards Development Division (PRSD), Center for Drug Regulation and Research (CDRR).

- The said records must be retained as long as the product is still registered. The records of the products suspended, canceled or withdrawn from its registration may only be disposed ten (10) years after removal from the registration.

C. REPORTING OF ADVERSE REACTION

1. Reporting Time Frame

Reports of serious adverse reaction, whether expected or unexpected must be submitted to FDA as soon as possible but no later than 15 calendar days. The reporting time clock starts after first knowledge of any personnel of the MAH on the said adverse reaction.

2. Reporting Requirements

Serious adverse reactions must be complete as possible and quality of reports must be taken into consideration to facilitate assessment. A valid report must provide the minimum mandatory information:

- i. one single identifiable patient, characterized by at least one of the following qualifying descriptions: initials, medical record number (from general practitioner, specialist, hospital, or investigation), date of birth, age, age group, gestation period, or gender

The information should be as complete as possible in accordance with Data Privacy Act.

- ii. one or more suspected adverse reaction - the report does not qualify as valid report if it is reported that the patient experienced an unspecified adverse reaction and there is no information on adverse reaction.
- iii. one or more suspected product/s - there should be at least one suspected drug substance or product. Interacting substance or product should also be considered as suspected.
- iv. one or more identifiable reporter, characterized by parameters such as qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional), name, initials, or address. In line with ICH-E2D, the term "identifiable" indicates that the organization notified about the case has sufficient evidence of the existence of a person who reports the facts based on the available information.

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission.

The Council for International Organisation of Medical Sciences (CIOMS) I form is required for reporting adverse reactions or otherwise submitted through electronic submission in E2B format. If the E2B format is the preferred medium of submission, contact directly or set an appointment with the Pharmacovigilance Section, FDA-CDRR-PRSDD. MAH utilizing the E2B submission process should not submit reports simultaneously with CIOMS I Form to avoid duplication of reports.

All MAHs should be ICH-E2B compliant before the end of Year 2025.

The latest Medical Dictionary for Regulatory Activities (MedDRA) terminology must be used for coding medical information.

The completed CIOMS I form should be submitted either through email at pharmacovigilance@fda.gov.ph or via FDA Action Center (FDAC). The submission of reports does not need to be formally acknowledged by the Pharmacovigilance Section, a Document Tracking Number (DTN) serves as an acknowledgement receipt either through email or FDAC.

When additional medically significant information is received for previously reported case, the MAH is required to submit the follow-up report as soon as possible but no later than 15 calendar days after the receipt of additional information. The report should be labelled as follow up report and should be in cross-reference with the previous report. The previously assigned Document Tracking Number (DTN) for the initial submission shall be stated or indicated in the follow-up reports.

3. What to Report

a. Local Serious Spontaneous Reports

Serious spontaneous adverse reactions that occurred locally are required to be reported to FDA following the reporting time frame as prescribed in this Circular. Submission of local spontaneous non-serious adverse reaction report is not mandatory. However, records must be maintained and readily available upon request.

For cases that occurred overseas and reported locally, when information is available that the patient is Filipino and the product is obtained from the Philippines, the case should be treated as a local case. However, only the serious adverse reaction qualifies reporting to FDA. The country of occurrence should also be stated.

Any adverse reactions occurring outside the Philippines other than the conditions above does not qualify for reporting to FDA, unless otherwise, requested.

b. Solicited reports

Solicited adverse reaction reports are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, patient support programs, and market research programs. Adverse reactions reports obtained from data collection systems must not be considered spontaneous but as study reports. Only serious adverse reaction reports must be submitted to FDA.

Post-authorization study to be conducted through clinical trial must follow the FDA guideline on Clinical Trial safety reporting requirement.

c. Reports for another MAH

If a distributor or sub-distributor is marketing products from different MAHs, the report of adverse reactions, whether serious or non-serious must be forwarded to the concerned MAH within 15 calendar days upon receipt of the information by any of its qualified personnel. The MAH concerned will be the one responsible for submission of the report to FDA within the reporting time frame and requirements provided by this Circular. The reporting time clock starts after first knowledge of any personnel of the MAH on the said adverse reaction.

The same is applied to the holder of Certificate of Listing of Identical Drug Product (CLIDP). The MAH of the Principal Certificate of Product Registration (PCPR) is responsible for the submission of reports to FDA.

d. Consumer Reports

Consumer reports are valuable source of information. However, adverse reaction reports provided by consumer may often lack sufficient clinical detail, attempts should be made to follow-up with the consumer to obtain consent to contact the attending healthcare professional for medical confirmation and obtain further relevant information. Only the serious adverse reaction is required for submission to FDA.

e. Reports of Lack of Efficacy

Lack of efficacy is reportable when the product fails to produce expected pharmacologic or therapeutic benefit and results in an adverse outcome including worsening of the condition of the patient. Products used in critical conditions or for the treatment of life-threatening disease, vaccines, contraceptives are examples of such cases.

Clinical judgement should be considered to qualify the report of lack of efficacy. For example, a report of lack of efficacy with an antibiotic used in a life-threatening situation where the use of the product was not in fact appropriate for the infective agent should not be submitted. However, a report of lack of efficacy for a life-threatening infection, which appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be submitted within 15 days.

For vaccines, cases of lack of prophylactic efficacy should be reported. This has potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement which may need prompt action and further investigation through post-authorization safety studies as appropriate. General guidance regarding the monitoring of vaccines failure as provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance may be followed.

f. Overdose and Off-label Use

Reports of overdose and/or off-label use must be submitted only when associated with serious adverse reaction.

g. Medication Errors

Only medication errors associated with serious adverse reaction is reportable. Information on medication errors, whether resulting in an adverse reaction or not, should be documented.

h. Product Defects

If an adverse reaction (serious or non-serious) is suspected to be related to a product defect, it must be reported as soon as possible but no later than 15 calendar days from knowledge of such by any qualified person of the MAH. The lot or batch number of the suspected product should be obtained and included in the report.

i. Outcomes of Use during Pregnancy

The outcome of report of product administration or product that was taken by pregnant woman or a case of paternal exposure must be followed up and reported only when it resulted to an abnormal outcome, i.e. congenital anomaly, malformations, etc. This case is referred to as a parent-child report.

When both the parent and exposed child or fetus experience suspected adverse reactions, two separate reports should be submitted but linked to each other.

Maternal or paternal exposure to drug products without adverse reaction does not qualify for reporting to FDA.

j. Adverse Reaction Reports from the Internet and Social Media

MAHs should regularly screen websites including social media under their management or responsibility for potential adverse reaction case reports on the use of their product. The case should be verified that the patient and reporter really exist. The report should be considered non-valid until it can be verified directly with the patient, the patient's healthcare professional or a reporter who had direct contact with the patient.

k. Local case reports from Scientific Literature

MAH is expected to regularly screen the worldwide scientific literature by accessing widely used systematic literature reviews or reference databases. Each identifiable patient should be reported individually. The publication reference should be given as the report source. Only the product as identified by their brand is reportable. Only the serious adverse reaction should be reported to FDA. A copy of the column or paper (with title and date of issue) relevant to the report may be requested.

l. Suspended, Cancelled or Withdrawn Product Registration

MAH of product/s suspended, cancelled or withdrawn must continue collecting and reporting adverse reaction up to three (3) years after the date of the last release of the product into the market.

D. UPDATING OF SIGNIFICANT SAFETY INFORMATION

Any scientific/medical literature, journal or information from unpublished or published study, surveys, registries or any information that could affect or change

the benefit-risk balance of the registered product must be communicated to the Pharmacovigilance Section of CDRR. A copy of relevant report should be provided.

It may either be submitted through email at update-safety-info@fda.gov.ph or via FDAC. The DTN serves as an acknowledgement receipt.

E. RISK MANAGEMENT PLAN

The Risk Management Plan (RMP) provides a detailed description of the risk management system. It is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to pharmaceutical products including the assessment of the effectiveness of those interventions.

2. Requirements for Submission

All biological product and new drug product applications must have an accompanying RMP submitted.

Submission of RMP for a generic drug is not required, but it is expected that the MAH will continue to evaluate the safety of their products on a regular basis and must be readily available upon request of FDA in case-to-case basis, such as but not limited to:

- In response to a new safety concern arising from a new route of administration;
- As a result of a new safety concern associated with a new indication that may require additional PV activities;
- If the innovator or reference product has safety concerns that have been identified to require additional local PV activities.

3. Submission of Documents

The RMP documents are to be provided as part of the application dossier in addition to the requirements for product registration. If there are significant changes or updates on the RMP while on its regulatory review process or evaluation, it must be submitted immediately through FDAC using the assigned DTN for product registration application.

The submission of RMP includes:

- RMP compliant with latest EMA/838713/2011 Guideline on good pharmacovigilance practices (GVP) Module V - Risk management systems
- RMP Philippine-specific Annex;
- RMP Philippine-specific Annex annotated version (with track changes) (as applicable)

If the product is already registered, submission of updated RMP must include the FDA Registration Number/s of the product/s involve. A new DTN will be assigned which serves as acknowledgement receipt. An updated RMP must be submitted either through email at RMP@fda.gov.ph or via FDAC.

RMP Philippine-specific Annex

The Philippine-specific Annex serves as documentation of the RMP to be implemented in the Philippines. It includes the following sections:

- Product Overview (Name of the product and active ingredient/s)
- Safety Specifications (important identified risk, important potential risk & missing information)
- Proposed local pharmacovigilance plan
- Plan for post authorization efficacy studies (if applicable only)
- Proposed local risk minimization measures

Philippine-specific Annex may not be submitted if the RMP is compliant with latest EMA/838713/2011 Guideline on good pharmacovigilance practices (GVP) Module V - Risk management systems which is made or intended for the Philippine market.

The latest template of the Philippine-specific Annex available in the FDA website must be used.

Updated RMP is submitted only on the following conditions:

- whenever there is a significant change to the RMP, including but not limited to:
 - when the RMP is modified as a result of new information that may lead to a change to the benefit-risk profile;
 - when an important (vigilance or risk minimization) milestone is reached, or an activity is terminated, added, or substantially altered;
 - when changes to the summary of ongoing safety concerns are made.
- upon request of FDA;

The CDRR will contact the Person Responsible for RMP or the Pharmacovigilance Officer or Qualified Person for Pharmacovigilance (QPPV) if there is a query or an issue that needs to be discussed.

4. Pharmacovigilance Plan

The purpose of the pharmacovigilance plan is to present an overview and discuss the MAH plans to further characterize the safety concerns in the safety specification.

Routine Pharmacovigilance activities

Routine pharmacovigilance should be conducted locally for all registered drugs and biological products for human use. It includes activities as required in this Circular such as systems and processes that ensure collection and recording of all suspected adverse reactions, submission of reports to FDA, signal detection, updates of significant safety information and actions taken by other regulatory agencies.

Additional Pharmacovigilance activities

Additional pharmacovigilance activities are pharmacovigilance activities that are not considered routine. It may be non-clinical studies, clinical trial or non-interventional studies. Examples include long-term follow up of patients from the clinical trial population or a cohort study to provide additional characterization of the long-term safety of the product.

Studies in the pharmacovigilance plan aim to identify and characterize risks, to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimization activities. They should relate to the safety concerns identified in the safety specification, be feasible and should not include any element of a promotional nature.

The studies may be categorized into:

- Category 1 – imposed because they are key to the risk-benefit profile of the product
- Category 2 – specific obligations granted under exceptional circumstances
- Category 3 – required to investigate a safety concern or to evaluate the effectiveness of risk minimization activities

Studies conducted or proposed to be conducted in other countries as additional pharmacovigilance activities do not need to be duplicated to include local study population. Such studies are recognized by the FDA. However, in certain circumstances, the FDA may require the MAH to conduct studies under Category 3, as appropriate, when there is a specific safety concern affecting Filipino population which needs further identification and characterization of risks.

A post-authorization safety study (PASS) may be interventional or non-interventional. If a PASS is interventional, and to be conducted locally, the provision and guideline on the conduct of clinical trial shall apply.

If a PASS is non-interventional, to be conducted locally, the protocol following the latest EMA/813938/2011 GVP Module VIII Section B.3.1. Format and content of the study protocol should be submitted as attachment to RMP Philippine-Specific Annex. Adverse reactions should be reported to FDA in accordance with the provisions of Reporting of Adverse Reactions of this Circular.

The final study report, following the format of GVP Module VIII Section B.4.3.2. should be submitted within 12 months of the end of data collection.

F. PERIODIC BENEFIT-RISK EVALUATION REPORTS (PBRER)

The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the

- reporting interval. PBRER is also referred to as Periodic Safety Update Report (PSUR).

1. Reporting Requirements

PBRER should only be submitted to FDA in the following situations;

- Whenever required by the FDA - (a) covering up to 12 months: submitted within 70 calendar days; and (b) covering more than 12 months: submitted within 90 calendar days from the data lock point set by the FDA
- New Drug Products (*applicable only to pharmaceutical products with new active substance that has not been previously registered in the Philippines*) & Biological Products (a) for initial period of 2 years at 6 months interval either from the date of local registration of the product or its international birthdate; and (b) annually for the next 3 years
- As part of a submission for variation application when PBRER contains the information supporting the variation.

2. Format and Content

The guidance on the format and content of the PBRER can be referenced from the latest version of ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER).

It should either be submitted through email at PBRER@fda.gov.ph or via FDAC. The DTN serves as an acknowledgement receipt.

G. UPDATE OF ACTIONS TAKEN BY OTHER NATIONAL DRUG REGULATORY AGENCIES

Regulatory actions taken by other national drug regulatory authorities which may influence the overall benefit-risk profile of the product must be communicated to the Pharmacovigilance Section, FDA-CDRR, PRSDD as soon as possible but not later than 72 hours after the receipt of information. This may include but not limited to the following;

- Product withdrawal;
- Product recall and product defects;
- Deletion or removal of approved indications by regulatory agencies;
- Failure to renew product registration due to safety reasons;
- Dissemination of Direct Healthcare Professional Communication (DHPC) Letter related to safety issues.

Dissemination of Direct Healthcare Professional Communication Letter is required whenever there are related safety issues on the product, as appropriate. It may either be an initiative of the MAH or as required by FDA as necessary. In certain circumstances, a joint DHCP letter among MAHs may be required as appropriate. A copy of the DHCP letter prior to dissemination should be submitted to notify the FDA. The letter should include the statement: "Alternatively, suspected adverse reactions may be reported online to the Food and Drug Administration at <https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=PH> or by email to pharmacovigilance@fda.gov.ph"

It should either be submitted through email at pv-actions-taken-by-nra@fda.gov.ph or via FDAC.

H. OUTSOURCING OF PHARMACOVIGILANCE ACTIVITIES

The MAH may transfer any or all of the pharmacovigilance task and functions, including the role of pharmacovigilance, to another person(s) or organization, but the ultimate responsibility for the fulfillment of all pharmacovigilance obligations and its quality and integrity always resides with the MAH.

I. PHARMACOVIGILANCE INSPECTIONS

To determine and ensure that a functional pharmacovigilance system is in place in all MAHs or any person or organization providing pharmacovigilance activities (outsourcing) to MAH, assessment and audits on compliance to pharmacovigilance obligations shall be conducted. The conduct of pharmacovigilance inspection will generally be upon notice; however, the FDA reserves the right to conduct unannounced inspection, if necessary.

VI. SANCTIONS

Any violation shall be ground for filing appropriate administrative charges and/or imposition of administrative sanctions such as but not limited to, imposition of fines, suspension, cancellation or revocation of any license, permit or registration issued by the FDA.

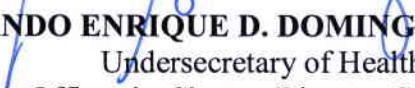
VII. REPEALING CLAUSE

Provisions of 1) FDA Circular No. 2013-003, Post Market Surveillance and Periodic Safety Update Report; 2) FDA Circular No. 2013-004, Post Market Surveillance (PMS) of Authorized Drug Products; 3) FDA Circular No. 2010-009, Amendment to Memorandum Circular No. 5 s. 1994 dated April 20, 1994 regarding Reports on Adverse Drug Reaction, as well as provisions that are inconsistent with this Issuance are hereby withdrawn, repealed, and/or revoked accordingly.

VIII. EFFECTIVITY

This Circular shall take effect fifteen (15) days after publication in the official gazette and in a newspaper of general circulation and after submission to University of the Philippines, Office of the National Administrative Register (ONAR).

Dissemination of the information to all concerned is requested.


ROLANDO ENRIQUE D. DOMINGO, MD, DPBO
Undersecretary of Health
Officer-in-Charge, Director General