



## GUIDELINES FOR SAFETY MONITORING OF MEDICINAL PRODUCTS

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## 1.0 INTRODUCTION

In pursuance to Public Health Act 2012, Act 851, Part 7, Section 125, subsections (1), (2), (3), these guidelines are hereby developed by the Food and Drugs Authority, hereafter, referred to as the **Authority**, to define the general norms and scientific principles and to set applicable standards for continuous safety monitoring of regulated products to ensure these products continue to be safe for patients and the general public. These guidelines are for information, guidance and strict compliance by Marketing Authorization Holders and Local Representatives of regulated products to help in the continuous safety monitoring of products granted marketing authorization in Ghana.

Medicinal products are approved based on clinical trials data available at the time and in most cases on several hundreds or thousands patients. The limited number of patients included in clinical trials, the exclusion of certain patients at-risk, the lack of significant long-term treatment experience and the limitation of concomitant therapies do not allow a thorough evaluation of the safety profile. Under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.

These guidelines therefore provide the requirements for the safety monitoring during the life cycle of registered medicinal products and communication of safety information related to these products.

## 2.0 GLOSSARY

In these guidelines, unless the context otherwise states:

### *Adverse Drug Reaction (ADR) / Adverse Reaction (AR)*

A response to a medicinal product which is noxious and unintended including lack of efficacy and which occurs at any dosage and can arise from:

- The use of product within the terms of the marketing authorization
- The use of product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse and medication errors;
- Occupational exposure

***Adverse Event (or adverse experience) (AE)***

Adverse event/experience is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.

***Adverse Events Following Immunization (AEFI)***

Adverse Event Following Immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

***Authority*** means Food and Drugs Authority.

***‘Dear Healthcare Professional (DHCP) Letter’***

A ‘Dear Healthcare Professional Letter’ is a correspondence usually in the form of a mass mailing from the Marketing Authorization Holder (MAH), the Local Representative or the Food and Drugs Authority addressed to doctors, pharmacists, nurses and other healthcare professionals regarding important new information. The DHCP letters are intended to inform the recipients of the need to take certain actions or adopt their practices to minimize particular risks and/or to reduce burden of adverse drug reactions with a medicinal product.

***Drug Abuse***

Drug abuse is a persistent or sporadic, intentional excessive use of medicines, which is accompanied by harmful physical or psychological effects.

***Herbal Medicinal Products***

A preparation with therapeutic or any other human health benefit which contains raw or processed ingredients from one or more plants or materials of organic or animal origin.

***Identified risk***

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. An important identified risk is an identified risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that is likely to be included in the contraindications or precautions section of the product information should be considered important.

***Local Representative***

The company or legal entity who represents the MAH in Ghana and perform functions delegated by the MAH.

***Local Distributor or Local Agent***

A company or legal entity appointed by the manufacturer or the Marketing Authorization Holder to import, receive as donation, distribute or sell a medicinal product in Ghana.

***Marketing Authorization Holder***

Marketing Authorization Holder: The company or legal entity in whose name the marketing authorization for a product has been granted and is responsible for all aspects of the product and compliance with the conditions of marketing authorization.

***Medicinal Product***

A medicinal product is:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in humans;
- (b) Any substance or combination of substances which may be used in or administered to humans, 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.

***Missing information***

Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

***New Chemical Entity***

A chemical or biologically Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product.

***Off Label Use***

Off label use of a medicine is use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling of the medicinal product.

***Periodic Benefit Risk Evaluation Report (PBRER)***

An update of the world-wide marketing experience of a medicinal product at defined times with focus on formal evaluation of benefit in special population at defined times during post-registration period.

***Periodic Safety Update Report (PSUR)***

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to the Authority at defined time points post-authorization. At these times, Marketing Authorization Holders are expected to provide succinct summary information together with a critical evaluation of the benefit-risk balance of the product in the light of new or changing information.

***Pharmacovigilance***

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

***Post-Authorization Safety Study (PASS)***

Any 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.

***Potential Risk***

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. An example is toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies. An important potential risk is a potential risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that is likely to be included in the contraindications or precautions section of the product information should be considered important.

***Qualified Person for Pharmacovigilance (QPPV)***

An individual named by a Marketing Authorization Holder (MAH) and approved by the Authority as the person responsible for ensuring that the company (the MAH) meets its legal

obligations in the Public Health Act, 2012, Act 851 Section 125 for monitoring of the safety of the product marketed in Ghana.

***Risk Management Plan***

A detailed description of the risk management system.

The Risk Management Plan is submitted as part of the dossier that is evaluated by the Authority before a medicine can be authorized and which is regularly updated as new information becomes available. Risk Management Plans include information on a medicine's safety profile and explain the measures that are taken in order to prevent or minimize the risks of medicine in patients.

***Risk Minimization Activity (used synonymously with Risk Minimization Measure)***

A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

***Risk Management System***

A set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions.

***Safety Concern***

An important identified risk, important potential risk or important missing information.

***Serious Adverse Drug Reaction or Serious Adverse Event***

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life threatening
- requires in-patient hospitalisation or results in prolongation of exist hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction



***Spontaneous Report or Spontaneous Notification of Adverse Reactions/Events***

A communication to a company, regulatory authority or an organization that describes a suspected adverse event/reaction in a patient who is given one or more medicines and which is not derived from a study.

***Target Population (Treatment)***

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information.

***Unexpected Adverse Reaction***

An unexpected adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the applicable product information (i.e., with the approved package inserts for registered medicines, or the investigator's brochure or other product information for unregistered medicines.

**3.0 REQUIREMENTS**

These guidelines contain the requirements for post approval safety monitoring of regulated products, including the requirements for the following:

- a. Periodic Safety Updates Reports (PSUR) or Periodic Benefit Risk Evaluation Reports (PBRER)
- b. Risk Management Plan (RMP)
- c. Post Authorization Safety Studies (PASS)
- d. Safety Communication

**3.1 Periodic Safety Updates Reports (PSUR) or Periodic Benefit Risk Evaluation Reports (PBRER)****3.1.1 Introduction**

PSURs/PBRERs should be submitted only for medicinal products issued with marketing authorization in Ghana.

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the benefit-risk balance of the medicinal product taking into account new or emerging information in the context of cumulative information on benefits and risks. The PSUR is a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.

The PBRER, however is aimed at presenting a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

*While PSUR and PBREER may be used interchangeably in this guideline, it must be understood that these documents are different. Whilst, the primary objective of the PSUR is to provide a comprehensive picture of the safety of approved medicinal products with recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the PRBER provides a greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly.*

*For additional information on the differences between the PSUR and PBRER reference is made to ICH E2C and ICH E2C (R2) Guidelines respectively.*

PSURs/PBRERs are generally not requested routinely for generic products, herbal medicines and homeopathic medicinal products. Under this condition, the PSUR/PBRER shall be submitted only when there is a condition in the marketing authorisation which requested for this or when requested by the Authority on the basis of safety concerns.

### **3.1.2 Objectives of PSUR/PBRER**

PSUR/PBRER presents the worldwide safety experience of a medicinal product at defined times post authorization, in order to:

1. Report all the relevant new information from appropriate sources;
2. Relate these data to patient exposure;
3. Summarize the market authorization status in different countries and any significant variations related to safety;
4. Create periodically the opportunity for an overall safety re-evaluation;
5. Provide a formal and concise evaluation of benefit, unless the safety or benefit-risk profile has changed significantly during the reporting interval.
6. Indicate whether changes should be made to product information in order to optimize the use of the product.

### **3.1.3 Frequency of Review and Submission**

For New Chemical Entities (NCEs) PSURs/PBRERs should be submitted as stated below unless otherwise requested by the Authority.

1. 6 monthly for the first two years

2. Annually for the following three years
3. Then every three years, at the time of renewal of the registration of the drug.
4. Immediately upon request by the Authority.

PSURs and PBRERs should be harmonized with the International Birth Date of the Product. Generally, each PSUR and PBRER should cover the period of time since the last PSUR/PBRER and should be submitted within 60 days after the Data Lock Point. Presentation of the information contained in the PSUR and PBRER shall be in the format recommended by ICH E2C and ICH E2CR2 Guidelines respectively.

For medicinal products with marketing authorization in different countries, the MAH may synchronize the Local Birth Date (LBD) with the International Birth Date (IBD). The Authority will accept a single harmonized IBD and Data Lock Point (DLP) for each product in order to reduce the burden of work in preparing PSURs/PBRERs for different regulatory authorities. In situations where an MAH is preparing PSURs/PBRERs on annual basis or longer period for different regulatory authorities based on the IBD and the Authority requires a six-month cycle based on the LBD, the most recent PSUR/PBRER with a longer time frame will be acceptable to the Authority.

The Authority may also request for Ad hoc PSUR/ PBRERs i.e., reports outside the specified reporting requirements when there are new risks, when risks have changed, when efficacy/effectiveness has changed, or when there are changes to the benefit-risk profile of a medicinal product.

The Authority will accept PSUR and PBRER presented in the format recommended by ICH E2C and ICH E2C (R2) Guidelines respectively.

## **3.2 RISK MANAGEMENT PLAN (RMP)**

### **3.2.1 Introduction**

RMPs include information on a medicine's safety profile and explain the measures that are taken in order to prevent or minimize the medicine's risks in patients post authorization. The RMP details the known safety concerns with the medicine and how they can be managed. It also includes details of any additional studies that have been recommended at the time of licensing to provide more information on the medicine's safety profile.

In relation to risk management of medicinal products, the Local representative or Marketing Authorization Holder is responsible for:

- Ensuring that it constantly monitors the risks of its medicinal products issued with marketing authorization in Ghana in compliance with relevant legislation and reports the results of this, as required, to the Food and Drugs Authority;
- Taking all appropriate actions to minimize the risks of the medicinal product and maximize the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available

### **3.2.2 Objectives of an RMP**

The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

As per the requirement of the guidelines for Safety Monitoring of Medicines in Ghana, the RMP must contain the following elements which:

- identify or characterize the safety profile of the medicinal product(s) concerned;
- indicate how to characterize further the safety profile of the medicinal product(s) concerned;
- document measures to prevent or minimize the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
- document post-authorization obligations that have been imposed as a condition of the marketing authorization.
- describe what is known and not known about the safety profile of the concerned medicinal product(s);
- indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorization phase (also known as effectiveness studies);
- include a description of how the effectiveness of risk minimization measures will be assessed.

### **3.2.3 When a Risk Management Plan (RMP) should be submitted**

RMP or an update, as applicable, may need to be submitted at any time during a product's life-cycle when requested by the Authority or for products considered as New Chemical Entity, the RMP should be submitted as part of an application for marketing authorization.

A Risk Management Plan should be submitted:

4.3.1 with an application for:

- any product containing a New Chemical Entity
- a similar biological medicinal product
- a generic medicinal product where the reference product has a risk management plan and a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product

4.3.2 with an application for pediatric use marketing authorization

4.3.3 with an application involving a significant change in marketing approval (for example: new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new pediatric indication) unless it has been agreed with the FDA that submission of a RMP is not required

4.3.4 with an application for generic product where the reference product has a RMP and a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product.

4.3.5 with an application for new fixed dose combination applications irrespective of how long any of the ingredient(s) in the combination has been used as single agent.

4.3.6 generic medicinal products where the changes compared with the reference medicinal product suggest different risks

4.3.7 on the request of the FDA (both pre-and post-authorization)

4.3.8 on the initiative of Marketing Authorization Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

### 3.2.4 Structure of the RMP

The RMP consists of seven parts as listed below; certain parts specifically the Safety specification are subdivided into modules so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan.

Part I : Product(s) overview

Part II : Safety specification

Module SI : Epidemiology of the indication(s) and target population(s)

Module SII : Non-clinical part of the safety specification

Module SIII : Clinical trial exposure

Module SIV : Populations not studied in clinical trials

Module SV : Post-authorization experience

- Module SVI : Additional requirements for safety specification not discussed in ICH-E2E (e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error)
- Module SVII : Identified and potential risks
- Module SVIII : Summary of the safety concerns
- Part III : Pharmacovigilance plan
- Part IV : Plans for post-authorization efficacy studies
- Part V : Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)
- Part VI : Summary of the risk management plan
- Part VII : Annexes

For detailed description of each part of the RMP and the format acceptable to the Authority, the Local representative or the Marketing Authorization Holder is directed to read GVP Module V – Risk management systems.

If the RMP is submitted as part of the marketing authorization application, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document.

### **3.2.5 Ghana Specific Annex to the EU-RMP**

The Authority recommends that where an existing global or EU-RMP is submitted, Ghana Specific Annex is included to the EU-RMP. The Ghana Specific Annex should identify any differences between the EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimization activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed Ghanaian Product Information (PI), and the reasons for the difference. This will allow the Authority to assess the appropriateness of the proposed RMP in the Ghanaian environment.

### **3.2.6 Purpose of the Ghana Specific Annex**

The Ghana Specific Annex should provide Ghana specific information that is important in assessing the ‘risk’ in Ghana (and therefore appropriateness of proposed plans/activities), the relevance of pharmacovigilance and risk management activities in Ghana, and identify and explain the reasons for any differences with activities planned in the EU.

### **3.2.7 Content of Ghana Specific Annex**

This should include:

- 4.6.2.1 Differences in indications between the European Union (EU) and Ghana if applicable.
- 4.6.2.2 Ghana specific epidemiological information on the population to be treated if available (information relating to the size of the target population or any specifics that is needed assess the safety of the use of the product in the Ghanaian population).
- 4.6.2.3 Ghana information if available, on potential for medication errors or other risks.
- 4.6.2.4 Applicability of EU activities to the Ghanaian environment if no specific Ghanaian data will be collected.

### **3.2.8 Format of Ghana Specific Annex**

A recommended format for the Ghana Specific Annex is as below.

**3.2.8.1 Introduction** - Purpose of Ghana Specific Annex

**3.2.8.2 Pharmacovigilance practice** - Routine pharmacovigilance systems in Ghana and Studies referenced in the RMP

Describe involvement of Ghana and applicability of global studies to the Ghanaian environment, or—if not applicable or relevant to the Ghanaian environment—include a justification.

**3.2.8.3 Risk minimization plan** - Address how risk minimization activities will be implemented and evaluated in Ghana. If surveys or studies are referenced in the Ghana Specific Annex, copies of outlines and protocols should be provided.

Provide a justification if activities in the EU are not to be implemented in Ghana. Indicate how and when evaluation of risk minimization activities, including educational activities, will be undertaken. Marketing Authorization Holders are responsible for showing that the measures they are using to mitigate risk are working and, if not, what actions they will take to ensure effectiveness.

**3.2.8.4 Contact person for RMP**-This is be the person the MAH considers responsible for the implementation of the RMP activities in Ghana, and will usually be the Qualified Person for Pharmacovigilance.

## **3.3 POST-AUTHORISATION SAFETY STUDY (PASS)**

### **3.3.1 Introduction**

PASS is initiated, managed or financed by the Local Representative or the Marketing Authorisation Holder (MAH) as well as those conducted by a third party on behalf of the Local Representative or the Marketing Authorisation Holder, conducted upon request by the Food and Drugs Authority. This guidance should be used for all PASS studies.

### 3.3.2 Objectives of PASS

PASS is conducted with the following objectives;

1. Quantify potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
2. Evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. special populations - pregnant women, specific age groups, patients with renal or hepatic impairment);
3. Assess patterns of drug utilization that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
4. Measure the effectiveness of a risk minimization activity
5. evaluate the risks of a medicinal product after long-term use
6. Provide evidence about the absence of risks

This guidance applies to studies that involve primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.

### 3.3.3 When a PASS may be conducted

PASS may be requested by the Authority and conducted by Local Representatives or MAHs under the following conditions:

1. As a condition to the granting of the marketing authorization, or after the granting of a marketing authorization if there are concerns about the risks of the authorized medicinal product.
2. As part of a marketing authorization granted under exceptional circumstances.
3. Required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimization activities.
4. PASS conducted voluntarily by the MAH.

The study protocol for Post Authorization Studies should be approved by the Ethics Committees and the Authority.

### 3.3.4 Study population

The study should be conducted in a Ghanaian population resident in Ghana or in a study population to be determined in consultation with the Authority.



### 3.3.5 Study Design

The study design will be submitted in the protocol for the PASS study and pharmacoepidemiological study designs may be adopted depending on the objectives of such studies.

### 3.3.6 Roles and Responsibilities

#### 3.3.6.1 Local Representative or Marketing Authorization Holder (MAH)

- The Local Representative or MAH shall bear sole responsibility for all regulatory and technical aspects of the PASS.
- The Local Representative or MAH shall develop the study protocol following the prescribed format by the Authority.
- The Local Representative or MAH shall ensure that the PASS study does not commence before the protocol for the study is approved by the Authority.
- All protocol amendments during the study shall be submitted to the Authority for approval before such amendments are carried out, however, where such amendments are needed to protect the safety of patients, this may be carried out and the Authority informed immediately by phone call, followed by a written report within 48 hours.
- The Local Representative or MAH shall submit the study progress reports to the Authority in the prescribed format (Refer to Appendix 1 for the Format for Submission of Progress Report).
- The MAH shall submit a final study report to the Authority not later than **9 months** after the end of data collection, unless a written waiver has been granted by the Authority.

#### 3.3.6.2 The Authority

- The Authority shall have regulatory oversight of all PASS.
- The Authority shall issue not later than **90 days** of submission of the protocol, decision letter to the Local Representative or MAH. This may be an approval, conditional approval, deferral or rejection.

### 3.3.7 Study Protocol

All PASS must be conducted in accordance to approved protocol; the protocol shall have the following sections:

**3.3.7.1 Title:** informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.

**3.3.7.2 Marketing authorisation holder:** name and address of the marketing authorisation holder.

**3.3.7.3 Responsible parties:** names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator. A list of all collaborating institutions and investigators should be made available to the Authority.

**3.3.7.4 Abstract:** stand-alone summary of the study protocol including the following sub-sections: Title with subtitles including version and date of the protocol and name and affiliation of main author, Rationale and background, Research question and objectives, Study design, Population, Variables, Data sources, Sample size, Data analysis, Milestones

**3.3.7.5 Amendments and updates:** any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.

**3.3.7.6 Milestones:** Table with planned dates for the following milestones: Start of data collection, End of data collection, Study progress report(s), Interim report(s) of study results, where applicable, in line with phases of data analyses, Final report of study results and any other important timelines in the conduct of the study should be presented.

**3.3.7.8 Rationale and background:** short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

**3.3.7.9 Research question and objectives:** research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.

**3.3.7.10 Research methods:** description of the research methods, including:

**3.3.7.11 Study design:** overall research design and rationale for this choice.

**3.3.7.12 Setting:** study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.

**3.3.7.13 Variables:** outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified. **Data sources:** strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.

**3.3.7.14 Study size:** any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

**3.3.7.15 Data management:** data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

**3.3.7.16 Data analysis:** the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

**3.3.7.17 Quality control:** description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

**3.3.7.18 Limitations of the research methods:** any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.

**3.3.7.19 Protection of human subjects:** safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in PASS.

**3.3.7.20 Management and reporting of adverse events/adverse reactions:** procedures for the collection, management and reporting of individual cases of adverse reactions and of any new

information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

**3.3.7.21 Plans for disseminating and communicating study results**, including any plans for submission of progress reports and final reports.

#### **3.3.7.22 References**

An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

#### **3.3.8 Amendments**

Any amendment to the PASS protocol and study arrangements shall be submitted to the Ethics Committee(s) that originally approved the protocol and the Authority for approval before such amendments are carried out.

- If such amendments are necessary to protect the life of subjects, an urgent amendment may be carried out but the investigator shall inform the Ethics Committee(s) and the Authority of such amendments with an immediate phone call, followed by a written report within forty-eight (48) hours.
- Reports of all amendments shall include but not be limited to the following:
  - Reasons for the amendments.
  - Possible consequences for subjects already included in the PASS.
  - Possible consequences for the evaluation of the report.
- All amendment shall attract a fee which shall be determined as per Food and Drugs Authority Fee Schedule

#### **3.3.9 Reporting Pharmacovigilance Data to the Authority**

##### **3.3.9.1 Data relevant to the risk-benefit balance of the product**

The Local Representative or MAH shall monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned. Any new information that may affect the benefit-risk balance of the medicinal product should be communicated immediately by email to the Authority and followed up by an official letter within 7days to the Chief Executive Officer of the Authority. Information affecting the risk-benefit balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data. This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSURs) or periodic benefit risk evaluation report (PBRER) and in risk management plan (RMP) updates, where applicable.

### **3.3.10 Reporting of adverse reactions/adverse events**

Adverse reactions/adverse events should be reported to Authority. Procedures for the collection, management (including a review by Local Representative or the MAH if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarized in the study protocol.

Reporting can be done using the adverse reaction reporting form which can be obtained from the Food and Drugs Authority's office or applicants may use their in-house reporting forms, provided all the necessary data elements are included on the forms in a readable format and the form also complies with the CIOMS 1 format (Refer to FDA Guidelines for reporting adverse reactions).

### **3.3.11 Study reports**

#### **3.3.11.1 Progress Report**

The progress report should be submitted in the Format approved by the Authority (refer to Appendix 1).

Progress report should be submitted within 21 days after the end of the preceding quarter. The quarter starts from the start date stated on the study certificate.

#### **3.3.11.2 Final Report**

- The final study report should be submitted to the Authority no later than 9 months after the end of data collection.
- If a study is discontinued, the MAH should inform the Authority with reasons for the termination within 10 days and a final report should be submitted no later than 90 days.

The final study report should contain information in the format prescribed in the Guideline on Good Vigilance Practices (GVP), Module VIII – Post-Authorization Safety Studies (Rev 1).

Where the result of the PASS affects the risk management system or the marketing authorization status of the medicinal product, this shall be communicated to the Authority and steps to incorporate these changes in the RMP and variation to the marketing authorization described.

The Authority may also request variation to the risk management system or the marketing authorization after review of the PASS study report.

## **3.4 SAFETY COMMUNICATION**

### **3.4.1 Introduction**

Throughout the life cycle of the medicinal product information relating to the benefit-risk profile of the product may need to be communicated to stakeholders including, regulatory authorities and marketing authorization holders, patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

### **3.4.2 Objectives of Safety Communication**

Safety communication aims at:

- providing timely evidence-based information on the safe and effective use of medicines;
- facilitating changes to healthcare practices (including self-medication practices) where necessary;
- improving attitudes, decisions and behaviour in relation to the use of medicines;
- supporting risk minimization behaviour;
- facilitating informed decisions on the rational use of medicines.
- Further, safety communication should support public confidence in the regulatory system.

### **3.4.3 Requirements**

All Safety Communication issued by the Local Representative or the Marketing Authorization Holders, Manufacturers shall receive prior approval from the Authority. Application for approval shall include a copy of the proposed communication, the medium of distribution and the targeted audience(s).

Safety communication should be effective, that is the message must be transmitted, received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience.

Systems should be put in place to measure the effectiveness of safety communication.

### **3.4.4 Types of Safety Communication**

- Direct healthcare professional communication (DHPC)
- Documents in lay language for patients
- Press communication or press releases
- Website

- Bulletins and newsletters
- Responding to enquiries from the public

### **3.4.5 Content of Safety Communication**

Safety communication should contain:

- important emerging information on any authorized medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use;
- the reason for initiating safety communication clearly explained to the target audience;
- any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- when applicable, a statement on the agreement between the marketing authorization holder and the Authority on the safety information provided;
- information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
- a list of literature references, when relevant or a reference to where more detailed information can be found;
- where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting system

## **4.0 PENALTIES**

Non-adherence to the requirements of these guidelines by Local Representatives Marketing Authorization Holders and Marketing Authorization Holders will result in the Authority imposing penalties as prescribed by the Public Health Act, 2012, Act 851, Section 142 and Section 148.

**REFERENCES**

1. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorization safety studies (Rev 1), European Medicines Agency, 2013,  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129137.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf)
2. Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication, European Medicines Agency, 2013,  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/07/WC500130396.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500130396.pdf)
3. Guidance for Industry and FDA Staff, Dear Health Care Provider Letters: Improving Communication of Important Safety Information, US Food and Drugs Administration, 2014.  
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4. Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2), 2012.  
[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E2C/E2C\\_R2\\_Step4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf)
5. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1), 2015.  
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