

Effective Date: 16-07-2026

Doc. Ref. No: PV-GDL-006-02

Review Date: 15-07-2031



## **National Agency for Food & Drug Administration & Control (NAFDAC)**

### **Pharmacovigilance Directorate**

### **NAFDAC Good Pharmacovigilance Practice Guideline**

#### **Chapter 6 Periodic Safety Update Reports (PSURs) / Periodic Benefit-Risk Evaluation Reports (PBRERs)**

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## **CHAPTER 6**

### **PERIODIC SAFETY UPDATE REPORTS /PERIODIC BENEFIT RISK EVALUATION REPORT**

#### **6.1 Purpose**

This section outlines the requirements and procedures for the preparation, submission, and regulatory assessment of Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs).

A Periodic Benefit-Risk Evaluation Report (PBRER)/PSUR is a comprehensive, concise, and critical assessment of new or emerging information on a medicine's benefits and risks, compiled by the sponsor. These ongoing evaluations support both sponsors and regulators in maintaining confidence in the medicine's benefit-risk balance, considering existing regulatory measures (e.g., approved indications, warnings, and labelling) and potential actions (e.g., restricting indications, expanding warnings and precautions, introducing contraindications, rescheduling, relabelling, or limiting use to specific populations).

The PBRER/PSUR supports the continuous evaluation of the safety, efficacy, and effectiveness of medicinal products and helps determine whether their benefit-risk balance remains favourable throughout the product lifecycle. It also specifies the information Marketing Authorisation Holders (MAHs) must submit to the Agency to facilitate appropriate regulatory action and protect public health.

#### **6.2 Scope**

This section applies to MAHs of human medicinal products registered or seeking registration in Nigeria, and to relevant applicants where PSUR/PBRERs are required as part of a marketing authorisation application. It covers reporting-cycle establishment, reporting frequency and timelines, report format and content, safety and benefit–risk evaluation, Nigeria-specific safety information, appendices, quality systems, submission and regulatory assessment. The requirements apply according to the product's risk category and any additional or ad hoc reporting requirements specified by the Agency. Low-risk products are exempt from routine submission unless a report is requested by the Agency or a new safety concern or change in risk category warrants submission.

#### **Definitions**

For the purposes of this section, the following definitions apply:

#### **Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER):**

A structured report prepared by the MAH that critically evaluates new or emerging safety, efficacy and effectiveness information in the context of cumulative information, to assess whether the benefit–risk balance of a medicinal product remains favourable.

**Marketing Authorisation Holder (MAH):** The person or legal entity holding the marketing authorisation or Certificate of Registration for a medicinal product and responsible for meeting the applicable regulatory obligations.

**International Birth Date (IBD):** The date of the first marketing authorisation granted to any company, in any country, for a medicinal product containing the active substance.

**Data Lock Point (DLP):** The date up to which data and information are included in a PSUR/PBRER for a defined reporting interval.

**Reporting interval:** The period covered by a PSUR/PBRER, established in accordance with the applicable reporting cycle and DLP.

**Nigerian birth date:** The date on which the Agency first granted a Certificate of Registration for the medicinal product in Nigeria.

**Reference Safety Information (RSI):** The version of the designated reference product information used to determine the expectedness of suspected adverse reactions during the reporting period.

**Adverse drug reaction (ADR):** A noxious and unintended response to a medicinal product for which a causal relationship is at least a reasonable possibility.

**Individual Case Safety Report (ICSR):** A report containing information about an individual patient who experiences one or more suspected adverse reactions or other reportable safety events associated with one or more medicinal products.

**Risk Management Plan (RMP):** A document describing the safety profile of a medicinal product, its important identified and potential risks, missing information, and the pharmacovigilance and risk-minimisation activities intended to address them.

**Benefit–risk balance:** An evaluation of the benefits of a medicinal product in relation to its risks, considering the available evidence and the authorised conditions of use.

## Key Elements of the Reporting Cycle

### 6.3 International Birth Date (IBD), Reporting Interval and Data Lock Point (DLP)

- 6.3.1 The reporting cycle for each PSUR/PBRER shall be established with reference to the **International Birth Date (IBD)** of the active substance. The IBD is the date of the first marketing authorisation granted to any company, in any country in the world, for a medicinal product containing the active substance.
- 6.3.2 The IBD, rather than the date on which the product was first registered or marketed in Nigeria (the **Nigerian birth date**), shall be used as the reference date for establishing

the reporting interval and Data Lock Point (DLP). The Nigerian birth date shall nevertheless be stated on the title page of the PSUR/PBRER (see Section 6.47).

- 6.3.3 The use of a common IBD and DLP facilitates preparation of a single PSUR/PBRER for submission to different regulatory authorities, while recognising that reporting frequencies may differ between jurisdictions in accordance with their respective regulatory requirements. This approach is consistent with ICH E2C(R2).
- 6.3.4 Where the IBD cannot be established despite reasonable efforts, the MAH shall use the earliest date of marketing authorisation for which reliable documentary evidence is available. The date used shall be stated on the title page, and the basis for its use shall be justified in the introduction to the report.

#### **6.4 Establishment and Harmonisation of the DLP**

- 6.4.1 The DLP is the date up to which data and information are included in a PSUR/PBRER. The DLP shall be established from the reporting cycle based on the IBD and the reporting interval applicable to the report.
- 6.4.2 To facilitate harmonisation across products containing the same active substance and across jurisdictions, the MAH may use an existing DLP established or agreed by another competent regulatory authority, if it is based on the same IBD. Where no such DLP has been established, the MAH shall establish the DLP in accordance with the IBD-based reporting cycle applicable to the product in Nigeria.
- 6.4.3 The DLP may correspond to the relevant anniversary of the IBD or to another DLP established within the IBD-based reporting cycle provided it is accepted by the Agency.
- 6.4.4 Once an IBD-based DLP convention has been established for an active substance, the MAH shall apply the same approach consistently to subsequent routine PSUR/PBRERs for that active substance, unless otherwise agreed with the Agency.
- 6.4.5 Where the reporting frequency required by the Agency differs from that applied in another jurisdiction, the MAH shall retain the same IBD as the reference date and establish the DLPs at the reporting milestones required to meet the Agency's applicable reporting frequency. (For more clarification, check ICH E2C(R2) guideline, which allows different regional reporting frequencies while retaining a harmonised IBD/DLP approach).

#### **6.5 Products Registered but Not Yet Marketed in Nigeria**

- 6.5.1 Where a medicinal product has been registered in Nigeria but has not yet been placed on the Nigerian market, the MAH shall submit PSUR/PBRERs in accordance with

the reporting frequency applicable to the product under Section 6.6, unless otherwise agreed in writing by the Agency.

## **6.6 Frequency of Submission of PSUR/PBRERs**

6.6.1 The frequency of PSUR/PBRER submission in Nigeria shall be determined by the requirements of the Agency, taking into consideration the risk category assigned to the product (see Sections 6.11 and 6.12) and whether the product contains a new drug molecule.

6.6.2 The reporting frequency required by the Agency shall be applied independently of the age of the active substance calculated from its global IBD. The IBD shall continue to be used to establish the reporting cycle and DLP.

Accordingly:

- a. New drug molecules: Where an active substance is being registered in Nigeria for the first time, the MAH shall submit PSUR/PBRERs at least every six (6) months for the first two (2) years following the first marketing authorisation in Nigeria, annually for the following three (3) years, and thereafter every five (5) years, unless the Agency requires more frequent submission. The reporting intervals and DLPs for these reports shall nevertheless be established with reference to the IBD in accordance with Sections 6.3 and 6.4.
- b. High-risk and medium-risk products that do not contain a new drug molecule: PSUR/PBRERs shall be submitted every five (5) years based on the IBD-established reporting cycle, irrespective of whether the reporting cycle aligns with the product renewal period, unless the Agency requires more frequent submission.
- c. Low-risk products: Low-risk products shall be exempt from routine submission of PSUR/PBRERs. The MAH shall nevertheless continue to collect, evaluate and report safety information in accordance with this Guideline and shall submit a PSUR/PBRER when requested by the Agency, when a signal or new safety concern arises, or when the Agency changes the risk category of the product.

6.6.3 Where a product is subject to a Nigerian reporting frequency that is more frequent than the frequency applicable to the same active substance in another jurisdiction, the MAH shall meet the Nigerian reporting requirement using DLPs established from the IBD-based reporting cycle. Where appropriate, the Agency may accept a PSUR/PBRER covering a longer interval, if it fulfils the applicable Nigerian reporting requirement and contains the required up-to-date information. (Read ICH E2C(R2) Q&A on managing different regional reporting frequencies for more information).

## **6.7 Authority to Require More Frequent or Ad Hoc Reporting**

6.7.1 Irrespective of the routine reporting frequency assigned to a product, the Agency may at any time require more frequent submission or an ad hoc PSUR/PBRER where this is considered necessary for the protection of public health.

Such a requirement may be made where:

- a. submission of PSUR/PBRERs is a condition of the marketing authorisation;
- b. the product is subject to a Risk Management Plan (RMP), additional pharmacovigilance activities or additional risk minimisation measures;
- c. there are concerns arising from pharmacovigilance data or other safety information;
- d. PSUR/PBRERs for the active substance have not been submitted where expected;
- e. regulatory action has been taken, or a significant new safety concern has arisen, in another jurisdiction; or
- f. other information indicates that more frequent monitoring of the benefit-risk balance is warranted.

6.7.2 For an ad hoc PSUR/PBRER, the Agency shall specify the reporting period and DLP, where these differ from the routine reporting cycle.

## **6.8 Products Already Marketed in Other Countries**

6.8.1 Where a medicinal product has already been authorised and marketed in another country, the applicant shall submit the most recent available PSUR/PBRER for the active substance as part of the application for registration in Nigeria.

6.8.2 Following registration in Nigeria, the MAH shall submit PSUR/PBRERs in accordance with the reporting frequency applicable in Nigeria under Section 6.6. The first routine report due after registration shall be determined using the next applicable reporting interval/DLP in the IBD-based reporting cycle.

6.8.3 For listed medicinal products subject to provisional registration, the MAH shall submit a PSUR/PBRER every six (6) months during the two (2) year listing period where the product is classified as high risk, unless otherwise specified by the Agency.

## 6.9 Timeline for Submission of PSUR/PBRERs

- 6.9.1 Each MAH shall be responsible for submitting PSUR/PBRERs for its own products to the Agency. For routine PSUR/PBRERs, **Day 0 shall be the DLP**. The completed report shall be submitted:
- a. within 70 calendar days of the DLP for PSUR/PBRERs covering reporting intervals of up to 12 months, including intervals of exactly 12 months; and
  - b. within 90 calendar days of the DLP for PSUR/PBRERs covering reporting intervals exceeding 12 months.
  - c. For an ad hoc PSUR/PBRER requested by the Agency, the submission timeline shall normally be specified in the Agency's request. Where no timeline is specified, the report shall be submitted within 90 calendar days of the DLP.

## 6.10 Risk Categorisation of Medicinal Products for PSUR submission

- 6.10.1 The Agency shall establish and maintain a **risk categorisation framework** for medicinal products subject to PSUR/PBRER requirements. The framework shall define the criteria and process to be applied in categorising medicinal products as **high, medium or low risk** for the purpose of determining the appropriate level of PSUR/PBRER oversight.
- 6.10.2 The Marketing Authorisation Holder (MAH) shall assess each of its registered medicinal products against the Agency's risk categorisation framework and determine the applicable risk category. The MAH shall ensure that the categorisation is based on the most current and relevant safety, clinical, regulatory and product-related information available.
- 6.10.3 The MAH shall state the risk category determined in accordance with the Agency's framework on the **title page of each PSUR/PBRER** and in the accompanying covering letter.
- 6.10.4 The MAH shall periodically review the risk category of each product and shall reassess the categorisation where new information becomes available that may affect the product's risk profile. Such information may include, but is not limited to:
- i. new or emerging safety information;
  - ii. identification, validation or confirmation of a safety signal;
  - iii. a new or emerging safety concern;
  - iv. a change in the known safety profile or benefit-risk balance of the product;

- v. significant changes to the Risk Management Plan (RMP), safety specification or risk minimisation measures, where applicable; or
  - vi. significant regulatory action or new safety information relating to the product in another jurisdiction.
- 6.10.5 Where the MAH determines that a product's risk category has changed, the MAH shall update the categorisation and apply the corresponding PSUR/PBRER reporting requirements from the next report due, unless otherwise specified by the Agency.
- 6.10.6 The Agency may review the risk categorisation applied by an MAH as part of its regulatory oversight, including during PSUR/PBRER assessment, pharmacovigilance inspections, review of safety information or other regulatory activities. Where the Agency considers that the categorisation does not appropriately reflect the available evidence or the criteria in the Agency's framework, it may require the MAH to reassess and, where appropriate, revise the risk category.
- 6.10.7 The risk category determined by the MAH in accordance with the Agency's framework shall be used to determine the applicable routine PSUR/PBRER reporting requirements set out in Section 6.6. The risk categorisation does not remove or limit the MAH's obligations to continuously monitor the safety profile of its products, maintain an effective pharmacovigilance system, and promptly notify the Agency of significant safety information in accordance with this Guideline.
- 6.10.8 Irrespective of the risk category determined by the MAH, the Agency may require additional pharmacovigilance measures or more frequent or ad hoc PSUR/PBRER submission where this is considered necessary for the protection of public health.

## **6.11 Structures and processes**

### **6.11.1 Objectives**

- 6.11.1.1 The main objective of a PSUR/PBRER is to present a comprehensive, concise and critical analysis of the benefit-risk balance of the medicinal product considering new or emerging information in the context of cumulative information on risks and benefits. The PSUR/PBRER is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.
- 6.11.1.2 For lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicinal product in everyday medicinal practice and long-term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trial. A different benefit-risk balance may emerge as pharmacovigilance reveals further safety

information. The Marketing Authorisation Holder should therefore re-evaluate the benefit-risk balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management (see Chapter 3) to facilitate optimisation of the benefit-risk balance through effective risk minimisation.

- 6.11.1.3 Urgent safety information should be reported through the appropriate mechanism. A PSUR/PBRER is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide how new safety issues are detected. It is acknowledged that the review of the data in the PSUR/PBRER may lead to new safety issues being identified.

## **6.11.2 Principles**

- 6.11.2.1 Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimisation.
- 6.11.2.2 After a Certificate of Registration is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long-term use, to confirm that the benefit-risk balance remains favourable.
- 6.11.2.3 The analysis of the benefit-risk balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available, with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.
- 6.11.2.4 The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medicinal practice including use in unauthorised indications and use which is not in line with the product information (e. misuse, abuse or overdose). If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR/PBRER (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation data, information from spontaneous reports and publications in the literature.

## **6.11.3 Scope of Information for the Benefit–Risk Evaluation**

- 6.11.3.1 The scope of the benefit-risk information should include both clinical trial and real-world data in authorised indications.

- 6.11.3.2 The integrated benefit-risk evaluation should be performed for all authorised indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorised indications).
- 6.11.3.3 The evaluation should involve:
- Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.
  - Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the benefit-risk balance of the medicinal product.(including safety, efficacy and effectiveness information generated in Nigeria.)
  - The PSUR/PBRER should include an overall benefit-risk evaluation covering all authorised indications using all cumulative data available since the Development International Birth Date (DIBD), which is the date the first clinical trial of the product was authorised in any country. If the DIBD is not known, or the Marketing Authorisation Holder does not have access to early clinical development data, the company should use the earliest date for which reliable information is available and use this as the starting point for the cumulative evaluation.
  - Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation actions that are planned to be implemented.
  - Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

## **6.12 Principles for the preparation of PSUR/PBRERs**

- 6.12.1 Unless the Agency instructs otherwise, the Marketing Authorisation Holder should submit one PSUR/PBRER covering all its products that contain the same active substance. The report should include all approved indications, routes of administration, dosage forms, and dosing regimens, even if the products are registered under different brand names.
- 6.12.2 Where necessary, the PSUR/PBRER should present separate information for different indications, dosage forms, routes of administration, or dosing regimens, and any related safety concerns should be discussed clearly.

- 6.12.3 In special cases, separate PSUR/PBRERs may be allowed for the same active ingredients, for example when different formulations are used for completely different indications. In such situations, the Marketing Authorisation Holder should obtain agreement from the Agency, preferably at the time of product authorisation.
- 6.12.4 Case narratives should be provided in the relevant risk evaluation section of the PSUR/PBRER where integral to the scientific analysis of a signal or safety concern. In this context, the term “case narratives” refers to clinical evaluations of individual cases rather than the CIOMS narratives.
- 6.12.5 If the Marketing Authorisation Holder receives safety information from a partner (such as a distributor, licensee, affiliate, or co-marketing company), and the information could affect how safe the product is considered or could lead to a change in the product information, the Marketing Authorisation Holder must review it and include it in the PSUR/PBRER. The Marketing Authorisation Holder remains responsible for evaluating all available safety information for the product, even if the data was not originally generated by them.
- 6.12.6 All PSUR/PBRERs shall be prepared in the format and with the table of contents of the ICH E2C(R2) Periodic Benefit-Risk Evaluation Report, as described in section 6.14 to 6.37. Each report should include interval as well as cumulative data.

### **6.13 Reference information**

- 6.13.1 Risk minimisation activities evaluated in the PSUR/PBRER include updates to the product information.
- 6.13.2 The reference product information for the PSUR/PBRER should include “core safety” and “authorised indications” components. In order to facilitate the assessment of benefit and benefit-risk balance by indication in the evaluation sections of the PSUR/PBRER, the reference product information document should list all authorised indications in Nigeria.
- 6.13.3 The basis for the benefit evaluation should be the important baseline efficacy and effectiveness information summarised in the PSUR/PBRER section 6.34.2 (“Important baseline efficacy and effectiveness information”).
- 6.13.4 Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.
- 6.13.5 The following possible options can be considered by the Marketing Authorisation Holders when selecting the most appropriate reference product information for a PSUR/PBRER:

#### **6.13.5.1 Company core data sheet (CCDS)**

- a. Many Marketing Authorisation Holders prepare a Company Core Data Sheet (CCDS). The CCDS contains important product information such as safety, approved uses (indications), dosage, pharmacology, and other product details. The safety section within the CCDS is called the Company Core Safety Information (CCSI). For the PSUR/PBRER, the Marketing Authorisation Holder should preferably use the CCDS version that was valid at the end of the reporting period as the reference product information. This document should be used to assess both the safety (risk) sections and the benefit of the authorised indications.
- b. If the CCDS does not include the approved indications, the Marketing Authorisation Holder must state in the PSUR/PBRER which document is being used as the reference for the authorised indications (for example, the approved SmPC or national product label).

#### **6.13.5.2 Other options for the reference product information**

6.13.5.2.1 If a product does not have a CCDS or CCSI (for example, an older or generic product), the Marketing Authorisation Holder must state which reference safety information they are using for the PSUR. This reference may be an approved national or regional product information document, such as the Summary of Product Characteristics (SmPC).

6.13.6 The company must attach the reference safety document used to evaluate expectedness of adverse reactions (e.g., CCDS/CCSI or approved SmPC) as an appendix. If the approved indications are contained in a different document, that document must also be attached. The version attached must be the one valid at the Data Lock Point.

6.13.7 During the reporting period, the Marketing Authorisation Holder should regularly review any new safety information to determine whether the reference product information or reference safety information needs to be updated. Any important updates made during the reporting period must be described in the “Changes to the reference safety information” section 4 of the PSUR/PBRER and, where applicable, further discussed in the “Signal and risk evaluation” section 16.

These changes may include:

- a. A change to contraindications, warnings/precautions sections;
- b. Addition to adverse reactions and interactions;
- c. Addition of important new information on use in overdose; and
- d. Removal of an indication or other restrictions for safety or lack

- 6.13.8 The Marketing Authorisation Holder must attach a clean copy of the reference product information to the PSUR/PBRER as an appendix. This should include all versions that were valid at the end of the reporting period (for example, where different formulations are covered in the same PSUR). Each reference document must show the date and version number.
- 6.13.9 If important new safety information becomes available after the data lock point but before the PSUR/PBRER is submitted, and this information leads to a change in the product information (for example a new adverse reaction, warning, or contraindication) it must be reported in the “Late-breaking information” section of the PSUR/PBRER.

#### **6.14 Format and contents of the PSUR/PBRER**

- 6.14.1 The PSUR/PBRER should be based on all available data including those generated from within Nigeria and should focus on new information which has emerged since the data lock point of the last PSUR/PBRER. Cumulative information should be considered when performing the overall safety evaluation and integrated benefit-risk assessment.
- 6.14.2 Safety information from studies carried out after the product has been registered must be included in the PSUR/PBRER. This includes results from post-authorisation studies and clinical trials, even if they involve uses, patient groups, or indications that are not yet approved.
- Safety information obtained from off-label use should also be considered and discussed in the risk evaluation where it is relevant to the product’s safety.
- 6.14.3 The PSUR/PBRER should provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the Certificate of Registration.
- 6.14.4 Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSUR/PBRERs include the following:
- a. Non-clinical studies;
  - b. Spontaneous reports (e.g. on the marketing authorization
  - c. Active surveillance systems (e.g. sentinel sites);
  - d. Investigations of product quality;
  - e. Product usage data and drug utilisation information;
  - f. Clinical trials, including research in unauthorised indications or populations;

- g. Observational studies, including registries;
  - h. Patient support programs;
  - i. Systematic reviews and meta-analysis;
  - j. Marketing Authorisation Holders sponsored websites;
  - k. Published scientific literature or reports from abstracts, including information presented at scientific meetings;
  - l. Unpublished manuscripts;
  - m. Licensing partners, other sponsors or academic institutions and research networks;
  - n. Competent authorities (worldwide).
- 6.14.5 The data sources listed above are not the only sources that may be used. The Marketing Authorisation Holder may use any other relevant information to describe the safety, benefits, and overall benefit-risk balance of the product, depending on the product and its known or emerging risks.
- The Marketing Authorisation Holder may also include, as an appendix to the PSUR/PBRER, a list of all information sources used to prepare the report.
- 6.14.6 The PSUR/PBRER shall be prepared following the format described in sections 6.14 to 6.37. All sections of the format shall be present; where the Marketing Authorisation Holder has no information for a section, this shall be stated.
- 6.14.7 The Marketing Authorisation Holder should use all safety information about the active substance or product that they can reasonably access and that is relevant to assessing safety and the benefit-risk balance.
- All PSURs should follow the same format, but the amount of information provided may differ depending on what data the Marketing Authorisation Holder can obtain. For example, if the Marketing Authorisation Holder sponsors a clinical trial, they should have access to detailed patient-level data. If they did not sponsor the trial, they may only have access to the published study report.
- 6.14.8 The amount of detail included in each section of the PSUR/PBRER should be based on the importance of the product's known or new safety and benefit information and should be proportionate to the risk category of the product. More detailed discussion is expected in sections that evaluate safety, efficacy, effectiveness, safety signals, and the overall benefit-risk balance, especially when important risks or new findings are identified.

- 6.14.9 When preparing the PSUR/PBRER, the Marketing Authorisation Holder shall follow the ICH E2C(R2) guideline on the Periodic Benefit-Risk Evaluation Report (PBRER). The structure, section titles, order, and required content of the PSUR/PBRER should follow the guidance provided in sections 6.15 to 6.37 of this document. If there is no relevant information for any section, the Marketing Authorisation Holder should clearly state that no data are available. NAFDAC is a member of the International Council for Harmonisation (ICH); the PBRER format is therefore the reference format for all periodic reports submitted to the Agency.

Part I: Title page including signature

Part II: Executive Summary

Part III: Table of Contents

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20. Appendices to the PSUR/PBRER

## **6.15 Title page**

- 6.15.1 The title page should include the following;

- a. Name of the medicinal product(s) and substance;
- b. International birth date (IBD), that is, the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world, and the data lock point (DLP) of the report;
- c. Nigerian birth date, that is, the date on which the Agency first granted a Certificate of Registration for the product, stated for information only (the reporting interval is calculated from the IBD, see 6.3);
- d. Reporting interval and sequence number of the report (e.g. PSUR/PBRER No. 4);
- e. Date of the report;
- f. Risk category assigned to the product by the Agency (see 6.10);
- g. Marketing Authorisation Holder details;
- h. Statement of confidentiality of the information included in the PSUR/PBRER.
- i. Signature of QPPV in Nigeria.

## **6.16 Executive summary**

- 6.16.1 An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR/PBRER and should contain the following information:
- a. Introduction and reporting interval.
  - b. Medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration.
  - c. Estimated cumulative clinical trials exposure.
  - d. Estimated interval and cumulative exposure from marketing experience.
  - e. Number of countries in which the medicinal product is authorised.
  - f. Summary of the overall benefit-risk analysis evaluation (based on section 6.35.3“Benefit-risk analysis evaluation” of the PSUR/PBRER).
  - g. Actions taken and proposed for safety reasons (e.g. significant changes to the reference product information, or other risk minimisation activities);
  - h. Conclusions.

## **6.17 Table of contents**

The table of contents should be as outlined in section 6.14.9 above.

## **6.18 Introduction**

- 6.18.1 The Marketing Authorisation Holder should provide a brief introduction to the product(s) to ensure the PSUR/PBRER functions as a "stand-alone" document. This introduction should also provide context relative to previous reports and evolving clinical circumstances. The following information must be included:
- a. International birth date (IBD), data lock point, reporting interval, and the Nigerian birth date;
  - b. Medicinal product(s) , therapeutic class(es), mechanism(s) of action, authorized indication(s), Dosage Form, dose(s) and route(s) of administration covered by the PSUR
  - c. Brief description of the population(s) being treated and studied;

## **6.19 Worldwide marketing authorisation status**

- 6.19.1 This section of the PSUR/PBRER should contain a brief narrative overview including:
- a. Date of the first authorisation worldwide,
  - b. Indications(s),
  - c. Authorised dose(s), and where authorised.

## **6.20 Actions taken in the reporting interval for safety reasons**

- 6.20.1 This section of the PSUR/PBRER should include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the marketing authorisation holder sponsors of clinical trial(s), data monitoring committees, ethics committees or the Agency that had either:
- a. A significant influence on the benefit-risk balance of the authorised medicinal product; and/or
  - b. An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme (if applicable).
- 6.20.2 If known, the reason for each action should be provided, and any additional relevant information should be included as appropriate. Relevant updates to previous actions should also be summarised in this section.

6.20.3 Examples of significant actions taken for safety reasons include:

- a. Actions related to investigational uses:
  - i. Refusal to authorise a clinical trial for ethical or safety reasons;
  - ii. Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
  - iii. Recall of investigational drug or comparator;
  - iv. Failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a Certificate of Registration application;
  - v. Risk management activities, including:
    - Protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
    - Restrictions in study population or indications;
    - Changes to the informed consent document relating to safety concerns;
    - Formulation changes;
    - Addition by regulators of a special safety-related reporting requirement;
    - Issuance of a communication to investigators or healthcare professionals; and
    - Plans for new studies to address safety concerns.
- b. Actions related to marketing experience:
  - I. Failure to obtain or apply for a Certificate of Registration renewal;
  - ii. Withdrawal or suspension of a Certificate of Registration;
  - iii. Actions taken due to product defects and quality issues;
  - iv. Suspension of supply by the Marketing Authorisation Holder;
  - v. Risk management activities including:
    - Significant restrictions on distribution or introduction of other risk minimisation measures;
    - Significant safety-related changes in labelling documents including restrictions on use or population treated;
    - Communications to health care professionals; and

- New post-marketing study requirement(s) imposed by the Agency.

## **6.21 Changes to reference safety information**

- 6.21.1 This PSUR/PBRER section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR/PBRER. Provide the type (Smpc, CDS, CCDS etc.) and version number of RSI being used in the reporting period.

## **6.22 Estimated exposure and use patterns**

- 6.22.1 PSUR/PBRERs should provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure should be accompanied by a qualitative and quantitative analysis of actual use, which should indicate, where appropriate, how actual use differs from the indicated use based on all data available to the Marketing Authorisation Holder, including the results of observational or drug utilisation studies.
- 6.22.2 This PSUR/PBRER section should provide estimates of the size and nature of the population exposed to the medicinal product including a brief description of the method(s) used to estimate the subject/patient exposure and the limitations of that method.
- 6.22.3 Consistent methods for calculating subject/patient exposure should be used across PSUR/PBRERs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR/PBRER introducing the change and any important difference between the results using the two methods should be highlighted.

### **6.22.4 Cumulative subject exposure in clinical trials**

- 6.22.4.1 This section of the PSUR/PBRER should contain the following information on the patients studied in clinical trials sponsored by the Marketing Authorisation Holder, if applicable presented in tabular formats:
- a. Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active

comparator(s) since the Development International Birth Date (DIBD). It is recognised that for “old products”, detailed data might not be available;

- b. More detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme);
- c. Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
- d. If clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;
- e. When there are substantial differences in time of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);
- f. Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;
- g. If the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;
- h. For individual trials of particular importance, demographic characteristics should be provided separately.

6.22.4.2 Provide examples in a table for the estimated exposure in clinical trials.

### **6.22.5 Cumulative and interval patient exposure from marketing experience**

6.22.5.1 Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR/PBRER). Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along

with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

6.22.5.2 In addition to the worldwide estimates, the Marketing Authorisation Holder shall provide an estimate of patient exposure in Nigeria for the reporting interval and cumulatively since the Nigerian birth date, derived from import, local manufacturing, distribution or sales data, and describe the method and its limitations. Where a product is not yet marketed in Nigeria, this shall be stated.

6.22.5.3 The data should be presented according to the following categories:

a. Post-authorisation (non-clinical trial) exposure: An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

b. Post-authorisation use in special populations:

Where post-authorization use has occurred in special populations, available data regarding cumulative patient exposure and the methodology for calculation should be provided. Data sources may include non-interventional studies, such as registries, designed to capture this information. Other sources may include data collected outside of a study environment, such as spontaneous reporting systems (e.g., reports of pregnancy exposure without an associated adverse event). Populations for consideration include, but are not limited to:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub - populations carrying relevant genetic polymorphism(s);
- Populations with specific racial and/or ethnic origins.

c. Other post-authorisation use:

- i. If the Marketing Authorisation Holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without reference to adverse reactions should be summarised in this section as applicable. Such information may be received via spontaneous reporting systems, medicinal information queries, customer's complaints, screening of digital media or via other information sources available to the Marketing Authorisation Holder. If quantitative information on use is available, it should be provided
- ii. Where known, the Marketing Authorisation Holder (MAH) may briefly comment on whether use beyond the recommendations in the Reference Product Information (RPI) is supported by clinical guidelines, clinical trial evidence, or an absence of authorized alternative treatments. To identify patterns of use outside the authorized terms, the Marketing Authorisation Holder should refer to the version of the RPI in effect at the close of the reporting interval (e.g., authorized indications, routes of administration, and contraindications).
- iii. Signals or risks identified from any data or information source should be presented and evaluated in the relevant sections of the PSUR/PBRER.

6.22.5.4 Insert tables for the estimated exposure from marketing experience.

## **6.23 Data in summary tabulations**

- 6.23.1 The objective of this PSUR/PBRER section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, the competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the Marketing Authorisation Holder graphical

displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

- 6.23.2 Adverse reaction reports originating from Nigeria shall be presented in a separate summary tabulation for the reporting interval and cumulatively since the Nigerian birth date, drawing on the Marketing Authorisation Holder's safety database and on the reports made available to the Marketing Authorisation Holder by the Agency. The line listing of the Nigerian cases shall be provided in the Nigeria-specific appendix (see 6.37).
- 6.23.3 When the Medicinal Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations.
- 6.23.4 The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A9. When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSUR/PBRERs.

#### **6.23.5 Reference information**

- 6.23.5.1 This section of the PSUR/PBRER should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

#### **6.23.6 Cumulative summary tabulations of serious adverse events from clinical trials**

- 6.23.6.1 This PSUR/PBRER section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the Marketing Authorisation Holder's clinical trials, from the DIBD to the data lock point of the current PSUR/PBRER. The Marketing Authorisation Holder should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables.
- 6.23.6.2 This section should not serve to provide analyses or conclusions based on the serious adverse events.
- 6.23.6.3 The following points should be considered:

- a. Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.
- b. In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.
- c. The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and Marketing Authorisation Holders should not unblind data for the specific purpose of preparing the PSUR/PBRER.
- d. Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

#### **6.23.7 Cumulative and interval summary tabulations from post-marketing data sources**

- 6.23.7.1 This section of the PSUR/PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR/PBRER. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, regulatory authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC (listed in the internationally agreed order).
- 6.23.7.2 For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. As described in

- ICH-E2D11 guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.
- 6.23.7.3 Analysis or conclusions based on the summary tabulations should not be provided in this PSUR/PBRER section.
- 6.23.7.4 Provide summary tables of adverse drug reactions from post-marketing data sources.

## **6.24 Summaries of significant findings from clinical trials during the reporting interval**

- 6.24.1 This PSUR/PBRER section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the Marketing Authorisation Holder's sponsored clinical trials during the reporting interval, from the sources specified in the sections listed below. When possible and relevant, data categorised by sex and age (particularly pediatrics versus adults), indication, dose, and region should be presented.
- 6.24.2 Signals arising from clinical trial sources should be tabulated in PSUR/PBRER section 15 ("Overview on signals: new, ongoing or closed"). Evaluation of the signals, whether categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR/PBRER section 6.33.5 ("Signal evaluation"). New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in PSUR/PBRER section 6.33.6 ("Evaluation of risks and new information") and section 6.33.7 ("Characterisation of risks") respectively.
- 6.24.3 Findings from clinical trials not sponsored by the Marketing Authorisation Holder should be described in the relevant sections of the PSUR/PBRER.
- 6.24.4 When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in authorised indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness should be summarised in section 6.102 ("Lack of efficacy in controlled clinical trials"). Information from other clinical trials/study sources should be included in the PSUR/PBRER section 6.26.1 ("other clinical trials").
- 6.24.5 In addition, the Marketing Authorisation Holder should include an appendix listing the sponsored post-authorisation interventional trials, with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety

profile of the medicinal products that were completed or ongoing during the reporting interval. The listing should include the following information for each trial:

- a. Study ID (e.g. protocol number or another identifier);
- b. Study title (abbreviated study title, if applicable);
- c. Study type (e.g. randomised clinical trial, cohort study, case-control study);
- d. Population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);
- e. Study start (as defined by the Marketing Authorisation Holder) and projected completion dates;
- f. Status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

#### **6.24.6 Completed clinical trials**

- 6.24.6.1 This section of the PSUR/PBRER should provide a summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

#### **6.24.7 Ongoing clinical trials**

- 6.24.7.1 If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or because of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes identified safety concerns previously, as well as evidence of new safety signals.

#### **6.24.8 Long term follow-up**

- 6.24.8.1 Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

#### **6.24.9 Other therapeutic use of medicinal product**

- 6.24.9.1 This section of the PSUR/PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH-E2D13 (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

#### **6.24.10 New safety data related to fixed combination therapies**

- 6.24.10.1 Unless otherwise specified by the Agency, the following options can be used to present data from combination therapies:
- a. If the active substance that is the subject of the PSUR/PBRERs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.
  - b. If the product itself is a fixed combination product, this PSUR/PBRER section should summarise important safety information arising from the individual components, whether authorised or under development.
- 6.24.10.2 The information specific to the combination can be incorporated into a separate section(s) of the PSUR/PBRER for one or all the individual components of the combination.

#### **6.25 Findings from non-interventional studies**

- 6.25.1 This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions.
- 6.25.2 The MAH should include an appendix listing of MAH-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval (see section 6.24 for the information that should be included in the listing).
- 6.25.3 Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR/PBRER.

- 6.25.4 Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PSUR/PBRER. As for other information sources, the MAH should present signals or risks identified from such information in the relevant sections of the PSUR/PBRER.

## **6.26 Information from other clinical trials and sources**

### **6.26.1 Other clinical trials**

- 6.26.1.1 This PSUR/PBRER section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the MAH during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

### **6.26.2 Medication errors**

- 6.26.2.1 This section should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

## **6.27 Non-clinical Data**

- 6.27.1 This PSUR/PBRER section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns should be included in the PSUR/PBRER, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR/PBRER.

## **6.28 Literature**

- 6.28.1 This PSUR/PBRER section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the MAH became aware of during the reporting interval, when relevant to the medicinal product.

- 6.28.2 Literature searches for PSUR/PBRERs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.
- 6.28.3 The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:
- a. Pregnancy outcomes (including termination) with no adverse outcomes;
  - b. Use in paediatric populations;
  - c. Compassionate supply, named patient use;
  - d. Lack of efficacy;
  - e. Asymptomatic overdose, abuse or misuse;
  - f. Medication error where no adverse events occurred;
  - g. Important non-clinical safety results.
- 6.28.4 If relevant and applicable, information on other active substances of the same class should be considered. The publication reference should be provided in the style of the Vancouver Convention.

## **6.29 Other periodic reports**

- 6.29.1 This PSUR/PBRER section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSUR/PBRERs are prepared in agreement with the Agency. In general, the MAH should prepare a single PSUR/PBRER for a single active substance (unless otherwise specified by the Agency); however, in exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, the regulatory authorities should be notified and their agreement obtained, preferably at the time of approval. If multiple PSUR/PBRERs are prepared for a single medicinal product, this section should also summarise significant findings from other PSUR/PBRERs if they are not presented elsewhere within the report.
- 6.29.2 For products manufactured and/or marketed by more than one company, each MAH is responsible for submitting PBRERs for its own products. When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the regulatory authorities should be clearly specified in the written agreement. When data received from a partner company(ies) might contribute meaningfully to the safety, benefit

and/or benefit-risk analyses and influence the reporting company's product information, these data should be included and discussed in the PBRER.

### **6.30 Lack of efficacy in controlled clinical trials**

- 6.30.1 This section should summarise data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute coronary syndromes) that could reflect a significant risk to the treated population.

### **6.31 Late-breaking information**

- 6.31.1 The MAH should summarise in this PSUR/PBRER section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR/PBRER. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or any competent authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR/PBRER (e.g. a well-documented case of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).
- 6.31.2 Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR/PBRER (see section 6.13).
- 6.31.3 The data presented in this section should also be considered in the evaluation of risks and new information (see section 6.33.6).

### **6.32 Overview of signals: new, ongoing, or closed**

- 6.32.1 The purpose of this section is to provide a high-level overview of signals that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing

- evaluation at the end of the reporting interval. For the purposes of the PSUR/PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the MAH. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicinal product/event combination, as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide).
- 6.32.2 Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation involve medicinal judgement and scientific interpretation of available data, which is presented in section 6.33“Signal and risk evaluation” of the PSUR/PBRER.
- 6.32.3 A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR/PBRER, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR/PBRER.
- 6.32.4 Examples of new signals would therefore include new information on a previously:
- a. Close and refute a signal, which would result in the signal being re-opened.
  - b. Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well-documented case report of agranulocytosis with no presence of possible alternative causes is received).
  - c. Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
  - d. Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.
- 6.32.5 Within this section or as an appendix, the Marketing Authorisation Holder should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:

- a. A brief description of the signal;
  - b. seriousness of the signal
  - c. Date when the Marketing Authorisation Holder became aware of the signal;
  - d. Status of the signal at the end of the reporting interval (close or ongoing);
  - e. Date when the signal was closed, if applicable;
  - f. Source of the signal;
  - g. A brief summary of the key data;
  - h. Plans for further evaluation; and
  - i. Actions taken or planned.
- 6.32.6 The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in section 6.33.5 (“Signal evaluation”) of the PSUR/PBRER.
- 6.32.7 Evaluation of new information in relation to any previously known, identified, and potential risks and not considered to constitute a new signal should be provided in PSUR/PBRER section 6.33.6 (“Evaluation of risks and new information”).
- 6.32.8 When any competent authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in PSUR/PBRER, the Marketing Authorisation Holder should summarise the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in section 6.33.5 (“Signal evaluation”).

### **6.33 Signal and risk evaluation**

- 6.33.1 The purpose of this section of the PSUR/PBRER is to provide:
- a. A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report (section 6.33.4).
  - b. An evaluation of all signals closed during the reporting interval (section 6.33.5)
  - c. An evaluation of new information with respect to previously recognised identified and potential risks (section 6.33.6).

- d. An updated characterisation of important potential and identified risks, where applicable (section 6.33.7).
  - e. A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (section 6.33.8).
- 6.33.2 The Marketing Authorisation Holder may present the mapping of signals and risks to the relevant sections of the PSUR/PBRER in tabular form or as a flow chart (see 6.37).
- 6.33.3 These evaluation sections should not summarise, or duplicate information presented in previous sections of the PSUR/PBRER but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR/PBRER but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided (see section 6.12).

#### **6.33.4 Summary of safety concerns**

- 6.33.4.1 The purpose of this section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR/PBRER. It should provide the following safety information:
- a. Important identified risks;
  - b. Important potential risks; and
  - c. Missing information.
- 6.33.4.2 The following factors should be considered when determining the importance of each risk:
- a. (medical )seriousness of the risk, including the impact on individual patients;
  - b. Its frequency, predictability, preventability, and reversibility;
  - c. Potential impact on public health (frequency; size of treated population); and

- d. Potential for avoidance of the use of a medicinal product with a preventive benefit due to a disproportionate public perception of risk (e.g. vaccines).
- 6.33.4.3 For products without an existing safety specification, this section should provide information on the important identified and potential risks and missing information associated with use of the product, based on pre- and post-authorisation experience. Important identified and potential risks may include, for example:
- a. Important adverse reactions.
  - b. Interactions with other medicinal products.
  - c. Interactions with food and other substances.
  - d. Medication errors (e.g Overdose).
  - e. Effects of occupational exposure; and
  - f. Pharmacological class effects.
- 6.33.4.4 The summary on missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

### **6.33.5 Signal evaluation**

- 6.33.5.1 This section of the PSUR/PBRER should summarise the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this section are:
- a. Those signals that, following evaluation, have been refuted as “false” signals based on medical judgement and scientific evaluation of the currently available information.
  - b. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.
- 6.33.5.2 For both categories of closed signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the Marketing Authorisation Holder.
- 6.33.5.3 It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe,

irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information, effect on vulnerable population.) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- a. Closed and refuted signals.
- b. Closed signals that are categorised as important potential risks.
- c. Closed signals that are categorised as important identified risks.
- d. Closed signals that are potential risks not categorised as important.
- e. Closed signals that are identified risks not categorised as important.

6.33.5.4 Where applicable the evaluations of closed signals can be presented by indication or population.

6.33.5.5 The description(s) of the signal evaluations can be included in this section of the PSUR/PBRER or in an appendix. Each evaluation should include the following information as appropriate:

- a. Source or trigger of the signal;
- b. Background relevant to the evaluation;
- c. Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOC, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
- d. Results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
- e. Discussion;
- f. Conclusion.

6.33.5.6 Marketing Authorisation Holder's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

#### **6.33.6 Evaluation of risks and new information**

6.33.6.1 This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in section 6.33.5 ("Signal evaluation").

- 6.33.6.2 New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the signals tabulation (see section 6.32.5) and evaluated in section 6.33.5 (“Signal evaluation”), if the signal is also closed during the reporting interval of the PSUR/PBRER.
- 6.33.6.3 Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information which allows any other further characterisation of a previously recognised risk.
- 6.33.6.4 New information can be organised as follows:
- a. New information on important potential risks.
  - b. New information on important identified risks.
  - c. New information on other potential risks not categorised as important.
  - d. New information on other identified risks not categorised as important.
  - e. Update on missing information.
- 6.33.6.5 The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR/PBRER. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in section 6.33.7 (“Characterisation of risks”) of the report. It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medicinal significance and public health relevance.
- 6.33.6.6 The evaluation(s) of the new information and missing information update(s) can be included in this section of the PSUR/PBRER, or in an appendix. Each evaluation should include the following information as appropriate:
- a. Source of the new information;
  - b. Background relevant to the evaluation;

- c. Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
  - d. Results – a summary and critical analysis of the data considered in the risk evaluation;
  - e. Discussion;
  - f. Conclusion, including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in section 6.33.7(“Characterisation of risks”).
- 6.33.6.7 Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

### **6.33.7 Characterisation of risks**

- 6.33.7.1 This section should characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe missing information.
- 6.33.7.2 Depending on the nature of the data source, the characterisation of risk may include, where applicable:
- a. Frequency;
  - b. Numbers of cases (numerator) and precision of estimate, considering the source of the data;
  - c. Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
  - d. Estimate of relative risk and precision of estimate;
  - e. Estimate of absolute risk and precision of estimate;
  - f. Impact on the individual patient (effects on symptoms, quality or quantity of life);
  - g. Public health impact;
  - h. Patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);

- i. Dose, route of administration;
  - j. Duration of treatment, risk period;
  - k. Preventability (i.e. predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
  - l. Reversibility;
  - m. Potential mechanism; and
  - n. Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.
- 6.33.7.3 When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long-term use, etc.) should be discussed.
- 6.33.7.4 PSUR/PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:
- a. Risks relating to the active substance;
  - b. Risks related to a specific formulation or route of administration (including occupational exposure);
  - c. Risks relating to a specific population; and
  - d. Risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

#### **6.33.8 Effectiveness of risk minimisation**

- 6.33.8.1 Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).
- 6.33.8.2 The PSUR/PBRER should contain the results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment.

- 6.33.8.3 Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section of the PSUR/PBRER.
- 6.33.8.4 Insights into the effectiveness of risk minimisation activities in Nigeria that may have utility in other countries or regions are of particular interest.
- 6.33.8.5 When required for reporting in a PSUR/PBRER, results of evaluations that became available during the reporting interval, should be provided in the PSUR/PBRER.

## **6.34 Benefit evaluation**

- 6.34.1 PSUR/PBRER section 6.34.2(“Important baseline efficacy and effectiveness information”) and section 6.34.3(“Newly identified information on efficacy and effectiveness”) provide the baseline and newly identified benefit information that support the characterisation of benefit described in section 6.34.4 (“Characterisation of benefits”) that in turn supports the benefit-risk evaluation in section 6.35 (“Integrated benefit-risk analysis for authorised indications”).

### **6.34.2 Important baseline efficacy and effectiveness information**

- 6.34.2.1 This section of the PSUR/PBRER summarises information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information should relate to authorised indication(s) of the medicinal product listed in the reference product information (see section 6.23.5).
- 6.34.2.2 For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.
- 6.34.2.3 The level of detail provided in this section should be sufficient to support the characterisation of benefit in the PSUR/PBRER section 6.34.4(“Characterisation of benefits”) and the benefit-risk assessment in section 6.35 (“Integrated benefit-risk analysis for authorised indications”).

### **6.34.3 Newly identified information on efficacy and effectiveness**

- 6.34.3.1 For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this section of the PSUR/PBRER. For authorised indications, new information on efficacy and effectiveness under conditions of actual use should also be described in this section, if available. New information on efficacy

and effectiveness in uses other than the authorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised indications.

- 6.34.3.2 Information on indications newly authorised during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in section 6.34.4 (“Characterisation of benefits”) and the benefit-risk assessment in section 6.35 (“Integrated benefit-risk analysis for authorised indications”).
- 6.34.3.3 In this section, particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

#### **6.34.4 Characterisation of benefits**

- 6.34.4.1 This section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorised indications.
- 6.34.4.2 The level of detail provided in this section should be sufficient to support the analysis of benefit-risk in section 6.35 (“Integrated benefit-risk analysis for authorised indications”).
- 6.34.4.3 When there are no new relevant benefit data, this section should provide a characterisation of the information in section 6.34.2 (“Important baseline efficacy and effectiveness information”).
- 6.34.4.4 When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.
- 6.34.4.5 This section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:
  - a. A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
  - b. New information that challenges the validity of a surrogate endpoint, if used;
  - c. Clinical relevance of the effect size;
  - d. Generalisability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
  - e. Adequacy of characterization of dose-response;

- f. Duration of effect;
- g. Comparative efficacy; and
- h. A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medicinal practice.

### **6.35 Integrated benefit-risk analysis for authorised indications**

6.35.1 The Marketing Authorisation Holder should provide in this PSUR/PBRER section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. Whereas section 6.33.7 (“Characterisation of risks”) and section 6.34.4 (“Characterisation of benefits”) present the risks and benefits, this section should provide a critical analysis and integration of the key information in the previous sections and should not simply duplicate the benefit and risk characterisation presented in the sections mentioned above.

#### **6.35.2 Benefit-risk context – medicinal need and important alternatives**

6.35.2.1 This section of the PSUR/PBRER should provide a brief description of the medicinal need for the medicinal product in the authorised indications and summarised alternatives (medicinal, surgical or other; including no treatment).

#### **6.35.3 Benefit-risk analysis evaluation**

- 6.35.3.1 A benefit-risk balance is specific to an indication and population. Therefore, for products authorised for more than one indication, benefit-risk balances should be evaluated and presented by each indication individually. If there are important differences in the benefit-risk balance among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.
- 6.35.3.2 The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks and should consider the following points:
- a. Whereas previous sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section should be carried forward for integration in the benefit-risk evaluation.

- b. Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).
  - c. With respect to the key benefits, consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
  - d. With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorized indications or populations, off-label use, or misuse.
  - e. The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.
- 6.35.3.3 Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:
- a. The assumptions, considerations, and judgement or weights that support the conclusions of the benefit-risk evaluation should be clear.
  - b. If a formal quantitative or semi-quantitative assessment of benefit risk is provided, a summary of the methods should be included.
  - c. Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.
- 6.35.3.4 When there is important new information or an ad hoc PSUR/PBRER has been requested, a detailed benefit-risk analysis should be presented based on cumulative data. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

## **6.36 Conclusions and actions**

- 6.36.1 A PSUR/PBRER should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.

- 6.36.2 Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the Marketing Authorisation Holder should assess the need for changes to the reference product information and propose changes as appropriate.
- 6.36.3 In addition, and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance for further discussion with the Agency. This may include proposals for additional risk minimisation activities.
- 6.36.4 For products with a pharmacovigilance or risk management plan, the proposals should also be considered for incorporation into the pharmacovigilance plan and/or risk minimisation plan, as appropriate (see Chapter 3).
- 6.36.5 Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the Marketing Authorisation Holder should conclude the PSUR/PBRER as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the product(s) for which the PSUR/PBRER is submitted.
- 6.36.6 Proposed changes to the reference product information should be described in this section of the PSUR/PBRER. The appendix should include proposals for summary of product information and package leaflet together with information on ongoing changes when applicable.

### **6.37 Appendices to the PSUR/PBRER**

- 6.37.1 A PSUR/PBRER should contain the following appendices as appropriate, numbered as follows:
- a. Reference information (see section 6.13).
  - b. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
  - c. Tabular summary of safety signals (if not included in the body of the report).
  - d. Listing of all Marketing Authorisation Holder-sponsored studies, including clinical trials and other interventional or non-interventional studies ongoing or completed during the reporting interval. Interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.
  - e. List of the sources of information used to prepare the PSUR/PBRER.

- f. Appendix: Mapping of signals and risks to PSUR/PBRER sections.
- g. Nigeria-specific appendix (regional appendix), containing:
  - i. A line listing of the individual case safety reports originating from Nigeria during the reporting interval;
  - ii. The estimate of patient exposure in Nigeria (see 6.22.5.2);
  - iii. The status of the risk management plan and of the risk minimisation measures implemented in Nigeria, including the results of any evaluation of their effectiveness;
  - iv. The currently approved Nigerian product information (summary of product characteristics and patient information leaflet) and any proposed changes, with the reasons for the proposal;
  - v. A summary of any safety information specific to Nigeria (e.g. local literature, product quality issues, medication errors, substandard or falsified versions of the product).

### **6.38 Quality systems for PSUR/PBRERs at the level of Marketing Authorisation Holders**

- 6.38.1 The information on signals and risks should be mapped in a flow chart.
- 6.38.2 Marketing Authorisation Holders should have in place structures and processes for the preparation, quality control, review and submission of PSUR/PBRERs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the Marketing Authorisation Holder's quality system (see Chapter 1).
- 6.38.3 There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSUR/PBRERs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality system should describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PSUR/PBRERs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSUR/PBRERs.

There are several areas within the pharmacovigilance system that may directly impact the quality of PSUR/PBRERs. These include, but are not limited to:

- 6.38.4 In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross-departmental input to PSUR/PBRER preparation.
- 6.38.5 The PSUR/PBRER should also contain the assessment of specific safety issues requested by the Agency in accordance with agreed timelines and procedures. The Marketing Authorisation Holder should have mechanisms in place to ensure that the requests made by the Agency during the time of their PSUR/PBRER assessment are properly addressed.
- 6.38.6 The provision of the data included in the summary tabulations (see section 6.23) should undergo source data verification against the Marketing Authorisation Holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.
- 6.38.7 An appropriate quality system should be in place in order to avoid failure to comply with PSUR/PBRER requirements such as:
- An appropriate and effective pharmacovigilance quality system shall be established and maintained to prevent non-compliance with PSUR/PBRER requirements. Such non-compliance may include, but is not limited to, the following.
- a. Non-submission: complete failure to submit a PSUR/PBRER as required.
  - b. Submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the Agency).
  - c. Unjustified omission of information required by section 6.14.
  - d. Poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardized medicinal terminology and inappropriate dismissal of cases with no reported risk factors in cumulative reviews.
  - e. Submission of a PSUR/PBRER where previous request from the Agency have not been addressed;
  - f. Failure to provide a clear and explicit evaluation of the benefit-risk balance of the medicinal product.
  - g. Failure to provide adequate proposals for the local authorised product information.

- 6.38.8 Any significant deviation from established procedures relating to the preparation or submission of PSUR/PBRERs shall be formally documented. Appropriate corrective and preventive actions (CAPA) shall be implemented promptly to address the identified deviation and prevent recurrence.

Documentation of such deviations, including root cause analysis and CAPA measures taken, shall always be maintained and made readily available for inspection by the Agency.

### **6.39 Submission and assessment of PSUR/PBRERs by the Agency**

- 6.39.1 PSUR/PBRERs shall be submitted electronically [through the NAFDAC pharmacovigilance portal / to the e-mail address designated by the Agency], accompanied by a covering letter signed by the QPPV in Nigeria that states the name, strength and dosage form of the product exactly as registered, the NAFDAC registration number, the IBD, the DLP, the reporting interval, the sequence number of the report and the risk category of the product. Submissions that do not meet these requirements, or that do not follow the format in 6.3 to 6.37, will not be accepted as valid and the Marketing Authorisation Holder will be notified.
- 6.39.2 The Agency shall acknowledge receipt of a valid PSUR/PBRER within [10] working days of submission.
- 6.39.3 The Pharmacovigilance Directorate shall assess the PSUR/PBRER within [ 30 ] working days of acknowledgement. During the assessment, the Agency may request additional information or clarification from the Marketing Authorisation Holder, who shall respond within [10] calendar days of the request or within the period specified in the request; the assessment period is suspended until the response is received.
- 6.39.4 On completion of the assessment, the Agency shall communicate one or more of the following outcomes to the Marketing Authorisation Holder in writing:
- a. The benefit-risk balance remains favourable, and no further action is required;
  - b. A request for further information or evaluation, to be provided in the next PSUR/PBRER or within a specified period;
  - c. A variation to the Certificate of Registration, including changes to the approved product information (summary of product characteristics and patient information leaflet)
  - d. Submission of a new or updated risk management plan, or of additional risk minimisation measures;

- e. Additional pharmacovigilance activities, including post-authorisation safety studies;
  - f. A change in the risk category of the product or in the frequency of submission of PSUR/PBRERs; or
  - g. Referral for regulatory action, including suspension, withdrawal or non-renewal of the Certificate of Registration, where the benefit-risk balance is no longer favourable.
- 6.39.5 The Marketing Authorisation Holder shall implement the outcome of the assessment within the timelines communicated by the Agency and shall report on its implementation in the next PSUR/PBRER. Requests made by the Agency during the assessment of a PSUR/PBRER shall be addressed in the subsequent report.
- 6.39.6 Failure to submit a PSUR/PBRER when due, submission of a report that does not meet the requirements of this Chapter, or failure to implement the outcome of an assessment constitutes non-compliance with this Guideline. The Agency may in such cases issue a compliance directive to the Marketing Authorisation Holder, conduct a pharmacovigilance inspection, refuse to renew the Certificate of Registration, and take any other regulatory action provided for under the NAFDAC Act and the relevant regulations.

#### **6.40 Contractual arrangements and third parties**

- 6.40.1 When Marketing Authorisation Holders are involved in contractual arrangements (e.g. licensor-licensee) respective responsibilities for preparation and submission of the PSUR/PBRER to the Agency should be clearly specified in the written agreement.
- 6.40.2 When the preparation of the PSUR/PBRER is delegated to third parties, the Marketing Authorisation Holder should ensure that they are subject to a quality system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the Marketing Authorisation Holder and third parties. The agreement may specifically detail the options to audit the PSUR/PBRER preparation process.

#### **6.41 Training of staff members related to the PSUR/PBRER process**

- 6.41.1 For all organisations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medicinal and quality personnel involved in the preparation, review, quality control, submission and assessment of PSUR/PBRERs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and Chapter 6). The appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR/PBRER should be in place.

- 6.41.2 Training to update knowledge and skills should also take place as necessary. Training should cover regulations, guidelines, scientific evaluation and written procedures related to the PSUR/PBRER process. Training records should demonstrate that the relevant training was delivered before performing PSUR/PBRER-related activities