



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

Pharmacovigilance Directorate

NAFDAC Good Pharmacovigilance Practice Guideline

Chapter 3 Risk Management System

TABLE OF CONTENTS

3.0 RISK MANAGEMENT SYSTEM	4
3.1 Introduction	4
3.2 Purpose	4
3.3 Scope	4
3.4 Definitions	5
3.5 Risk Management Framework	7
3.6 MAH Responsibilities for Risk Management	8
3.7 Structure of the Risk Management Plan	10
3.7.1 Product Overview	10
3.7.1.1 Administrative Information on the RMP	10
3.7.1.2 Active Substance Information	10
3.7.1.3 Information for Each Medicinal Product Included in the RMP	10
3.8.2 Safety Specification	11
3.8.2.1 Epidemiology of the Indications and Target Population	12
3.8.2.2 Non-clinical Part of the Safety Specification	12
3.8.2.3 Clinical Trial Exposure	13
3.8.2.4 Populations Not Studied in Clinical Trials	14
3.8.2.5 Additional Requirements for Safety Specification by the Agency	15
3.8.2.6 Additional Requirements for the Safety Specification	16
3.8.2.6.1 Potential for Harm from Overdose	16
3.8.2.6.2 Potential for Transmission of Infectious Agents	16
3.8.2.6.3 Potential for Misuse, Abuse or Use for Illegal Purposes	16
3.8.2.6.4 Potential for Medication Errors	16
3.8.2.6.5 Potential for Off-label Use	18
3.8.2.6.6 Specific Paediatric Issues	18
3.8.2.6.7 Product- and Administration-Related Safety Considerations	18
3.8.2.6.8 Consideration of the Nigerian Context	19
3.8.2.7 Post-Authorisation Experience	19
3.8.2.7.1 Post-authorisation Use in Populations Not Studied in Clinical Trials	20
3.8.2.7.2 Post-authorisation Off-label Use	21
3.8.2.7.3 Epidemiological Study Exposure	21
3.8.2.8 Identified and Potential Risks	21
3.8.2.8.1 Newly Identified Safety Concerns	21
3.8.2.8.2 Recent Study Reports with Implications for Safety Concerns	21
3.8.2.8.3 Identified and Potential Interactions	21
3.8.2.8.4 Identified and Potential Risks (ATMP Version)	22
3.8.2.9 Summary of Safety Concerns	22
3.8.3 Pharmacovigilance Plan	23
3.8.3.1 Routine Pharmacovigilance Activities	23
3.8.3.2 Specific Adverse Reaction Follow-up Questionnaires	23
3.8.3.3 Additional Pharmacovigilance Activities	24
3.8.3.4 Studies to Measure the Effectiveness of Risk Minimisation Measures	24
3.8.3.5 Drug Utilisation Studies	24

TABLE OF CONTENTS (continued)

3.8.3.6 Registries	25
3.8.3.7 Action Plans for Safety Concerns with Additional Pharmacovigilance Requirements	25
3.8.3.8 Summary Table of Additional Pharmacovigilance Activities	26
3.8.4 Plans for Post-Authorisation Efficacy Studies	26
3.8.4.1 Summary of Existing Efficacy Data	27
3.8.4.2 Assessment of Uncertainties in Efficacy	28
3.8.4.3 Post-Authorisation Efficacy Study Plan	28
3.8.4.4 Evaluation of New Efficacy Information	29
3.8.5 Risk Minimisation Measures	29
3.8.5.1 Routine Risk Minimisation	30
3.8.5.1.1 Summary of Product Characteristics (SmPC) and Package Leaflet (PL)	30
3.8.5.1.2 Pack Size	30
3.8.5.1.3 Legal Status	31
3.8.5.1.4 Restricted Medical Prescription	32
3.8.5.1.5 Special Medical Prescription	33
3.8.5.2 Additional Risk Minimisation Activities	33
3.8.5.2.1 Risk Minimisation Communication Materials	34
3.8.5.2.2 Engagement with NAFDAC	34
3.8.5.2.3 Engagement with Healthcare Professionals and Patients	35
3.8.5.3 Educational Material	35
3.8.5.4 Format of Risk Minimisation Plan(s)	35
3.8.5.5 Evaluation of the Effectiveness of Risk Minimisation Activities	36
3.8.5.6 Gap Analysis	37
3.8.5.7 Summary of Risk Minimisation Measures	37
3.8.6 Summary of Activities in the RMP by Medicinal Product	37
3.8.6.1 Format and Content of the Summary of the RMP	38
3.8.6.2 Overview of Disease Epidemiology	38
3.8.6.3 Summary of Treatment Benefits	38
3.8.6.4 Unknowns Relating to Treatment Benefits	38
3.8.6.5 Summary of Safety Concerns	38
3.8.6.6 Summary of Risk Minimisation Activities by Safety Concern	39
3.8.6.7 Planned Post-authorisation Development Plan	39
3.8.6.8 Studies Which Are a Condition of the Certificate of Registration	40
3.8.6.9 Summary of Changes to the RMP over Time	40
3.8.7 Annexes to the Risk Management Plan	40
3.8.7.1 Principles for Assessment of Risk Management Plans	40
3.8.7.2 Safety Specification	41
3.8.7.3 Pharmacovigilance Plan	41
3.8.7.4 Plans for Post-authorisation Studies on Efficacy	42
3.8.7.5 Risk Minimisation Measures	42
3.8.7.6 Summary of the Risk Management Plan	43
3.8.7.7 When an Update Is Being Assessed	43
3.8.7.8 Quality Systems and Record Management	43

CHAPTER 3

3.0 RISK MANAGEMENT SYSTEM

3.1 INTRODUCTION

Prior to marketing authorisation, the safety profile of a medicinal product is established primarily from clinical trial data, which are limited by relatively small, selected study populations, controlled conditions use and short durations of exposure as well as follow-up. Therefore, some adverse reactions, particularly those that are rare, delayed or occur in specific populations may only become evident after the product is used in routine clinical practice.

A medicinal product is authorised when its overall benefit–risk balance is considered favourable for the approved indication(s) and target population based on the available evidence at the time of authorisation. However, not all identified or potential risks are fully known at this stage. Additional safety information may emerge during post-authorisation use thus requiring continuous monitoring and evaluation of the medicinal benefit–risk profile.

Risk Management Plan (RMP) provides a structured approach to identifying, characterising, preventing or minimising important risks while generating additional safety information where needed. It supports the proactive management of a medicinal product's safety throughout its lifecycle and helps ensure that its benefits continue to outweigh its risks.

3.2 PURPOSE

The purpose of this guideline is to provide Marketing Authorisation Holders (MAHs) with guidance for establishing and maintaining an effective Risk Management System (RMS). It also aids with preparing and implementing a Risk Management Plan that will ensure the continuous identification, characterisation, monitoring, prevention and minimisation of risks associated with medicinal products thereby maintaining a positive benefit–risk balance throughout the product lifecycle.

3.3 SCOPE

This guideline applies to all Marketing Authorisation Holders responsible for medicinal products authorised by the National Agency for Food and Drug Administration and Control (NAFDAC). It outlines the requirements for the development, submission, implementation, evaluation and updating of the Risk Management Plans (RMPs) throughout the lifecycle of a medicinal product.

The provisions of this guideline are consistent with the NAFDAC Good Pharmacovigilance Practice (GVP) Regulations (2021) and reflect internationally recognised best practices

including the European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Module V on Risk Management Systems.

3.4 DEFINITIONS

Additional Pharmacovigilance Activities: Activities undertaken beyond routine pharmacovigilance to further investigate or better characterise specific safety concerns.

Additional Risk Minimisation Measures: Measures implemented in addition to routine risk minimisation where routine measures alone are insufficient to manage important risks.

Adverse Drug Reaction (ADR): A response to a medicinal product that is noxious and unintended and occurs at doses normally used in humans for prevention, diagnosis or treatment of disease or for restoration, correction or modification of physiological function.

Anatomical Therapeutic Chemical (ATC) Code: A unique classification code assigned to a medicinal product or active substance under the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification System which groups medicines according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Benefit–Risk Balance: An evaluation of the positive therapeutic effects of a medicinal product in relation to its risks to individual patients and public health.

Benefit–Risk Evaluation: The ongoing assessment of the benefits and risks of a medicinal product using available evidence to support regulatory decision-making.

DUS - Drug utilisation studies

Effectiveness of Risk Minimisation Measures: The extent to which implemented risk minimisation activities achieve their intended objectives in reducing the frequency or severity of safety concerns while preserving the medicinal product's benefits.

Good Pharmacovigilance Practices (GVP): A set of standards, requirements and guidance governing the conduct of pharmacovigilance activities so as to ensure the continuous monitoring, assessment, understanding and prevention of adverse effects as well as other

medicine-related problems thus maintaining a favourable benefit–risk balance throughout the lifecycle of a medicinal product.

Identified Risk: An adverse event which has adequate information/evidence of an association with the medicinal product.

Identified Risk: This could have a significant impact on the benefit–risk balance of a medicinal product or has implications for public health outcome thus requires further

characterisation, routine or additional pharmacovigilance activities or even risk minimisation measures.

International Nonproprietary Name (INN): A unique generic name assigned by the World Health Organization (WHO) to a pharmaceutical substance or active pharmaceutical ingredient for global identification and consistent use in healthcare and regulatory practice.

Marketing Authorisation Holder (MAH): The legal entity responsible for obtaining and maintaining the marketing authorisation for a medicinal product and ensuring compliance with applicable pharmacovigilance requirements.

Missing Information: Evidence relating to the safety of a medicinal product is unavailable at the time of assessment and represents gaps in knowledge within the approved indication(s), target population or conditions of use.

NAFDAC Registration Number (NRN): The unique identification number assigned by NAFDAC to a medicinal product following the granting of marketing authorisation or product registration

Periodic Safety Update Report (PSUR): A periodic report prepared by the Marketing Authorisation Holder (MAH) that provides an evaluation of the worldwide safety data for a medicinal product during a defined period so as to determine if there are any new or changed risks affecting its benefit–risk balance.

Periodic Benefit–Risk Evaluation Report (PBRER): A periodic report that provides a comprehensive evaluation of the cumulative benefit–risk balance of a medicinal product by assessing both its benefits and risks during a defined reporting period. The PBRER is prepared in accordance with ICH E2C(R2).

Periodic Safety Update Report (PSUR)/Periodic Benefit–Risk Evaluation Report (PBRER): A periodic report prepared by the Marketing Authorisation Holder which provides a comprehensive evaluation of the worldwide safety data as well as the benefit–risk balance of a medicinal product during a defined reporting period. The report is intended to identify new safety information, evaluate changes in the benefit–risk profile and determine if updates to the product information or risk management activities are required.

Pharmacovigilance Activity: An activity undertaken to detect, assess, understand and prevent adverse effects or any other medicine-related problem.

Post-Authorisation Safety Study (PASS): A study conducted after marketing authorisation to identify, characterise or quantify a safety hazard, confirm the safety profile of a medicinal product or evaluate the effectiveness of risk minimisation measures.

Potential Risk: An adverse event suspected to be associated with a medicinal product but available evidence is insufficient to confirm a causal relationship.

Product Lifecycle: The period beginning with the development of a medicinal product and continuing through marketing authorisation, post-authorisation use and eventual withdrawal or discontinuation.

Risk Management Plan (RMP): A document describing the Risk Management System for a medicinal product including the safety specification, pharmacovigilance activities and risk minimisation measures designed to identify, characterise, prevent or minimise risks while maintaining a favourable benefit–risk balance.

Risk Management System (RMS): A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks associated with a medicinal product as well as to assess the effectiveness of those interventions throughout the product lifecycle.

Risk Minimisation Measure: An intervention intended to prevent or reduce the occurrence or severity of adverse reactions associated with a medicinal product.

Routine Pharmacovigilance Activities: Pharmacovigilance activities conducted as part of standard post-marketing surveillance to monitor the safety of a medicinal product.

Routine Risk Minimisation Measures: Standard measures applied to all medicinal products including the approved product information, labelling and legal classification.

Safety Concern: An identified risk, potential risk or missing information that requires further evaluation or risk management activities.

Safety Specification: A summary of the identified risks, potential risks and missing information that forms the basis for the pharmacovigilance and risk minimisation activities described in the RMP.

Signal: Information arising from one or multiple sources suggesting a new potentially causal association or a new aspect of a known association between a medicinal product and an adverse event that warrants further investigation.

Paediatric Investigation Plan (PIP): is a development plan designed to ensure that the necessary data are obtained to support the authorization of a medicine for use in children. It describes how the medicine will be studied in the paediatric population, including the timing and measures proposed to assess its quality, safety, and efficacy in different age groups.

3.5 Risk Management Framework

The Risk Management Framework provides a structured approach for the continuous identification, assessment, management, communication and monitoring of risks associated with medicinal products throughout its lifecycle. It supports the systematic implementation of pharmacovigilance activities and risk minimisation measures to ensure that the benefit–risk balance of a medicinal product remains favourable during routine clinical use

Planning the necessary pharmacovigilance activities to characterize the safety profile of the medicinal product will be improved if it is based on specific issues identified from pre- or post-authorization data and from pharmacological principles. However, the purpose of risk identification and characterization is to allow for risk minimization or mitigation wherever possible. Therefore, risk management has three stages which are inter-related and reiterative:

- a. **Safety profile characterisation:** Characterization of the safety profile of the medicinal product including what is known and not known

- b. Pharmacovigilance planning: Planning of pharmacovigilance activities to characterize risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product
- c. Risk minimization and effectiveness evaluation planning and implementation of risk minimization, mitigation and assessment of the effectiveness of these activities.
(See Annex for Components of RMP)

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

3.6 MAH Responsibilities for Risk Management

3.6.1 In relation to the risk management of medicinal products, the MAH shall,

- a. Maintain an appropriate risk management system throughout the lifecycle of the medicinal product.
- b. Continuously monitor and critically evaluate the safety profile of the medicinal product including emerging safety information, new or changing risks and changes to the benefit-risk balance.
- c. Identify, characterise and evaluate identified and potential risks, as well as areas where important information is missing.
- d. Promptly notify NAFDAC of significant new safety information and submit updated RMP where such information results in, or may result in a significant change to the product's safety profile, risk management system or benefit-risk balance.
- e. Implement appropriate pharmacovigilance and risk minimisation activities that are proportionate to the identified risks and areas of missing information.
- f. Ensure that product information and risk communication materials remain accurate, current and consistent with the latest available safety information and promptly update and communicate such information where necessary.
- g. Evaluate the effectiveness of risk minimisation measures and submit the results to NAFDAC as required.

3.6.2 Preparation and maintenance of an RMP shall involve appropriately qualified and experienced personnel from relevant scientific and technical disciplines as appropriate to the nature and safety profile of the medicinal product. The expertise may include pharmacovigilance, clinical pharmacology, toxicology, pharmacoepidemiology, epidemiology, clinical medicine, regulatory affairs, biostatistics, risk communication and other relevant disciplines.

3.6.3 Preparation of an RMP may involve personnel from different departments within the MAH or appropriately qualified external experts or service providers. Where RMP activities

are outsourced, the MAH shall retain overall responsibility for the completeness, accuracy, scientific integrity and regulatory compliance of the RMP and associated risk management activities.

3.6.4 The RMP shall be prepared, reviewed and maintained under the oversight of appropriately qualified and trained personnel with relevant pharmacovigilance and risk management expertise. The MAH shall maintain documented evidence of the review and approval of the RMP by the designated responsible person(s).

3.6.5 The MAH shall ensure the RMP is kept current throughout the lifecycle of the medicinal product and shall submit revisions to NAFDAC when required by emerging safety information, changes in the product's benefit-risk profile, completion of important pharmacovigilance or risk minimisation activities, evaluation of the risk minimisation activities, regulatory requirements or other circumstances that may materially affect the risk management system.

3.6.6 The MAH shall ensure that all commitments and activities described in the approved RMP are implemented within the agreed timelines and that adequate records are maintained to demonstrate implementation and effectiveness to NAFDAC upon request.

3.6.7 The MAH shall ensure that risk management activities adequately address the Nigerian context, including local safety information, patterns of medicinal product use, healthcare practices, identified or potential local safety concerns, implementation of risk minimisation measures and evaluation of their effectiveness in Nigeria.

3.7. Structure of the risk management plan

The Risk Management Plan (RMP) is a live, dynamic and stand-alone document that must be updated throughout the life cycle of the medicinal product. It should be reviewed regularly and revised to reflect new safety information including updates arising from periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs) and signal management activities.

The RMP consists of seven elements:

1. Product(s) Overview which provides basic information on the medicinal product(s), therapeutic area and target population.
2. Safety Specification summarizes identified, potential and missing safety concerns.
3. Pharmacovigilance Plan describes routine and additional pharmacovigilance activities to monitor and characterize risks.
4. Plans for Post-Authorization Efficacy Studies outlines studies to further evaluate the product's effectiveness in routine clinical practice.

5. Risk Minimization Measures contain details of routine and additional measures to prevent or reduce risks including evaluation of their effectiveness.
6. Summary of the Risk Management Plan provides a concise overview of key risks, activities and measures for quick reference.
7. Annexes should contain supporting documentation, study protocols and additional data referenced in the RMP

3.7.1. Product overview

This section must provide a complete and comprehensive Product Overview including all administrative and product-specific information listed below; partial or selective submission of these elements does not fulfil the requirements of the risk-management system.

The information should include:

3.7.1.1. Administrative information on the RMP

- i. Data lock point of the current RMP
- ii. Date submitted and the version number
- iii. List of all chapters of the RMP with date and version of the RMP when the chapter was last (updated and) submitted.

3.7.1.2. Active substance information:

- i. Active substance(s) (INN or common name)
- ii. Pharmacotherapeutic group(s) (ATC code)
- iii. Name of Marketing authorization holder
- iv. Date and country of first authorization worldwide (if applicable);
- v. Date and country of first launch worldwide (if applicable);
- vi. Number of medicinal product(s) to which this RMP refers.

3.7.1.3. For each medicinal product included in the RMP:

- i. Authorization number
- ii. Trade mark/brand name(s) as well as Nigerian name (if applicable)
- iii. Brief description of the product including:
 - Chemical class
 - Summary of mode of action

- Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines)
- iv. NAFDAC Registration Number (NRN): For registered products, provide the applicable NRN & For products not yet registered, indicate **New**.
- v. Indications: Current (if applicable) - Proposed (if applicable)
- vi. Hyperlink to the product information
- vii. Dosage: Current (if applicable) - Proposed (if applicable) as well as the Dosage in Nigeria.
- viii. Pharmaceutical forms and strengths: Current (if applicable) Proposed (if applicable)
- ix. State clearly whether the product is subjected to additional monitoring.

3.8.2. Safety specification

The purpose of the Safety Specification is to provide a comprehensive synopsis of the safety profile of the medicinal product(s) including the current knowledge, identified risks, potential risks and other uncertainties relevant to the benefit–risk balance of the product(s). It should be a summary of the important identified risks, potential risks and missing information of a medicinal product. **Missing information** is defined as gaps in knowledge about a medicinal product related to safety or use in particular patient populations which could be clinically significant (see RMP Annex I). It should also address the populations potentially at risk (where the product is likely to be used i.e. both labelled and off-labelled use) and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk balance during the post-authorization period. In the RMP, the safety specification will form the basis of the pharmacovigilance plan and the risk minimization plan. The safety specification consists of eight elements:

- i. Epidemiology of the indication(s) and target population(s)
- ii. Non-clinical part of the safety specification
- iii. Clinical trial exposure
- iv. Populations not studied in clinical trials
- v. Post-authorization experience
- vi. Additional requirements for the safety specification by the Agency
- vii. Identified and potential risks
- viii. Summary of the safety concerns

The elements of the safety specification included are only a guide. Elements which might be incorporated but not limited to include:

- a) Quality aspects if relevant in relation to the safety and efficacy of the product
- b) The disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches)
- c) Innovative pharmaceutical forms or
- d) Use a medical device.

3.8.2.1 Epidemiology of the indications and target population

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality as well as relevant co-morbidity and whenever possible be stratified by age, sex, racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed where feasible (because the epidemiology of the indication(s) may vary across regions) but the emphasis should be on the epidemiology in Nigeria of the proposed indication. Information should be provided on the important co-morbidities in the target population. For example: if a medicinal product is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group not taking the medicinal product. Estimation of the risk in the target population as compared with the same age/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

The RMP should include a statement of the intended purpose and impact of the product e.g. whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease.

3.8.2.2. Non-clinical part of the safety specification

This should present a summary of the important non-clinical safety findings, for example:

- Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity)
- General pharmacology (e.g. cardiovascular including QT interval prolongation as well as nervous system)
- Drug interactions
- Other toxicity-related information or data.

What constitutes an important safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Normally significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans should be discussed. Quality aspects if relevant to safety (e.g. important information on the active substance or its impurities, e.g. genotoxic impurities) should be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population discussed. Where the non-clinical safety finding could constitute an important risk to the target population, it should be included as a safety concern. Special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

3.8.2.3. Clinical trial exposure

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format like tables/graphs. The size of the study population should be detailed using both numbers of patients and where appropriate patient time (patient-years, patient-months) exposed to the medicinal product.

This should be stratified for relevant categories and also by the type of trial (randomized blinded trial population only and all clinical trial populations.) Stratifications would normally include:

- a. Age and gender
- b. Indication
- c. Dose
- d. Racial origin

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format. The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism. These categories are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied and route of administration, number of courses/immunizations or repeat administrations may be important categories to be added.

When presenting age data, categories should be chosen which are relevant to the target population. Broad artificial divisions which are not clinically relevant, such as <65 and >65 should be avoided. Pediatric data should be divided by categories; similarly, the data on elderly patients should be considered for stratification into categories such as 65-74, 75-84 and 85+. The age strata should reflect the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

Data should not be presented by individual trials but should be pooled. Totals should be provided for each table/graph as appropriate. Where patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/sex/ethnic origin tables. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for discrepancy.

When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the chapter as well as being included in the summary tables (as described above) representing pooled data across all indications.

3.8.2.4 Populations not studied in clinical trials

Limitations of the clinical trials should be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug. Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these on the overall development programme in relation to the target population should be provided. The implications of predicting the safety of the product in the marketplace of any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database regarding the detection of adverse reactions due to:

1. Number of patients studied
2. Cumulative exposure (e.g. specific organ toxicity)
3. Long-term use (e.g. malignancy) should be discussed. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP.

Populations to be considered for discussion should include (but not limited to):

- a. Paediatric population: children (from birth to 18 years with consideration given to the different age categories or if justified, to other developmentally meaningful groups i.e. considering specific organ maturation). If paediatric development has been limited to certain age categories, then the implications for other paediatric age groups should also be discussed.
- b. Elderly population: implications for use in patients over the age of 65 should be discussed with appropriate consideration given to use in the older end of the age spectrum. The effects of

impairments e.g. renal, hepatic or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The cumulative effects of multiple impairments and multiple medications should be discussed. Consideration of whether laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. Any adverse reactions which might be of special concern in the elderly, e.g. dizziness or central nervous system effects, should be explored.

c. Pregnant or breast-feeding women: if the target population includes women of child-bearing age, the implications for pregnancy and/or breast-feeding should be discussed. If the medicinal product is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed. For products where pregnancy should be avoided for safety reasons, the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medicinal practice.

d. Patients with hepatic impairment

e. Patients with renal impairment

f. Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)

g. Patients with disease severity different from that studied in clinical trials

h. Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

i. Sub-populations with known and relevant genetic polymorphisms: The MAH should assess whether genetic differences among patients may affect the safety of the medicinal product. Where the medicinal product has been studied or is intended for use only in patients with specific genetic markers or mutations, the MAH should evaluate the safety implications of use in patients with other or unknown genetic profiles. Where the effect of a clinically relevant genetic variation has not been adequately investigated, it should be considered as missing information and/or an important potential risk as appropriate and reflected in the Safety Specification and Pharmacovigilance Plan. The need for risk minimisation measures should be based on the potential clinical impact.

j. Patients of different racial and/or ethnic origins: MAH should assess whether racial or ethnic differences can affect the efficacy or safety of the medicinal product in the target population. Available evidence including relevant pharmacokinetic and pharmacodynamic data should be considered. In situations, where such differences may have clinically significant implications, it should be reflected as appropriate in the Risk Management Plan (RMP) including as a safety concern where justified. The need for post-authorisation efficacy and/or safety studies should also be considered.

3.8.2.5 Additional Requirements for Safety Specification by the Agency

The Agency may require the MAH to provide additional information in regards to Safety Specification if necessary to adequately characterise the safety profile of a medicinal product and address safety concerns relevant to the usage in Nigeria.

The MAH shall provide additional information if the Agency identifies gaps or uncertainties in the submitted Safety Specification. Such information may include, but is not limited to:

1. Safety concerns identified from local or international post-marketing data.
2. Safety concerns relevant to the Nigerian population or specific sub-populations.
3. Important identified risks and potential risks requiring further characterisation.
4. Missing information that may affect the benefit–risk balance of the medicinal product.
5. Safety concerns associated with specific indications, age groups, pregnancy, lactation or other special populations.
6. Drug interactions or medication-use issues that may contribute to safety risks.
7. Safety concerns identified from regulatory actions, scientific literature, epidemiological studies or safety signals from other regulatory authorities.
8. Additional data or analyses required to assess the frequency, severity, seriousness, reversibility or risk factors associated with an identified safety concern.

The Agency may request the MAH to update the Safety Specification where new safety information becomes available or where the benefit–risk profile of the medicinal product changes. The MAH shall incorporate the requested information into the RMP and submit the revised RMP within the timeframe specified by the Agency. NAFDAC, may also require additional pharmacovigilance activities or risk minimisation measures where the available evidence is insufficient to adequately characterise or control a safety concern.

3.8.2.6 Additional Requirements for the Safety Specification

3.8.2.6.1 Potential for harm from overdose

If overdose occurred during clinical trials, the MAH should describe the associated safety findings. The potential risks of overdose should be assessed, if clinically relevant it should be included as a safety concern in the RMP. Appropriate risk minimisation measures should also be proposed where necessary.

3.8.2.6.2 Potential for transmission of infectious agents

The MAH should discuss the potential for the transmission of an infectious agent. This may be due to the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed explicitly.

3.8.2.6.3 Potential for misuse, abuse or use for illegal purposes

The MAH should assess the potential for the medicinal product to be intentionally misused for illegal purposes. Evidence or a reasonable potential for such misuse should be evaluated in the Safety Specification and addressed in the Risk Management Plan (RMP) as appropriate including the sale of medicinal products for recreational use, use to facilitate criminal acts or other forms of illegal misuse. The MAH should propose risk minimisation measures like product formulation, pack size restrictions or controlled distribution to reduce the risk of such misuse.

3.8.2.6.4 Potential for medication errors

For the purpose of the RMP, medication errors are unintended errors in the prescribing, dispensing, preparation or administration of a medicinal product by healthcare professionals, patients or caregivers. Medication errors may result in patient harm and should be assessed as part of the Safety Specification. They fall broadly into 4 categories:

1. Wrong medication: Administration, dispensing or prescribing of a medicinal product different from the one intended or prescribed for the patient. This may occur due to confusion between drug names, packaging or prescribing mistakes.
2. Wrong dose (including strength, form, concentration, amount): Administration of a dose that differs from the prescribed or intended dose including errors in strength, dosage form, concentration or the amount of medicine given (e.g. giving too much or too little of a medicine).
3. Wrong route of administration: Administration of a medicinal product by a route different from the one intended or authorized (e.g. giving a medicine intravenously instead of orally).
4. Wrong patient: Administration of a medicinal product to a patient for whom the medicine was not prescribed or intended.

MAH should consider routinely the likelihood of medication errors. In particular, they should assess prior to marketing the common sources of medication errors. If a product has potential for serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route. In this situation, medication errors should be included as a safety concern.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.

When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment. Consideration should be given to the prevention of accidental, ingestion or other unintended use by children.

Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design. If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated RMP and ways of limiting the errors proposed.

If the formulation or strength of a product is being changed, medication error should be included as a safety concern and the measures that the Marketing Authorization Holder will put in place to reduce confusion between old and new “product” should be discussed in the risk minimisation plan. Similarly, it may be appropriate to discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicinal product.

If the product is to be administered with a medicinal device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medicinal device malfunction).

3.8.2.6.5 Potential for off-label use

The potential for off-label use should be discussed. Off-label use relates to situations where the medicinal product is intentionally used for a medicinal purpose not in accordance with the authorised product information. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely. The MAH should consider data comparing actual use with the authorised use of the medicinal product in other markets.

3.8.2.6.6. Specific paediatric issues

The MAH shall assess safety issues that are specific to, or particularly relevant for the paediatric population, taking into consideration available clinical trial data, paediatric development programmes, post-marketing experience and the characteristics of the medicinal product. Where applicable, the assessment shall consider:

- a. important long-term paediatric safety concerns and how these are addressed through pharmacovigilance and risk minimisation activities.
- b. unresolved paediatric safety concerns arising from clinical studies or paediatric development.
- c. the justification for not conducting proposed long-term paediatric safety studies or other relevant pharmacovigilance activities.
- d. whether safety concerns identified in children are relevant to adults or other populations.
- e. the potential for use in paediatric age groups for which the product is not authorised, particularly where treatment alternatives are limited.
- f. medication errors, dosing errors, formulation-related risks and other factors that may be particularly relevant to children.

Where an important paediatric safety concern or potential for harmful paediatric off-label use is identified, the MAH shall include the concern in the Safety Specification and propose appropriate pharmacovigilance and risk minimisation measures. Similarly, the MAH shall Summarise any long-term paediatric safety or efficacy concerns identified in the PIP and describe how they are addressed in the RMP. If a concern has been resolved or is no longer considered important, provide a justification for such action.

3.8.2.6.7 Product- and Administration-Related Safety Considerations

The MAH shall consider additional risks arising from the formulation, strength, dosage form, route of administration, method of administration, packaging, delivery device or disposal of the medicinal product. If any of these factors may result in clinically important harm, the MAH shall assess whether they constitute an important identified or potential risk and where appropriate, include them in the Safety Specification and address them through suitable risk minimisation measures.

3.8.2.6.8 Consideration of the Nigerian Context

The MAH shall ensure the Safety Specification and associated risk management activities take into consideration relevant factors specific to the use of the medicinal product in Nigeria, where such factors may affect its safety profile, pattern of use, risk of medication error, adherence to authorised use, implementation of risk minimisation measures or overall benefit-risk balance.

The assessment should consider available Nigerian data and information, including;

- a. local pharmacovigilance data and reported adverse drug reactions.
- b. patterns of prescribing, dispensing and use of the medicinal product.
- c. healthcare delivery settings and prescribing or administration practices.
- d. patient, caregiver and healthcare professional factors that may influence safe use.
- e. local epidemiology and disease patterns relevant to the safety profile.

- f. availability and accessibility of healthcare services, diagnostic facilities and monitoring capacity.
- g. potential for medication errors, misuse, abuse, diversion or off-label use.
- h. availability of alternative treatments.
- i. experience with the medicinal product or similar products in Nigeria.
- j. any other local factors that may materially influence the identified or potential risks or the effectiveness of proposed risk minimisation measures.

The MAH shall provide appropriate justification where relevant Nigerian data are unavailable or where international data are considered applicable to the Nigerian context. If the assessment identifies a safety concern, important difference in the pattern of use, a limitation in the applicability of international evidence or a potential challenge to the implementation or effectiveness of risk minimisation measures in Nigeria, the MAH shall address the issue in the RMP and propose additional pharmacovigilance activities, local data generation, enhanced monitoring or risk minimisation measures. Similarly, the MAH shall update the assessment when new Nigerian safety information or other relevant local evidence becomes available.

3.8.2.7 Post-Authorisation Experience

The purpose is to provide information on the number of patients exposed post authorization. Post-authorisation exposure should be stratified by indication, dose, route, age group and region. It should also include brief information on the number of patients in completed observational studies conducted either to elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicinal product should also be provided. Action taken by regulatory authorities and/Marketing authorization holders for safety reasons include but not limited to:

- a. List any significant regulatory action (including those initiated by the MAH) taken in relation to a safety concern in any market. Significant regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning or any action to suspend or revoke a Certificate of Registration. The Agency will perform oversight monitoring of the implementation of MAH risk minimization activities.
- b. This list should be cumulative and specify the country, action taken and the date as appropriate. Rollout in multiple countries of a new safety statement initiated by the MAH can be presented as one action.
- c. When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided to the Agency, it may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations.

Where the medicinal product has been marketed, the MAH should provide cumulative data on patient exposure. The data should be presented by relevant categories such as age, sex, indication, dose and geographical region. Other relevant factors like route of administration, duration of treatment and number of vaccine doses should also be included where applicable.

When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used. Exposure data based on the number of kilograms of medicinal product sold divided by the average dose is only valid if the medicinal product is always used at one dose level for a fixed length of time, which is not the situation with most medicinal products. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used. For example, for medicinal products used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

If the medicinal product has more than one route of administration (e.g., oral or subcutaneous), exposure data should be presented separately for each route. The Agency may request additional stratification of the data such as by age group or approved indication. Where the medicinal product is used for different indications with different dosing regimens or other relevant characteristics, the MAH should, where possible, provide exposure data accordingly. A more accurate breakdown of drug exposure based on market research should be provided where possible. If a drug utilisation study has been performed, the MAH should provide a detailed breakdown of patient exposure based on market research or drug utilisation studies. Such data should reflect the use of the medicinal product in routine clinical practice and support the assessment of its safety profile.

3.8.2.7.1 Post-authorisation use in populations not studied in clinical trials

Post-authorisation data available for special populations with no or limited clinical trial exposure should be provided with an estimate of the number of patients exposed, the method used to generate the estimate and indicate whether the use was within or outside the approved indication. Information on the safety profile of the medicinal product in these special populations as compared with the rest of the target population should also be provided. In particular, any information regarding an increased or decreased benefit in a special population should be provided. Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP but reference should be made in this section as to which risks and populations are affected.

3.8.2.7.2 Post-authorisation off-label use

Post marketing updates to the safety specification should include information on off-label use. Off-label use includes use in non-authorised paediatric age categories. Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. When off-label use is a safety concern or a concern has been raised regarding off-label use, MAH should attempt to quantify such use along with a description of the methods used to arrive at these figures.

3.8.2.7.3 Epidemiological study exposure

The MAH should provide a list of all epidemiological studies conducted, sponsored, funded or otherwise available to support the evaluation of the medicinal product's safety, efficacy, drug utilisation or the effectiveness of risk minimisation measures. This includes studies conducted by the MAH, marketing partners or third parties where the results are available to the MAH. For each study, the MAH should provide the study title, study design, study population (including country, where applicable), duration, sample size, study objective and current status (completed or ongoing).

Where a study has been published, the MAH should provide the reference, include a summary in the Annex and submit the full publication in the Annexure.

3.8.2.8 IDENTIFIED AND POTENTIAL RISKS

This provides information on the important identified and potential risks associated with use of the product. These should include the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods as well as other substances and the pharmacological class effects.

3.8.2.8.1 Newly identified safety concerns.

Safety concerns (important identified and potential risks) recognised from the last submission of the RMP should be listed here and further discussed in the appropriate section. The source of the safety concern should be stated if it is an important identified or potential and if new studies or even risk minimisation activities are proposed (with further details in the appropriate RMP parts).

3.8.2.8.2 Recent study reports with implications for safety concerns

Study reports (either interim or final from whichever type of study) since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the sections of the safety specification as appropriate. Details of important identified and potential risks from clinical development and post-authorisation experience should be properly captured.

This RMP section should be concise and provide more information on the important identified and potential risks. What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here.

3.8.2.8.3 Identified and potential interactions including food-drug and drug-drug interactions.

Pharmacological class effects Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, also in relation to commonly used medications in the target population. For each, the evidence supporting the interaction and possible mechanism should be summarised and the potential health risks posed for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in the relevant sections of the “Summary of the safety concerns.”

3.8.2.8.4 Identified and potential risks (ATMP version)

Advanced therapy medicinal products (ATMPs) owing to their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products. Hence any;

- Newly identified safety concerns (ATMP)
- Recent study reports with implications for safety concerns (ATMP)
- Details of important identified and potential risks (ATMP)

Should be properly documented and explicitly explained.

3.8.2.9. Summary of Safety Concerns

A summary of all identified safety concerns should be provided at the end of the Safety Specification section of the RMP. A safety concern is:

1. An important identified risk
2. An important potential risk
3. Missing information

RMPs covering multiple products that have significant differences in the identified and potential risks for different products, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include but not limited to:

- Safety concerns related to the active substance
- Safety concerns related to a specific formulation or route of administration
- Safety concerns relating to the target population
- Risks associated with switching to non-prescription status

Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

3.8.3. Pharmacovigilance plan

The purpose of the pharmacovigilance plan is to describe how the MAH will further identify, characterise and monitor the risks outlined in the safety specification. Routine pharmacovigilance activities apply by default to all medicinal products however, additional pharmacovigilance activities should be implemented where routine activities are insufficient to adequately address specific safety concerns. Safety concerns and the corresponding pharmacovigilance activities should be clearly linked and traceable within the RMP safety concern activity grid. The Pharmacovigilance plan provides a structured plan for;

1. The identification of new safety concerns
2. Further characterisation of known safety concerns including elucidation of risk factors, increased frequency of safety concern, change in pattern of a known safety concern
3. The investigation of whether a potential safety concern is real or not
4. How missing information will be sought.
5. It does NOT include actions intended to reduce, prevent or mitigate risks

The pharmacovigilance plan should be based on the safety concerns summarised in section 3.8.2 of the safety specification. Early discussions between the Agency and the MAH are recommended to identify which additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable therefore, signal detection which is part of routine pharmacovigilance will be an important element in identifying new risks for all products.

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the MAH should list their planned pharmacovigilance activities for that concern. Pharmacovigilance plans should be proportionate to the risks of the product. If routine pharmacovigilance is considered sufficient for post authorisation safety monitoring, without the need for additional actions (e.g. safety studies) “routine pharmacovigilance” should be entered against the safety concern.

3.8.3.1. Routine pharmacovigilance activities

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for Pharmacovigilance Regulations of the Agency. The Pharmacovigilance System Master File (Chapter 2 confirm) contains details of the system and processes each MAH has in place to achieve this.

In certain situations, the Agency may make recommendations for specific activities related to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine pharmacovigilance (Chapter 1 confirm).

3.8.3.2. Specific adverse reaction follow-up questionnaires

If the MAH uses or is requested by the Agency to use specific questionnaires to collect additional information on adverse reactions of special interest, copies of the questionnaires

should be included in the Annex of the RMP. The use of such questionnaires for the follow-up of suspected adverse reactions is considered a routine pharmacovigilance activity. Where possible, MAHs are encouraged to use standardised questionnaires to promote consistency and reduce the reporting burden on healthcare professionals.

3.8.3.3. Additional pharmacovigilance activities

Additional pharmacovigilance activities may include non-clinical studies, clinical trials or non-interventional studies undertaken to further characterise or investigate a safety concern. Depending on the nature of the safety concern, its level of characterisation and the feasibility of further investigation, additional pharmacovigilance activities may or may not be required. The MAH should consider additional pharmacovigilance activities where routine pharmacovigilance is insufficient to adequately assess a safety concern. This may include situations where long-term safety data are limited, pre-clinical findings require further evaluation or the background incidence of an event in the target population makes it difficult to determine whether the medicinal product increases the risk. If there is uncertainty regarding the need for additional pharmacovigilance activities, the MAH should consult the Agency.

The objectives of additional pharmacovigilance activities should be tailored to the safety concern being addressed. Important identified and potential risks may include further characterising the risk, estimating its frequency, identifying risk factors, evaluating the effect of dose or duration of exposure or assessing causality. For missing information, the objective may be to investigate a potential risk or provide evidence to support its absence.

Studies included in the Pharmacovigilance Plan should address the safety concerns identified in the Safety Specification or evaluate the effectiveness of risk minimisation measures. The MAH should include all relevant post-authorisation safety studies initiated, managed or funded by the MAH whether conducted voluntarily or in response to a requirement from the Agency. Additional pharmacovigilance studies included in the Pharmacovigilance Plan such as pharmacoepidemiology, pharmacokinetic, clinical or non-clinical studies should be designed and conducted in accordance with applicable good scientific and regulatory practices. The MAH remains responsible for the scientific quality and validity of the study protocols including those discussed with the Agency.

3.8.3.4 Studies to measure the effectiveness of risk minimisation measures

Studies undertaken to evaluate the effectiveness of risk minimisation measures including PASS shall be described in the Pharmacovigilance Plan and cross-referenced in the Risk Minimisation Plan for the relevant safety concern(s).

3.8.3.5. Drug utilisation studies

Drug utilisation studies (DUS) can provide useful information on whether risk minimisation activities are effective and on the demographics of target populations. DUS may be requested by the Agency if information on the use, prescribing, dispensing or administration of a

medicinal product in Nigeria is needed to support risk management. Although drug utilisation studies are not primarily designed to collect adverse drug reaction data, they provide important information to support the RMP including;

- a. the characteristics and size of the treated population.
- b. prescribing, dispensing and utilisation patterns.
- c. use in populations or indications not covered by the authorised product information.
- d. adherence to recommended dosing, contraindications, warnings and other conditions of use.
- e. patterns of medication error, misuse or off-label use.
- f. the implementation and the effectiveness of risk minimisation measures.

Where a drug utilisation study is included in the RMP or requested by the Agency, the MAH shall provide a study protocol, objectives, methodology, target population, data sources, timelines and reporting arrangements for Agency review and approval. The MAH shall assess and report the findings of the study within the agreed timelines and shall evaluate whether the findings indicate a need to modify the Safety Specification, strengthen or revise risk minimisation measures, undertake additional pharmacovigilance activities or otherwise update the RMP.

Where appropriate, drug utilisation studies may be conducted using routinely available healthcare or medicines-use data, provided that the data source and methodology are adequate to address the specific risk management objective.

3.8.3.6 Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).

3.8.3.7. Action plans for safety concerns with additional pharmacovigilance requirements

For safety concerns with additional pharmacovigilance activities, the action plan for each safety concern should be presented according to the following structure;

- a. Safety concern.
- b. Proposed action(s)
- c. Individual objectives of proposed action(s) (i.e. what aspects of the safety concern they are intended to characterise) and for each action
- d. Details of individual action

e. Steps

f. Milestones (including expected dates).

3.8.3.8. Summary table of additional pharmacovigilance activities

The RMP shall include a summary table of all additional pharmacovigilance activities proposed or required for the medicinal product. The table shall clearly identify the purpose, regulatory basis, status, key milestones and expected outputs of each activity to enable NAFDAC and other relevant stakeholders to monitor its implementation. Additional pharmacovigilance activities shall be categorised as follows:

3.8.3.8.1. Activities imposed as conditions of the Marketing Authorisation: Pharmacovigilance activities required by NAFDAC as a condition of the marketing authorisation, which are subject to specific regulatory obligations and timelines.

3.8.3.8.2. Specific obligations associated with a Marketing Authorisation under exceptional circumstances: Pharmacovigilance activities required as specific obligations where a marketing authorisation has been granted under exceptional circumstances in accordance with applicable regulatory requirements. Such obligations shall be clearly identified and distinguished from other RMP activities.

3.8.3.8.3. Additional pharmacovigilance activities to investigate a safety concern or evaluate the effectiveness of risk minimisation measures: Studies or other pharmacovigilance activities required to further characterise an identified or potential risk, address an area of missing information, investigate a safety concern or evaluate the effectiveness of specific risk minimisation measures. These may include post-authorisation safety studies, drug utilisation studies, targeted clinical or epidemiological studies, registries, enhanced monitoring or other appropriate activities.

3.8.3.8.4. Other studies conducted by the MAH: Other studies or activities conducted by the MAH that may generate safety-relevant information but are not undertaken primarily to investigate an important identified or potential risk, address missing information or evaluate the effectiveness of risk minimisation measures. Where such studies generate information that may affect the benefit-risk balance or the RMP, the MAH shall assess the findings and take appropriate regulatory action. The summary table shall, as a minimum, include the following information for each additional pharmacovigilance activity:

Activity	Purpose	Objectives	Safety concern or missing information addressed	Regulatory category	Study design/methodology	

The MAH shall ensure the status of each activity is kept up to date and significant changes to the agreed activities, timelines, methodology or objectives are communicated to NAFDAC and appropriately reflected in subsequent RMP updates.

3.8.4 Plans for Post-Authorisation Efficacy Studies

The benefit-risk assessment of a medicinal product at the time of marketing authorisation is based on available clinical and other relevant evidence. Efficacy is expected to remain reasonably consistent following authorisation, additional evidence may be required where there is uncertainty regarding the maintenance, magnitude, duration or generalisability of the treatment benefit in routine clinical practice. Post-authorisation efficacy studies are not routinely required for all medicinal products. However, NAFDAC may require or the MAH may propose such studies where they are necessary to address an identified uncertainty regarding efficacy or to further evaluate the benefits of a medicinal product. Such studies may be particularly relevant where:

- a. the duration of available efficacy data is limited in relation to the expected duration of treatment.
- b. long-term maintenance of efficacy requires further evaluation.
- c. efficacy may vary substantially between different patient populations or clinical settings.
- d. there are important uncertainties regarding the generalisability of clinical trial results to routine clinical practice in Nigeria.
- e. the product is intended for a population for which clinical evidence is limited, including certain paediatric populations.
- f. the medicinal product is an advanced therapy medicinal product or another product for which long-term follow-up of therapeutic benefit is clinically relevant.
- g. new evidence raises a material uncertainty regarding the established benefit of the medicinal product.

Where a post-authorisation efficacy study is required or proposed as part of the RMP, the MAH shall describe the objective, rationale, study design, population, endpoints, data sources, timelines and expected outcomes and explain how the results will contribute to the evaluation of the product's benefit-risk balance.

3.8.4.1 Summary of Existing Efficacy Data

The RMP shall include a concise summary of the efficacy data supporting each authorised indication and relevant target population. The summary shall provide sufficient information to place the demonstrated benefits of the medicinal product in the context of the therapeutic setting and shall include:

- a. the current standard of care or relevant treatment alternatives.
- b. the place of the medicinal product within the therapeutic pathway.
- c. the key clinical studies supporting the authorised indication.
- d. the relevant study populations, treatment regimens and duration of follow-up.
- e. the principal efficacy endpoints and the key results.

- f. a concise description of the clinical relevance of the demonstrated treatment benefits.

If the RMP covers multiple indications or substantially different target populations, the efficacy information shall be presented separately where necessary to allow appropriate assessment of the benefit-risk balance.

3.8.4.2 Assessment of Uncertainties in Efficacy

The MAH shall assess whether there are uncertainties or limitations in the available efficacy evidence that may require further evaluation following marketing authorisation.

The assessment should consider:

- a. the robustness and clinical relevance of the efficacy endpoints
- b. the duration of available efficacy data in relation to the intended duration of treatment
- c. the applicability and generalisability of clinical trial findings to the authorised target population
- d. factors that may influence treatment effectiveness in routine clinical practice
- e. differences in treatment benefit across relevant sub-populations
- f. adherence, treatment persistence or other factors that may affect effectiveness
- g. the availability and representativeness of data in populations relevant to the Nigerian setting
- h. any other evidence that may introduce uncertainty regarding the magnitude or durability of the treatment benefit.

Where significant uncertainty is identified, the MAH shall justify if additional post-authorisation efficacy data are required and propose a suitable study or other data-generating activity.

3.8.4.3 Post-Authorisation Efficacy Study Plan

Where a post-authorisation efficacy study is included in the RMP, the MAH shall provide a summary of the study in the pharmacovigilance plan including:

- a. the efficacy question or uncertainty being addressed
- b. the rationale for conducting the study
- c. the study objectives and design
- d. the study population and relevant sub-populations
- e. the primary and other relevant efficacy endpoints
- f. the data sources and methodology

- g. the planned study milestones and completion date
- h. the expected outputs and reporting arrangements
- i. the manner in which the study findings will inform the benefit-risk assessment and where applicable future regulatory action.

The MAH shall communicate significant changes to the study protocol, methodology or timelines to NAFDAC and shall update the RMP as appropriate.

3.8.4.4 Evaluation of New Efficacy Information

The MAH shall continuously review new evidence that may affect the efficacy or benefit-risk balance of the medicinal product. For RMP updates, any new evidence that affects the magnitude, duration, consistency or applicability of the treatment benefit shall be summarised and its implications for the benefit-risk balance shall be evaluated. If new evidence identifies a significant uncertainty or change in the established benefit of the medicinal product, the MAH shall notify NAFDAC and propose additional post-authorisation efficacy studies or other regulatory actions.

Efficacy studies which are specific obligations and/or conditions of MAH:

Description of study	Milestone (may be several per activity)	Due date (may be several per activity)

Other efficacy and effectiveness studies

Description of study	Milestone (may be several per activity)	Due date (may be several per activity)

3.8.5. Risk minimisation measures

Based on the Safety Specification, the MAH should determine the appropriate risk minimisation measures for each safety concern. The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated

with individual safety concerns. It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Example, when multiple risk minimisation plans could be considered include:

- i. An active substance available as both prescription-only and non-prescription medicinal products.
- ii Medicinal products with significant safety risks that are used across different medical specialties may require additional educational materials tailored to the needs of the intended healthcare professionals, particularly where specialist safety knowledge cannot be assumed. For example, a medicinal product associated with a significant risk of QT prolongation may not require educational materials when used exclusively by cardiologists but may require such materials when prescribed by healthcare professionals in non-specialist settings, where awareness of QT prolongation and drug interactions may be limited.

Active substances with significant safety risks that vary across different target populations may require population-specific risk minimisation measures.

Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally authorised product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communications/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective and should be reviewed at regular intervals and their effectiveness assessed and feedback provided to the Agency.

3.8.5.1. Routine risk minimisation

Routine risk minimisation activities are those which apply to every medicinal product. These relate to:

- a) The summary of product characteristics (SmPC)
- b) The labelling
- c) The package leaflet
- d) The pack size(s)
- e) The legal status of the product

3.8.5.1.1. Summary of product characteristics (SmPC) and package leaflet (PL)

The SmPC and PL are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal

product. The design of the packaging as well as the formulation itself may play an important role in preventing medication error.

3.8.5.1.2 Pack size

Pack size is an aspect of product presentation that may contribute to the safe and appropriate use of a medicinal product and may be considered as a routine or additional risk minimisation measure where justified by the product's safety profile.

The MAH shall consider if the proposed pack size and number of dosage units may influence;

- a. the potential for overdose or accidental ingestion.
- b. prolonged use without appropriate clinical review or monitoring.
- c. accumulation or inappropriate storage of the medicinal product.
- d. access to medicines with potential for misuse, abuse or diversion
- e. the safe use of the medicinal product by patients, caregivers and healthcare professionals.

Where appropriate, limiting the number of dosage units per pack may encourage more regular clinical review, monitoring or reassessment of treatment especially for medicinal products requiring periodic laboratory or clinical monitoring.

For medicinal products associated with a significant risk of overdose, misuse, abuse, diversion and accidental ingestion or other safety concerns that may be mitigated through control of the quantity supplied, the MAH should consider whether smaller or appropriately restricted pack sizes would reduce the risk. If pack size is proposed as a risk minimisation measure, the MAH shall provide a clear scientific and public health justification for the proposed pack size and describe how its effectiveness will be monitored.

If more than one pack size is authorised or proposed, the MAH shall justify the range of pack sizes in relation to the authorised indications, dosing regimens, treatment duration and identified or potential risks.

NAFDAC may require modification or restriction of pack sizes where this is considered necessary to minimise an identified or potential risk and is proportionate to the level of risk.

3.8.5.1.3 Legal status

The legal status and conditions under which a medicinal product is supplied, prescribed, dispensed, administered or used may constitute an important risk minimisation measure where restrictions are necessary to reduce identified or potential risks associated with its use or misuse.

When a Certificate of Registration is granted, NAFDAC may specify conditions or restrictions relating to the supply, prescribing, dispensing, administration or use of a medicinal product,

where justified by the product's safety profile and in accordance with applicable regulatory requirements. Some of the conditions may include restrictions on:

- a. the availability of the whether the medicinal product on prescription or without prescription.
- b. the healthcare professional authorised to prescribe or administer the medicinal product.
- c. the healthcare setting in which the medicinal product may be prescribed, dispensed or administered like a specified healthcare facility.
- d. requirements for specialist supervision or involvement of appropriately qualified healthcare professionals
- e. conditions relating to patient monitoring, laboratory testing or clinical assessment before or during treatment
- f. other conditions necessary to ensure the safe and appropriate use of the medicinal product.

For medicinal products available only on prescription, additional restrictions may be applied if warranted by the nature and severity of the identified or potential risks. Such restrictions may include requirements for specialist prescribing, administration in specified healthcare settings or other controlled conditions of supply and use. Where the legal status or conditions of supply and use are proposed as an additional risk minimisation measure, the MAH shall provide a clear scientific and public health justification, describe how the measure will be implemented and where appropriate, propose measures to monitor its implementation and effectiveness.

The MAH shall ensure the product information, packaging, labelling and relevant risk communication materials are consistent with the approved legal status and conditions of supply and use. If available evidence indicates that the existing legal status or conditions of supply and use are insufficient to adequately manage an identified or potential risk, NAFDAC may require additional or modified restrictions, proportionate to the level of risk and taking into account the availability of alternative risk minimisation measures.

3.8.5.1.4 Restricted medical prescription

A medicinal product may be subjected to restricted medical prescription so there is control over who may initiate or prescribe treatment, the healthcare setting in which the product is supplied or administered or the level of specialist supervision required is necessary to minimise identified or potential risks. To determine if a medicinal product should be subjected to restricted medical prescription, the following factors should be considered;

1. Hospital or specialised treatment: The medicinal product has pharmaceutical or clinical characteristics or presents safety or public health considerations that require treatment to be initiated and/or administered in a hospital or other appropriately equipped healthcare facility.
2. Specialised diagnosis: The medicinal product is intended for the treatment of conditions that require diagnosis in a hospital or healthcare institution with adequate diagnostic facilities, even where subsequent administration or follow-up may be undertaken in another appropriate setting.
3. Serious adverse reactions requiring specialist supervision: The medicinal product is intended for outpatient treatment but may cause serious or potentially life-threatening adverse reactions, such treatment should be initiated or prescribed by an appropriately qualified specialist and require specific clinical supervision or monitoring during treatment.

Where restricted medical prescription is identified as a risk minimisation measure, the MAH shall describe in the RMP:

- a. the safety concern(s) necessitating the restriction.
- b. the proposed conditions of prescribing, dispensing, administration or monitoring.
- c. the healthcare professionals and/or healthcare settings to which the restriction applies.
- d. the measures required to support implementation of the restriction
- e. the measures for monitoring and evaluating the implementation and effectiveness of the restriction.

The level of restriction should be proportionate to the identified or potential risk and should be reviewed when new safety information becomes available.

3.8.5.1.5. Special medical prescription

A medicinal product may be subject to special medical prescription where its characteristics, composition or potential for abuse, dependence, misuse or diversion require additional controls over its prescribing, supply, dispensing or use. To determine whether a medicinal product should be subject to special medical prescription, the following factors should be considered:

1. **Narcotic or psychotropic substances:** The medicinal product contains a quantity not otherwise exempted under applicable legislation, a substance classified as a narcotic or psychotropic substance under applicable national requirements.
2. **Potential for abuse, dependence or illegal use:** The medicinal product, if incorrectly or inappropriately used, may present a substantial risk of abuse, dependence, addiction, diversion or misuse for illegal purposes.
3. **Precautionary classification:** The medicinal product contains a substance which, because of its novel properties, pharmacological characteristics or emerging safety information, may warrant special medical prescription as a precautionary measure due to a potential for abuse, dependence, misuse or diversion.

Where special medical prescription is considered necessary as part of risk management, the MAH shall provide appropriate justification and describe the relevant conditions for prescribing, dispensing, supply, administration as well as monitoring of use. Likewise, the MAH shall also consider if additional risk minimisation measures are necessary to support the safe use of the medicinal product. These measures may include controlled distribution, prescriber or dispenser education, patient information, treatment agreements, prescription controls, monitoring of use or other measures proportionate to the identified or potential risk.

The need for special medical prescription and associated risk minimisation measures should be reviewed when significant new safety information becomes available or when there is a change in the benefit-risk profile or pattern of use of the medicinal product. It is important to note where routine risk minimisation measures are insufficient to adequately manage an identified or potential risk, additional risk minimisation measures may be required.”

3.8.5.2 Additional risk minimisation activities

Additional risk minimisation measures (aRMMs) are risk minimisation measures that are required beyond routine risk minimisation activities to address specific identified or potential risks or important missing information associated with a medicinal product. aRMMs should be proposed if routine risk minimisation measures are insufficient to adequately manage the relevant safety concern and where the additional measures are considered necessary to support the safe and effective use of the medicinal product. The measures must be proportionate to the risk, evidence-based, feasible and capable of being implemented and evaluated within the Nigerian healthcare setting. Where aRMM is proposed, the MAH shall:

- a. clearly identify the safety concern or missing information that necessitates the measure.
- b. provide a clear scientific and public health justification for the proposed measure.
- c. describe the objectives, target population, intended users and implementation arrangements in sufficient detail.
- d. ensure that the measure is developed, reviewed and implemented by appropriately qualified personnel.
- e. describe how implementation and where appropriate, effectiveness will be monitored and evaluated.
- f. specify the criteria and circumstances under which the measure may be modified, strengthened or discontinued.

3.8.5.2.1 Risk Minimisation Communication Materials

aRMMs involve communication materials intended to reinforce or clarify information contained in the approved Summary of Product Characteristics (SmPC), package leaflet or other approved product information. Hence, Risk minimisation communication materials should;

- a. be clearly focused on the specific risk minimisation objective and provide accurate, clear as well as consistent safety information.
- c. be targeted to the relevant healthcare professionals, patients, caregivers or other intended recipients.
- d. be consistent with the approved product information and other regulatory requirements.
- e. be clearly distinguishable from promotional or marketing materials.

Risk minimisation communication materials must not contain promotional claims or content that could encourage inappropriate prescribing, dispensing or use of the medicinal product.

3.8.5.2.2 Engagement with NAFDAC

The MAH should engage with NAFDAC as early as practicable where aRMMs are likely to be required especially if their implementation may need to be adapted to the Nigerian healthcare system, regulatory framework, healthcare delivery arrangements or available monitoring infrastructure. The MAH should discuss with NAFDAC:

- a. the proposed risk minimisation objectives and target population
- b. the suitability and feasibility of the proposed intervention within Nigeria
- c. the content and format of educational or communication materials
- d. implementation arrangements and responsibilities
- e. the proposed approach for monitoring implementation and evaluating effectiveness.

Early engagement does not replace the formal regulatory review and approval processes applicable to the RMP or associated risk minimisation materials.

3.8.5.2.3 Engagement with Healthcare Professionals and Patients

If aRMMs are directed towards healthcare professionals, patients or caregivers, the MAH should where feasible and appropriate seek input from relevant stakeholders during the development of the measures. This engagement may help ensure that the proposed materials and interventions are understandable, relevant, practical and appropriate for the intended users and healthcare setting. Stakeholder input should be appropriately documented and the MAH should consider and address relevant feedback when finalising the proposed aRMMs.

3.8.5.3. Educational material

Educational material should be non-promotional. It is recommended that communication experts, patients and healthcare professionals are consulted on the design and wording of educational material and that it is piloted before release for use.

The final version of the educational material will need to be approved by the Agency who will check and ensure that the material contains the key elements in an appropriate design and format and is not promotional.

For public health reasons, where multiple MAHs have medicinal products containing the same active substance, the Agency may require educational materials to have, as far as practicable, a similar layout, content, colour scheme and format to minimise the risk of patient confusion. This requirement may also apply to other patient-facing materials like patient alert cards and patient monitoring cards. Accordingly, MAHs are strongly encouraged to avoid the use of company logos, trademarks or other proprietary or patented elements in educational materials where these may hinder standardisation or create confusion among patients and healthcare professionals.

3.8.5.4. Format of risk minimisation plan(s)

Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed, then “none proposed” should be entered against the objective. For each safety concern, the following information should be provided:

1. Objectives of the risk minimisation activities
2. Routine risk minimisation activities
3. Additional risk minimisation activities (if any), individual objectives and justification of why it is needed
4. How the effectiveness of each (or all) risk minimisation activities will be evaluated in terms of attainment of their stated objectives.
5. What the target is for risk minimisation, i.e. the criteria for judging achievement
6. Milestones for evaluation and reporting.

For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC) should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

3.8.5.5. Evaluation of the Effectiveness of Risk Minimisation Activities

The effectiveness of RMMs should be evaluated throughout the lifecycle of a medicinal product to determine if the intended objectives are being achieved, whether the burden of adverse reactions is being reduced and if the overall benefit-risk balance remains favourable.

The evaluation should be proportionate to the identified safety concern and the nature of the risk minimisation measure. Where applicable, the MAH should use appropriate process, intermediate and outcome indicators supported by relevant data sources to assess the effectiveness of the measures.

a) Process indicators: These assess whether the risk minimisation measure has been implemented as planned. Examples include the distribution and availability of educational materials, number and proportion of targeted healthcare professionals reached or trained and implementation of required monitoring or prescribing procedures.

b) Intermediate indicators: These assess changes in knowledge, awareness, understanding, behaviour among the target population including healthcare professionals and patients. Examples include healthcare professional knowledge of the identified risk, adherence to recommended monitoring requirements, appropriate prescribing or dispensing practices and patient understanding of relevant precautions.

c) Outcome indicators: These assess if the identified risk has been reduced following implementation of the risk minimisation measures. Examples include changes in the

incidence, frequency, severity or reporting rate of the relevant adverse reactions or other safety outcomes.

The MAH should define the objectives, indicators, targets, data sources, methods of assessment and frequency of evaluation for each additional risk minimisation activity. The methodology should be scientifically justified and sufficiently sensitive to detect meaningful changes in the effectiveness of the measure. Likewise, if the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities. Results of studies, surveys, audits, utilisation studies or other formal assessments conducted to evaluate the effectiveness of risk minimisation activities should be submitted to the Agency when available.

The MAH should critically assess the results and provide an explanation of factors that may have contributed to the success, partial effectiveness or failure of the risk minimisation activities. Where the available evidence indicates that a risk minimisation strategy is ineffective, insufficient or imposes an excessive or undue burden on patients, healthcare professionals or the healthcare system, the MAH should propose appropriate corrective or alternative measures. Any important identified or potential safety concern for which risk minimisation is required, the MAH should state if the existing measures remain adequate and whether additional, modified or alternative risk minimisation activities are necessary.

If risk minimisation measures are demonstrated to be insufficient to adequately control a safety concern and maintain a favourable benefit-risk balance, the Agency may require further regulatory action. Such action may include strengthening or modifying risk minimisation measures, restricting the use of the medicinal product to appropriately selected patients or healthcare settings, suspending or revoking the marketing authorisation or even withdrawal of the product from the Nigerian market.

3.8.5.6. Gap analysis

If the safety data for a specific product is obtained from a different region, the MAH should include a gap analysis (population, practice, genetics, comorbidity, co-medication) of the safety specifications, pharmacovigilance plan and risk minimization activities in the risk management plan. The gap analysis should discuss the differences between RMP developed for Nigeria and that of the other region, highlighting and justifying any gaps or missing information. Where appropriate, the evaluation should take into account the Nigerian healthcare context and any factors that may influence the implementation or effectiveness of the risk minimisation activities. These may include availability and accessibility of healthcare services, prescribing and dispensing practices, healthcare professional coverage, patient access and understanding of educational materials, availability of required laboratory or monitoring facilities and other relevant healthcare-system factors. MAHs should provide data that demonstrate the implementation and effectiveness of the measures within Nigeria.

3.8.5.7. Summary of risk minimisation measures

A table summarising the routine and additional risk minimisation activities of safety concern should be provided.

3.8.6. Summary of activities in the risk management plan by medicinal product

A summary of the RMP for each medicinal product should be made publicly available. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. In regards to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information. It is difficult for one summary to satisfy the needs of all stakeholders and there may be a need for a summary of the RMP to be provided for different stakeholders in varying formats. The summary of the RMP will be evaluated during the assessment of the RMP.

3.8.6.1. Format and content of the summary of the RMP

This is a scientific summary written for unprofessional reader to fulfil the requirements in the regulation. In situations where the RMP covers more than one product, a separate section should be prepared for each product. To present a balanced picture, the risks discussed in the RMP should be put into context with a very concise and focussed description of the benefits of the medicinal product. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

The summary of the sections, should contain the following information:

- a. Overview of disease epidemiology
- b. Summary of treatment benefits
- c. Unknowns relating to treatment benefits
- d. Summary of safety concerns:
 - i. Important identified risks
 - ii. Important potential risks
 - iii. Missing information: Summary of risk minimisation activities by safety concern
 - iv. Planned post authorisation development plan;
 - v. Studies which are a condition of the Certificate of Registration
 - vi. Major Changes to the Risk Management Plan over time.

The summaries in the Risk Management Plan (RMP) need to be concise, targeted and aligned with the word limits set in the official templates.

3.8.6.2. Overview of disease epidemiology

The Marketing Authorization Holder should summarize the epidemiology of the disease/condition the medicinal product is intended to treat or prevent in a non-alarmist manner and in language appropriate to the target population. If the product is used in a range of disease severity, this fact should be emphasized and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy.

If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5 year survival) figures relate to historical treatment. If the product is a diagnostic, product used for anaesthesia or similar usage not associated with a particular disease/condition then this section of the overview may be omitted.

3.8.6.3. Summary of treatment benefits

This should consist of very concise and factual high level key messages concerning the results of the pivotal trials and any important supplementary evidence and should adhere to the word limits in the template.

3.8.6.4. Unknowns relating to treatment benefits

This should discuss the applicability of efficacy to all patients in the target population. It should describe very briefly any relevant parts of the target population where experience is limited and whether efficacy is expected to be different in these people, e.g. factors such as age, sex, and race

3.8.6.5. Summary of safety concerns

3.8.6.5.1 Important Identified Risk: This section should briefly describe the safety concerns in suitable language for the general public. It should include the frequency and severity of the safety concern for the important identified risks and their preventability.

Risk	What is known	preventability
Risk1		
Risk 2		

3.8.6.5.2 Identified Potential Risk: For important potential risks the reasons why it is assumed to be a Potential Risk (e.g. toxicology in animal study, known effect in other members of the pharmaceutical class) should be explained together with the uncertainties, e.g. “occurs in other medicinal products in the same class but was not seen in the clinical trials for this medicinal product which was studied and the number of people that were involved in the study”.

Risk	What is not Known (unknown)	Proactive Measure
Risk 1		
Risk 2		

3.8.6.5.3 Missing Information: it should be stated using the above format as well that there is no, or insufficient information regarding the safety concern, the possible relevance to the target population should be highlighted as well as the associated recommendations e.g. contraindication, Pregnant women, use with caution e.t.c

3.8.6.6. Summary of risk minimization activities by safety concern

Details of routine risk minimization measures should be provided in the published summary by a link to the product information. For each safety concern which has additional risk minimization measures, brief details of the measures for that concern should be provided. The objective and rationale for each measure should be stated along with the proposed actions

3.8.6.7. Planned post-authorization development plan

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and any further investigation of safety concerns. This table would combine the data from different sections. Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

List of studies in post authorisation development plan

Study	Objectives	Safety concern /efficacy issue addressed	Status	Planned date for submission of interim and final results
Study 1				
Study 2				

3.8.6.8. Studies which are a condition of the Certificate of Registration

Statement on which studies in the above table are conditions of the MA e.g. “None of the above studies is a condition of the Certificate of Registration.”

3.8.6.9. Summary of changes to the risk management plan over time

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date and version number of the RMP when new safety concerns were added or existing ones removed or changed, dates and version of the RMP when new studies were added or finished and a brief summary of changes to risk minimization activities and the associated dates these changes were agreed. Since changes to risk minimization activities involve a variation, the date used for changes to risk minimization activities should be agreed with the Agency. The date for safety concerns and studies should be the date of the RMP in which they are first added.

3.8.7. Annexes to the risk management

The RMP should contain the annexes listed below. RMP annexes should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing an issue in the RMP, it should be included in RMP with a cross reference in RMP annex.

- a. RMP annex 1: Interface between RMP and National Data Base (electronic only)
- b. RMP annex 2: Current (or proposed if product is not authorized) summary of product characteristics (SmPC) and package leaflet.
- c. RMP annex 3: Worldwide Certificate of Registration status by country. This should include:
 - i. Current licence status (approved/refused/under review/Suspended/expired/withdrawn)
 - ii. Date(s) of approval/refusal/suspension/expiration/withdrawal
 - iii. Date(s) marketed/withdrawn from market
 - iv. Trade name(s)
 - v. Any explanatory comments.
- d. RMP annex 4: Synopsis of on-going and completed clinical trial programme.
- e. RMP annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme.
- f. RMP annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section
- g. Summary table of additional pharmacovigilance activities” in sections 3.80 to 3.98.
- h. RMP annex 7: Specific adverse event follow-up forms.

- i. RMP annex 8: Protocols for proposed and on-going studies in sections 3.99 to 3.101.
- j. RMP annex 9: Synopsis of newly available study reports for section 3.80 to 3.101
- k. RMP annex 10: Details of proposed additional risk minimization activities (if applicable).
- l. RMP annex 11: Mock up examples in English of the material provided to healthcare professionals and patients
- m. professionals and patients
- n. RMP annex 12: Other supporting data (including referenced material).

3.8.7.1. Principles for assessment of risk management plans

The principle points which need to be considered when preparing or reviewing a risk management plan for a medicinal product are.

3.8.7.2. Safety specification

- a. Have all appropriate parts of the safety specification been included?
- b. Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification?
- c. If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
- d. What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicinal product?
- e. Are there specific risks in addition to those addressed under ICH-E2E, e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error, etc.?
- f. Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?
- g. If a generic or hybrid application, have all safety concerns from the reference medicinal product been included in the safety specification?
- h. Does its place in the therapeutic armamentarium as described concur with the intended indication and current medicinal practice?

3.8.7.3. Pharmacovigilance plan

- i. Are all safety concerns from the safety specification covered in the pharmacovigilance plan?

- j. Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
- k. Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?
- l. Are the safety studies which have been imposed by the Agency as conditions clearly identified?
- m. If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
- n. Are the proposed additional studies necessary and/or useful?
- o. When draft protocols are provided, are the proposed studies in
- p. Are the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
- q. Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

3.8.7.4. Plans for post-authorisation studies on efficacy

- 1. Does the description of the efficacy of the product and what studies and endpoints it was based on conform with the contents of the dossier?
- 2. Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product?

3.8.7.5. Risk minimisation measures

- t. Does the product information adequately reflect all important identified risks and missing information?
- u. Are any potential risks sufficiently relevant to the safe and effective use of the product that information about them should be included in the product information?
- u. Is the proposed wording about the risks and location in the product information appropriate and in line with relevant guidelines?
- v. Has the Marketing Authorization Holder considered ways to reduce medication errors?
- w. Has this been translated into appropriate product information (including device design where appropriate) and pack design?
- x. Are proposed risk minimization activities appropriate and adequate?
- y. Have additional risk minimization activities been suggested and if so, are they risk proportionate and adequately justified?

- z. Are the methodologies for measuring and assessing the effectiveness of risk minimization activities well described and appropriate?
- aa. Have criteria for evaluating the success of additional risk minimization activities been defined a priori?

3.8.7.6. Summary of the Risk Management Plan

- bb. Is it a true representation of the RMP?
- cc. the facts been presented appropriately
- dd. Are the content, format and language suitable for the intended audience?
- ee. Have all required formats been provided?

3.8.7.7. When an update is being assessed

- ff. Has new data been incorporated into the safety specification?
- gg. Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?
- hh. Is there an evaluation of the effectiveness of risk minimisation measures?
- ii. Have appropriate changes to risk minimisation measures been proposed if necessary?
- jj. Does the new data suggest that a formal evaluation of the benefit-risk balance (if not already done in a PSUR/PBRER) is needed?

3.8.7.8. Quality systems and record management

Several qualified experts may contribute to the preparation of the Risk Management Plan (RMP), the Marketing Authorisation Holder retains the ultimate responsibility for the quality, accuracy, completeness and scientific integrity of the RMP. The Qualified Person responsible for Pharmacovigilance in Nigeria (QPPV) should be fully aware of the content of the RMP and have sufficient authority and oversight to ensure that it accurately reflects the safety profile of the medicinal product and the pharmacovigilance and risk minimisation activities being implemented in Nigeria.

The Marketing Authorisation Holder (MAH) is responsible for ensuring that the RMP is kept up to date whenever new safety information or other relevant information becomes available. The MAH should apply the quality principles set out throughout the preparation, implementation, review and maintenance of the RMP.

The MAH should maintain appropriate records of all RMP submissions to the Agency including the dates of submission and a clear description of significant changes made between successive versions. The submitted RMPs, supporting documentation, and records relating to the information contained in the RMP should be retained and made available to the Agency upon request and may be subject to regulatory inspection or audit.

Effective Date: 16-07-2026
Review Date: 15-07-2031

Doc. Ref. No: PV-GDL-003-02