



NAFDAC GOOD PHARMACOVIGILANCE PRACTICE GUIDELINES 2016

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ACRONYMNS

ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced Therapy Medicinal Products
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CIOMS	Council for International Organizations of Medical Sciences
DFID	UK Department for International Development
DHPC	Direct Healthcare Professional Communication
GVP	Good Pharmacovigilance Practices
IBD	International Birth Date
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
ISO	International Standards Organization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NAFDAC	National Agency for Food and Drug Administration and Control
NPC	National Pharmacovigilance Centre
PASS	Post-Authorisation Safety Studies
PATHS 2	Partnership for Transforming Health Systems
PBRER	Periodic Benefit -Risk Evaluation Report
PL	Package Leaflet
PSMF	Pharmacovigilance Systems Master File
PSUR	Periodic Safety Update Reports
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
WHO	World Health Organization

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INTRODUCTION

The World Health Organization has defined pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The ultimate goal of pharmacovigilance is to improve the safe and rational use of medicines, thereby improving patient care and public health.

The National Agency for Food and Drug Administration and Control (NAFDAC) ACT Cap N1, LFN 2004 empowers the Agency to control and regulate the manufacture, importation, exportation, distribution, advertisement, sale and use of its regulated products. This mandate requires the Agency to ensure the quality, safety and efficacy of all regulated products.

The Agency therefore has developed NAFDAC Good Pharmacovigilance Practice Regulations to ensure safety of medicinal products that it regulates. The NAFDAC GVP regulations describes the obligations of the Marketing Authorization Holder to set up a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions of products it puts into the Nigerian market. The ultimate goal is to ensure that medicinal products put into the Nigerian market are safe and effective, and continue to provide a satisfactory balance between their benefits and risks. The obligations concerned with the monitoring of adverse reactions occurring in clinical trials do not fall within the scope of pharmacovigilance activities, as described in these guidelines. The relevant obligations in safety reporting for clinical trials are as prescribed in NAFDAC Good Clinical Practice Regulations.

These guidelines are intended to help all stakeholders comply with the provisions of the GVP regulations. They provide detailed guidance for marketing authorization holders on establishing and maintaining a pharmacovigilance system including its quality management, pharmacovigilance system master file, adverse reaction reporting, risk management, post authorization safety studies, risk communication and pharmacovigilance audit.

These guidelines have been adapted mainly from the European Medicines Agency's guidelines for Good Pharmacovigilance Practices (GVP), which currently provide the most comprehensive description of best practices in safety monitoring and reporting for marketing authorization holders.

This document is to be used in conjunction with other existing relevant medicinal product statutes in the country. The good practices outlined below are to be considered general guides, and they may be adapted to meet individual needs as long as the

marketing authorisation holder achieves compliance with regulatory objectives. All stakeholders are encouraged to send their comments to the Agency during the use of these guidelines in order to improve future editions.

Scope

These guidelines apply to all entities that have authorisation to put medicinal products into the Nigerian market. The marketing authorisation holders include but are not limited to NAFDAC license holders, individuals, public and private institutions, manufacturers, importers and donors of medicinal products.

These guidelines apply to products whose authorisation to market or distribute include requirements for active safety monitoring. The products include but are not limited to:

- a. Products developed wholly or to a greater extent in other regions.
- b. Products with less than ten (10) years post marketing experience elsewhere or five (5) years in Nigeria
- c. Advanced therapeutic products such as tissue, cell or gene based products
- d. Products that are subject to risk management plan in any other country
- e. Orphan medicinal products
- f. Products that received accelerated or conditional marketing approval in any country
- g. Products for use solely in special populations such as children and the elderly
- h. Products that act via the immune system such as cytokines and monoclonal antibodies
- i. CNS therapeutic products such as medicines for epilepsy, neurodegenerative diseases, antipsychotics, antidepressants
- j. Any other product based on benefit risk assessment of the Agency

The Agency may also require a marketing authorisation holder to adhere to these guidelines where the Agency identifies safety concerns in the course of post marketing surveillance. This does not discharge the marketing authorisation holder of the responsibility of monitoring the safety of all its medicinal products through the established pharmacovigilance systems required by the Agency.

CHAPTER

1 PHARMACOVIGILANCE SYSTEM

- 1.1. A pharmacovigilance system is defined as a quality system used by the marketing authorisation holder to fulfil its regulatory responsibilities in relation to pharmacovigilance. It is designed to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance.
- 1.2. A pharmacovigilance system is characterised by its structures, processes and outcomes. It covers organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.

Quality objectives

- 1.3. The overall quality objectives of a pharmacovigilance system are:
- Complying with the legal requirements for pharmacovigilance tasks and responsibilities;
 - Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation such as off label use, misuse, abuse or medication errors which result in ADR or from occupational exposure;
 - Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
 - Contributing to the protection of patients and public health.

General Principles

- 1.4. With the aim of fulfilling the overall quality objectives, the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:
- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.
 - Top management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.

- c. All persons within the organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- d. All persons involved with the entire organisation should engage in continuous quality improvement.
- e. Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- f. All available evidence on the benefit-risk balance of medicinal products should be sought and all relevant aspects, which could impact on the benefit-risk balance and the use of a product, should be considered for decision-making.
- g. Good cooperation should be fostered between marketing authorisation holders, the Agency, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

Personnel

- 1.5. A sufficient number of competent and appropriately qualified and trained personnel should be available for the performance of pharmacovigilance activities. Their responsibilities should include adherence to the principles defined in section 1.6.
- 1.6. Managerial staff should be responsible for:
 - a. Ensuring that the organisation documents the quality system as described in sections 1.29 to 1.34.
 - b. Ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
 - c. Ensuring that adequate resources are available and that training is provided (see sections 1.9 to 1.16);
 - d. Ensuring that suitable and sufficient premises, facilities and equipment are available (see section 1.16 to 1.20);
 - e. Ensuring adequate compliance management (see section 1.21);
 - f. Ensuring adequate record management (see sections 1.22 to 1.28);
 - g. Reviewing the pharmacovigilance system including its quality system at regular intervals in a risk-based manner to

- verify its effectiveness (see sections 1.37 to 1.45) and introducing corrective and preventive measures where necessary;
- h. Ensuring that mechanisms exist for timely and effective communication of safety concerns relating to medicinal products within the organisation;
 - i. Identifying and investigating concerns arising within the organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective and preventive action as necessary;
 - j. Ensuring that audits are performed (see section 1.37 to 1.45)
- 1.7. In relation to the management responsibilities described above, top management within the organisation should provide leadership through:
- a. Motivating all staff members' based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members contributions within the organization;
 - b. Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

Training of personnel for pharmacovigilance

- 1.8. Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel.
- 1.9. All personnel involved in the performance of pharmacovigilance activities should receive initial and continued training. This training should relate to the roles and responsibilities of the personnel.
- 1.10. The organisation should keep training plans and records for documenting, maintaining and developing the competences of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.
- 1.11. The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive

- and be able to seek information about what to do if they become aware of a safety concern.
- 1.12. There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities. The system should also be able to identify unmet training needs, in line with professional development plans agreed for the organisation as well as the individual staff members.
 - 1.13. Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.
 - 1.14. Appropriate instructions on the processes to be used in case of urgency, including business continuity (see sections 1.35 to 1.36), should be provided by the organisation to their personnel.

Facilities and equipment for pharmacovigilance

- 1.15. Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes.
- 1.16. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space.
- 1.17. Facilities and equipment should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see section 1.4) and also be available for business continuity (see section 1.35 to 1.36).
- 1.18. Facilities and equipment which are critical for the conduct of pharmacovigilance (see sections 1.35 to 1.36) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.
- 1.19. There should be processes in place to keep awareness of the valid terminologies (see section 5.90) in their valid versions and to keep the IT systems up-to-date accordingly.

Specific quality system procedures and processes *Compliance management by marketing authorisation holders*

- 1.20. For the purpose of compliance management, marketing authorisation holders should have specific quality system procedures and processes in place in order to ensure the following:
- a. The continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder;
 - b. The scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorisation or associated with occupational exposure [see Chapters 5, 6 & 7];
 - c. The submission of accurate and verifiable data on serious and non-serious adverse reactions to the Agency within the legally required time-limits (see Chapter 5);
 - d. The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals (see Chapters 3, 5, 6 & 7);
 - e. Effective communication by the marketing authorisation holder with the Agency, including:
 - i. Communication on new or changed risks (see Chapter 4),
 - ii. The pharmacovigilance system master file (see Chapter 2),
 - iii. Risk management systems (see Chapter 3),
 - iv. Risk minimisation measures (see Chapter 3),
 - v. Periodic safety update reports (see Chapter 6),
 - vi. Corrective and preventive actions (see Chapter 2 & 8) and
 - vii. Post-authorisation safety studies (see Chapter 7);
 - f. The update of product information by the marketing authorisation holder in the light of scientific knowledge;
 - g. Appropriate communication of relevant safety information to healthcare professionals and patients (see Chapter 4).

Record management

- 1.21. The organisation should record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information.
- 1.22. A record management system should be put in place for all documents

used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

- 1.23. The record management system should support:
 - a. The management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
 - b. Timely access to all records;
 - c. Effective internal and external communication; and
 - d. The retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.
- 1.24. Marketing authorisation holders should establish mechanisms enabling the traceability and follow-up of adverse reaction reports. In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions.
- 1.25. As part of a record management system, specific measures should be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.
- 1.26. There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.
- 1.27. The record management system should be described in a record management policy.

Documentation of the quality system

- 1.28. All elements, requirements and provisions adopted for the quality system should be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.
- 1.29. A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them.
- 1.30. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction

- or quality manual.
- 1.31. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two.
 - 1.32. A quality record is a document stating results achieved or providing evidence of activities performed.
 - 1.33. In order to have a systematic approach, the organisation should define in advance:
 - a. Quality objectives specific to the organization in accordance with the overall quality objectives and the structure-and process-specific quality objectives; and
 - b. Methods for monitoring the effectiveness of the pharmacovigilance system (see sections 1.37 to 1.45).
 - c. The documentation of the quality system should include:
 - I. Documents on organisational structures and assignments of tasks to personnel;
 - ii. Training plans and records which should be kept and made available for audit and inspection (see sections 1.9 to 1.15);
 - iii. Instructions for the compliance management processes (see section 1.21);
 - iv. Appropriate instructions on the processes to be used in case of urgency, including business continuity (see sections 1.35 to 1.36);
 - v. Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;
 - vi. Reports of quality audits and follow-up audits, including their dates and results.
 - vii. The methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
 - viii. A record management policy;
 - ix. Records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
 - x. Records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
 - xi. Records to demonstrate that deficiencies and deviations from the established quality system are monitored, that

corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

Additional quality system documentation

- d. In addition to the quality system documentation in accordance with sections 1.29 to 1.34., marketing authorisation holders should document:
 - i. The human resource management in the pharmacovigilance system master file (PSMF) (see Chapter 2);
 - ii. Job descriptions defining the duties of the managerial and supervisory staff;
 - iii. An organisational chart defining the hierarchical relationships of managerial and supervisory staff;
 - iv. Instructions on critical processes (see sections 1.29 to 1.34) in the pharmacovigilance system master file (PSMF) (see Chapter 2); and
 - v. The record management system in the pharmacovigilance system master file (PSMF) (see Chapter 2).
 - vi. Organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

Critical pharmacovigilance processes and business continuity

- 1.34. The following pharmacovigilance processes should be considered as critical:
 - a. Continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
 - b. Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;
 - c. Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely transmission of individual case safety reports (ICSRs) from any source;
 - d. Signal management;
 - e. Scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
 - f. Meeting commitments and responding to requests from the

- Agency, including provision of correct and complete information;
- g. Interaction between the pharmacovigilance and product quality defect systems;
 - h. Communication about safety concerns between marketing authorisation holders and the Agency, in particular notifying changes to the risk-benefit ratio of medicinal products;
 - i. Communicating information to patients and healthcare professionals about changes to benefit-risk balance of products for the aim of safe and effective use of medicinal products;
 - j. Keeping product information up-to-date with the current scientific knowledge, including conclusions of assessment and recommendations from the Agency;
 - k. Implementation of variations to marketing authorisations for safety reasons according to the urgency required.
- 1.35. Business continuity plans should be established in a risk-based manner and should include:
- a. Provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
 - b. Back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and the Agency.

Monitoring the pharmacovigilance system and its quality system

- 1.36. Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:
- a. Reviews of the systems by those responsible for management
 - b. Audits
 - c. Compliance monitoring
 - d. Inspections
 - e. Evaluating the effectiveness of actions taken with medicinal products for the purpose of minimizing risks and supporting their safe and effective use in patients
- 1.37. The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities in relation to the quality requirements. The quality requirements for each

- pharmacovigilance process are provided in each chapter of GVP as appropriate.
- 1.38. The adequacy of the requirements for the quality system should be monitored by managerial staff, who should review the documentation of the quality system at regular intervals, with the frequency and the extent of the reviews to be determined in line with the provisions of these guidelines in a risk-based manner. Pre-defined programmes for the review of the system should therefore be in place.
 - 1.39. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.
 - 1.40. Risk-based audits of the quality system should be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness.
 - 1.41. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in Chapter 8.
 - 1.42. In relation to the pharmacovigilance system of a marketing authorisation holder, a report should be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited.
 - 1.43. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder's pharmacovigilance system.
 - 1.44. As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, should be taken where necessary

Preparedness planning in public health emergencies

- 1.45. Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

Responsibilities of the MAH in relation to the QPPV

- 1.46. As part of the pharmacovigilance system, the marketing authorisation holder should have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance (QPPV).
- 1.47. The MAH should submit the name and contact details of the QPPV to the Agency.
- 1.48. The duties of the QPPV should be defined in a job description.
- 1.49. The hierarchical relationship of the QPPV should be defined in an organisational chart together with those of other managerial and supervisory staff.
- 1.50. Information relating to the QPPV should be included in the pharmacovigilance systems master file (PSMF) (see Chapter 2).
- 1.51. Each pharmacovigilance system can have only one QPPV.
- 1.52. A QPPV may be employed by more than one MAH, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder, provided that the QPPV is able to fulfil all obligations.
- 1.53. The MAH should ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorization holder.
- 1.54. The MAH should ensure that the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it.
- 1.55. The authority over the pharmacovigilance system and the PSMF should allow the QPPV to implement changes to the system and to provide input into risk management plans (see Chapter 3) as well as into the preparation of regulatory action in response to emerging safety concerns.
- 1.56. Overall, the MAH should ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed in sections 1.67 to 1.72. In order to do this, the MAH should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:
 - a. Emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;
 - b. Ongoing or completed clinical trials and other studies the MAH is aware of and which may be relevant to the safety of

- the medicinal products;
 - c. Information from sources other than from the specific MAH, e.g. from those with whom the MAH has contractual arrangements; and
 - d. The procedures relevant to pharmacovigilance which the MAH has in place at every level in order to ensure consistency and compliance across the organisation.
- 1.57. The outcome of the regular reviews of the quality system referred to in sections 1.37 to 1.45 and the measures introduced should be communicated by the managerial staff to the QPPV.
- 1.58. Compliance information should be provided to the QPPV on a periodic basis. Such information may also be used to provide assurance to the QPPV that commitments in the framework of risk management plans and post-authorisation safety systems are being adhered to.
- 1.59. The managerial staff should also inform the QPPV of scheduled pharmacovigilance audits. The QPPV should be able to trigger an audit where appropriate. The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit relevant to the pharmacovigilance system the QPPV is responsible for, so that the QPPV can assure that appropriate corrective actions are implemented.
- 1.60. In particular with regard to its adverse reaction database (or other systems to collate adverse reaction reports), the MAH should implement a procedure to ensure that the QPPV is able to obtain information from the database, for example, to respond to urgent requests for information from the Agency, at any time. If this procedure requires the involvement of other personnel, for example database specialists, then this should be taken into account in the arrangements made by the MAH for supporting the QPPV outside of normal working hours.
- 1.61. When a marketing authorization holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another MAH, the QPPV should be notified as early as possible in the due diligence process in order that the potential impact on the pharmacovigilance system can be assessed and the system be adapted accordingly.
- 1.62. The QPPV may also have a role in determining what pharmacovigilance data should be requested from the other company, either pre- or post-acquisition. In this situation, the QPPV should be made aware of the sections of the contractual arrangements that relate to responsibilities for pharmacovigilance activities and safety data

- exchange and have the authority to request amendments
- 1.63. When a MAH intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system, the QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements so that all necessary provisions relevant to the pharmacovigilance system are included.

Qualifications of the qualified person responsible for pharmacovigilance (QPPV)

- 1.64. The QPPV should have skills for the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences, epidemiology and biostatistics.
- 1.65. The marketing authorisation holder should provide the QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the medicinal products covered by the pharmacovigilance system.

Roles and responsibilities of the QPPV

- 1.66. The qualified person responsible for pharmacovigilance is a natural person and should be at the marketing authorisation holder's disposal permanently and continuously. The QPPV should reside and operate in Nigeria. Back-up procedures in the case of absence of the QPPV should be in place and should be accessible through the QPPV's contact details. The QPPV should ensure that the back-up person has all necessary information to fulfil the role.
- 1.67. The QPPV should be responsible for the establishment and maintenance of the marketing authorisation holder's pharmacovigilance system and therefore should have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements. Hence, the QPPV should have access to the pharmacovigilance system master file (PSMF) (see Chapter 2) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.
- 1.68. In relation to the medicinal products covered by the pharmacovigilance

system, specific additional responsibilities of the QPPV should include:

- a. Having an overview of medicinal product safety profiles and any emerging safety concerns;
 - b. Being aware of any conditions or obligations adopted as part of the marketing authorisation and other commitments relating to safety or the safe use of the product;
 - c. Being aware of risk minimisation measures;
 - d. Being involved in the review and sign-off of protocols of post-authorisation safety studies;
 - e. Being aware of post-authorisation safety studies requested by the Agency including the results of such studies;
 - f. Providing input into risk management plans;
 - g. Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;
 - h. Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the Agency;
 - i. Ensuring full and prompt response to any request from the Agency for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product;
 - j. Providing any other information relevant to the benefit-risk evaluation as may be requested by the Agency;
 - k. Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);
 - l. Acting as a single pharmacovigilance contact point for the Agency on a 24-hour basis and also as a contact point for pharmacovigilance inspections.
- 1.69. This responsibility for the pharmacovigilance system means that the QPPV has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance).
- 1.70. The QPPV should be aware of the validation status of the adverse reaction database if applicable, including any failures that occurred

during validation and the corrective actions that have been taken to address the failures. The QPPV should also be informed of significant changes that are made to the database (e.g. changes that could have an impact on pharmacovigilance activities).

- 1.71. The QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

Tasks subcontracted by the marketing authorisation holder

- 1.72. A marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties (i.e. to another organization or person). This may include the role of the QPPV.
- 1.73. The marketing Authorisation Holder should nevertheless retain the full responsibility for the completeness and accuracy of the pharmacovigilance system master file. The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities as well as the quality and integrity of the pharmacovigilance system always remain with the Marketing Authorisation Holder.
- 1.74. Where a marketing authorisation holder has subcontracted some tasks of its pharmacovigilance tasks, it should retain responsibility for ensuring that an effective quality system is applied in relation to those tasks. All guidance provided in GVP is also applicable to the other organisation to which the tasks have been subcontracted.
- 1.75. When subcontracting tasks to another organisation, the marketing authorisation holder should draw up subcontracts and these should be detailed, up-to-date and clearly document the contractual arrangements between the marketing authorisation holder and the other organisation, describing arrangements for delegation and the responsibilities of each party.
- 1.76. A description of the subcontracted activities and/or services should be included in the pharmacovigilance system master file (Chapter 2) and a list of the subcontracts should be included in an annex to the PSMF, specifying the product(s) organisation may be subject to inspection at the discretion of the Agency.
- 1.77. Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the marketing authorisation holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data exchange, together with, for

- example, agreed definitions, tools, assignments and timelines.
- 1.78. The contractual arrangements should also contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases. Further, they should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.

CHAPTER

2 Pharmacovigilance System Master File

- 2.1. The pharmacovigilance system master file provides an overview of the pharmacovigilance system put in place by the MAH and contributes to the appropriate management of and improvement(s) to the pharmacovigilance system. The PSMF enables the marketing authorisation holder and the Qualified Person for Pharmacovigilance (QPPV) to:
- Gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
 - Confirm aspects of compliance in relation to the system;
 - Obtain information about deficiencies in the system, or non-compliance with the requirements;
 - Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

Maintenance of pharmacovigilance system master file

- 2.2. Marketing authorisation holders in Nigeria are required to maintain a pharmacovigilance system master file and submit to the Agency during application for marketing authorization of a medicinal product. The pharmacovigilance system master file should be located either at the site in Nigeria where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in Nigeria where the qualified person responsible for pharmacovigilance operates.
- 2.3. Applicants for, and holders of listing for traditional herbal medicinal products are also required to submit a pharmacovigilance system master file.

Transfer of responsibility for the PSMF

- 2.4. Transfer or delegation of responsibilities and activities concerning the master file should be documented (see sections 2.18. and 2.35) and managed to ensure that the marketing authorisation holder fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the QPPV

- are:
- a. Updates to the pharmacovigilance system master file or its location;
 - b. The addition of corrective and/or preventive actions to the pharmacovigilance system master file (e.g. following audits and inspections). The QPPV should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;
 - c. Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
 - d. Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
 - e. Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
 - f. Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications or studies.
- 2.5. Any recipient QPPV should explicitly accept the transfer of responsibility for a pharmacovigilance system in writing. The QPPV should be in a position to ensure and to verify that the information contained in the pharmacovigilance system master file is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see Chapter 1).

The representation of pharmacovigilance systems

- 2.6. The pharmacovigilance system master file may describe the pharmacovigilance system for one or more medicinal products of the marketing authorisation holder. For different categories of medicinal products the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each such system should be described in a separate pharmacovigilance system master file. Those files should cumulatively cover all medicinal products of the marketing authorisation holder for which a marketing authorisation has been issued.
- 2.7. It is anticipated that there will be circumstances where a single marketing authorisation holder may establish more than one pharmacovigilance system e.g. specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one

marketing authorisation holder. In either case, a single and specific pharmacovigilance system master file should be in place to describe each system.

- 2.8. A single QPPV should be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.
- 2.9. Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible for ensuring that a pharmacovigilance system master file exists to describe the pharmacovigilance system applicable for his products. For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the authorities. The marketing authorisation holder should be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the pharmacovigilance system master file in a current and accessible state can be delegated.
- 2.10. Where applicable, a list of all pharmacovigilance system master files held by the same marketing authorisation holder should be provided in the annex (see section 2.35); this includes:
 - a. Their location(s),
 - b. Details of the responsible QPPV(s) and
 - c. The relevant product(s).
- 2.11. The address of the location of the pharmacovigilance system master file should be an office address which reflects either the site in Nigeria where the main pharmacovigilance activities of the marketing authorisation holder are performed or the site in Nigeria where the qualified person responsible for pharmacovigilance operates. This address may be different to that of the marketing authorisation holder, for example, a different office of the marketing authorisation holder or when a third party undertakes pharmacovigilance activities.
- 2.12. Similarly, the QPPV details aligned to a product may be those of a

- contract QPPV responsible for the pharmacovigilance system for a particular medicinal product, and not necessarily a QPPV directly employed by the marketing authorisation holder.
- 2.13. When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to the Agency. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.
- 2.14. When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own pharmacovigilance system master files. Accessibility of the pharmacovigilance system master file to all the applicable marketing authorisation holder(s), and its provision to the Agency should be defined in written agreements. It is vital that marketing authorisation holder(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

Content of a Pharmacovigilance System Master File (PSMF)

- 2.15. The pharmacovigilance system master file should include documents to describe the pharmacovigilance system. The content of the pharmacovigilance system master file should have the headings used in sections 2.17 to 2.35 and should reflect the global availability of safety information for medicinal products authorised in Nigeria. The content should be indexed to allow for efficient navigation around the document.
- 2.16. The main principle for the structure of the content of the pharmacovigilance system master file is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes.

Qualified person responsible for pharmacovigilance (QPPV)

- 2.17. The information relating to the QPPV provided in the PSMF should

include:

- a. A description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance
- b. A summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance;
- c. Contact details;
- d. Details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance and
- e. Registrations relevant to pharmacovigilance (if any)
- f. A list of tasks that have been delegated by the qualified person for pharmacovigilance should also be included in the Annexes (see section 2.35). This should outline the activities that are delegated and to whom, and include the access to a medically qualified person if applicable (Chapter I). This list may be supplied as a copy of a written procedural document provided the required content is covered.
- g. The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied should include name, postal, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

Organisational structure of the marketing authorisation holder

2.18. A description of the organisational structure of the marketing authorisation holder relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the pharmacovigilance system master file should describe:

- a. The organisational structure of the marketing authorisation holder(s), showing the position of the QPPV in the organisation.

- b. The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, management of the risk management plan, pre- and post-authorisation study management, and management of safety variations to product particulars.
- c. Flow charts may be particularly useful; the name of the department or third party should be indicated.

Delegated activities

- 2.19. The pharmacovigilance system master file, where applicable, should contain a description of the delegated activities and/or services relating to the fulfillment of pharmacovigilance obligations. This includes arrangements with other parties in any country, worldwide and if applicable, to the pharmacovigilance system applied to products authorised in Nigeria.
- 2.20. Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s). The list should be organised according to; service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.).

Sources of safety data

- 2.21. The description of the main units for safety data collection should include all parties responsible on a global basis for solicited and spontaneous case collection for products authorized in Nigeria. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity, and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and email) for the site. The list may be located in the annexes of the PSMF. The information about third parties (licensed partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements. (see sections 2.18 and 2.35)

- 2.22. Flow diagrams indicating the main stages, time frames and parties involved may be used. However represented, the description of the process for ICSRs from collection to reporting to the Agency, should indicate the department and/or third parties involved.
- 2.23. Sources may include data arising from study sources, including any studies, registries, surveillance or support programs sponsored by the MAH through which ICSRs could be reported. The MAH should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight.
- 2.24. The list should describe on a worldwide basis the status of each study/program the applicable country(ies), the product(s), and the main objective. It should distinguish between interventional and non-interventional studies and should be organized per active substance. The list should be comprehensive for all studies/programs and should include on-going studies/programs as well as studies/programs completed in the last 2 years and may be located in an annex or provided separately.

Computerized systems and databases

- 2.25. The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose should be described in the pharmacovigilance system masterfile.
- 2.26. Where multiple computerized systems/databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerization within the pharmacovigilance system can be understood. The validation status of key aspects of the computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described. For paper based system (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular, the collation of information about adverse drug reactions should be described.

Pharmacovigilance processes

- 2.27. An essential element of any pharmacovigilance system is that there are

clear written procedures in place. Chapter I describes the required minimum set of written procedures for pharmacovigilance. A description of the procedural documentation available (standard operating procedures, manuals, etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the pharmacovigilance system master file.

- 2.28. A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects should be included in the pharmacovigilance system master file:
- a. Continuous monitoring of product benefit-risk profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
 - b. Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
 - c. ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
 - d. PSUR scheduling, production and submission, if applicable (see Chapter 6);
 - e. Communication of safety concerns to consumers, healthcare professionals and the Agency;
 - f. Implementation of safety variations to the summary of product characteristics and patient information leaflets; procedures should cover both internal and external communications.
- 2.29. In each area, the marketing authorisation holder should be able to provide evidence of a system that supports appropriate and timely decision making and action.
- 2.30. The description must be accompanied by the list of processes for compliance management as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to requests for information by the Agency, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, should comprise the procedural

document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

Pharmacovigilance system performance

- 2.31. The pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file should include a description of the monitoring methods applied and contain as a minimum:
- a. An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
 - b. A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by the Agency regarding the quality of ICSR reporting, PSURs or other submissions;
 - c. An overview of the timeliness of PSUR reporting to the Agency (the annex should reflect the latest figures used by the marketing authorisation holder to assess compliance);
 - d. An overview of the methods used to ensure timeliness of safety variation submissions including the tracking of required safety variations that have been identified but not yet been submitted;
 - e. Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance.
- 2.32. Targets for the performance of the pharmacovigilance system should be described and explained.
- 2.33. A list of performance indicators must be provided in the Annex to the pharmacovigilance system master file, alongside the results of (actual) performance measurements.

Quality system

- 2.34. A description of the quality management system should be provided, in terms of the structure of the organisation and the application of the quality to pharmacovigilance. This should include:

Document and Record Control

- a. A description of the archiving arrangements for electronic and/or hardcopy versions of the pharmacovigilance system master file should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents (see also Chapter1).

Procedural documents

- b. A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc.), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.
- c. Information about the documentation systems applied to relevant procedural documents under the control of third parties.
- d. A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided, and the detailed guidance for the inclusion of these is in sections 2.27 to 2.30.

Training

- e. A description of the resource management for the performance of pharmacovigilance activities:
- f. The organisational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational structure (see sections 2.21 to 2.24)
- g. Information about sites where the personnel are located (sections 2.18 to 2.24) whereby the sites are provided in the PSMF in relation to the organisation of specific pharmacovigilance activities and in the Annexes which provide the list of site contacts for sources of safety data. However, a description should be provided in order to explain the training organisation in relation to the personnel and site information;
- h. A summary description of the training concept, including a reference to the location training files.
- I. Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.

Auditing.

- j. Information about quality assurance auditing of the pharmacovigilance system should be included in the pharmacovigilance system master file. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to in section 2.35. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the regulations, and cover a period of 5 years.
- k. The pharmacovigilance system master file should also contain a note associated with any audit where significant findings are raised. The audit report must be documented within the quality system; in the pharmacovigilance system master file it is sufficient to provide a brief description of the corrective and/or preventive action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventive action plan(s). In the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, should be identified. The note and associated corrective and preventive action(s), should be documented in the pharmacovigilance system master file until the corrective and/or preventive action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes must therefore be recorded in the logbook.
- l. As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the pharmacovigilance system master file should also describe the process for recording, managing and resolving deviations from the quality system. The master file should also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

Annex to the PSMF

- 2.35. An annex to the pharmacovigilance system master file should contain the following documents:
- a. A list of medicinal products covered by the pharmacovigilance system master file including the name of the medicinal product, the name of the active substance(s) and the corresponding NAFDAC registration number.
 - i. The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity. The monitoring information may be provided as a secondary list.
 - ii. For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional pharmacovigilance system master file(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of pharmacovigilance system master files.
 - iii. Where pharmacovigilance systems are shared, all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organised per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;
 - b. A list of written policies and procedures;
 - c. A list of contractual agreements covering delegated activities including the medicinal products;
 - d. A list of tasks that have been delegated by the qualified person for pharmacovigilance;
 - e. A list of all completed audits, for a period of five years, and a list of audit schedules;
 - f. Where applicable, a list of performance indicators;
 - g. Where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder. This list should include the pharmacovigilance system master file number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not a marketing authorisation holder, the name of the service provider should also be included.

- h. A logbook and other change control documentation should be included as appropriate. Documented changes should include at least the date, person responsible for the change and the nature of the change.

Change control, logbook, versions and archiving

- 1.36. It is necessary for marketing authorisation holders to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the pharmacovigilance system master file accordingly. The Agency may request information about important changes to the pharmacovigilance system, such as, but not limited to:
 - a. Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
 - b. Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
 - c. Organisational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of pharmacovigilance system master file management.
- 1.37. In addition to these changes being documented in the pharmacovigilance system master file for the purpose of change control (in the logbook), the QPPV should always be kept informed of these changes.
- 1.38. Changes to the pharmacovigilance system master file should be recorded, such that a history of changes is available (specifying the date and the nature of the change), changes to the PSMF must be recorded in the logbook. Descriptive changes to the content of the master file must be recorded in the logbook.
- 1.39. Change history for the information contained in the annexes may be 'on demand', in which case the logbook would indicate the date of the revision of PSMF content and/or annex update(s), the history of changes for annex content would also be updated. Information that is being regularly updated and is contained in the annexes, such as product and standard operating procedure lists or compliance figures, may include outputs from controlled systems (such as electronic document management systems or regulatory databases). The superseded versions of such content may be managed outside of the pharmacovigilance system master file content itself, provided that the

history of changes is maintained and available to the Agency on request. If the pharmacovigilance system master file has not been requested, or has remained unchanged for a period of time (for example, if the changes in the content of annexes are managed outside of the pharmacovigilance system master file), it is recommended that a review is conducted periodically. Marketing authorisation holders need to ensure that the obligations concerning the timely provision of the pharmacovigilance system master file can be met. It is also noted that the QPPV must be able to gain access to current and accurate information about the pharmacovigilance system, hence permanent access to the pharmacovigilance system master file must be enabled, including the information contained in the annexes (either via the pharmacovigilance master file itself or via access to the systems used to generate the annex content).

- 1.40. Marketing authorisation holders should be able to justify their approach and have document control procedures in place to govern the maintenance of the pharmacovigilance system master file.
- 1.41. Changes to the pharmacovigilance system master file should also account for shared pharmacovigilance systems and delegated activities. A record of the date and nature of notifications of the changes made available to the Agency, the QPPV and relevant third parties should be kept in order to ensure that change control is fully implemented.
- 1.42. The pharmacovigilance master file should be retained in a manner that ensures its legibility and accessibility.

Presentation

- 1.43. The pharmacovigilance system master file should be continuously accessible to the QPPV and to the Agency. The information should be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements.

Format and layout

- 1.44. The pharmacovigilance system master file may be in electronic form on condition that a clearly arranged printed copy can be made available to the Agency. In any format, the pharmacovigilance system master file should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes.

Therefore, it may be appropriate to restrict access to the pharmacovigilance system master file in order to ensure appropriate control over the content and to assign specific responsibilities for the management of pharmacovigilance system master file in terms of change control and archiving.

- 1.45. The pharmacovigilance system master file should be indexed in a manner consistent to allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.
- 1.46. The documents and particulars of the pharmacovigilance system master file should be presented with the following headings and, if in hardcopy, in the order outlined:
- 1.47. Cover Page to include:
 - a. The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
 - b. The name of other concerned MAH(s) (sharing the pharmacovigilance system)
 - c. The list of pharmacovigilance system master files for the MAH (concerning products with a different pharmacovigilance system)
 - d. The date of preparation/last update
- 1.48. The headings referred to in section 2.15 should be used for the main content of the pharmacovigilance system master file. The minimum required content of the annexes is outlined in section 2.35, and additional information may be included in the annexes, provided that the requirements for the content of the main sections (2.17 to 2.34) are also met. The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):
 - a. The Qualified Person responsible for pharmacovigilance, Annex A
 - i. The list of tasks that have been delegated by the QPPV, or the applicable procedural document
 - ii. The curriculum vitae of the QPPV and associated documents
 - iii. Contact details
 - b. The Organisational Structure of the MAH, Annex B
 - I. The lists of contracts and agreements
 - c. Sources of safety data, Annex C
 - i. Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

- d. Computerised systems and Databases, Annex D
 - e. Pharmacovigilance Process, and written procedures, Annex E
 - i. Lists of procedural documents
 - f. Pharmacovigilance System Performance, Annex F
 - i. Lists of performance indicators
 - ii. Current results of performance assessment in relation to the indicators
 - g. Quality System, Annex G
 - i. Audit schedules
 - ii. List of audits conducted and completed
 - h. Products, Annex H
 - i. List(s) of products covered by the pharmacovigilance system
 - ii. Any notes concerning the MAH per product
 - i. Document and Record Control, Annex I
 - i. Logbook
 - j. Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself
- 1.49. Documentation to support notifications and signatures concerning the pharmacovigilance system master file, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerised systems and databases is used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the pharmacovigilance system master file are assured that missing content is intended.

CHAPTER

3 RISK MANAGEMENT SYSTEM

- 3.1. It is recognized that at the time of authorization, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.
- 3.2. A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk ratio is judged to be positive for the target population. A typical medicinal product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post authorisation.
- 3.3. Planning of the necessary pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles.
- 3.4. However, the purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore risk management has three stages which are inter-related and iterative:
 - a. Characterization of the safety profile of the medicinal product including what is known and not known;
 - b. Planning of pharmacovigilance activities to characterise risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product;
 - c. Planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these

- activities.
- 3.5. 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.

MAH responsibility for risk management

- 3.6. In relation to risk management of its medicinal products, a marketing authorisation holder is responsible for:
- a. Ensuring that it constantly monitors the risks of its medicinal products and reports the results of this, as required, to the Agency;
 - b. Taking all appropriate actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available;
- 3.7. Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts.

The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training.

- 3.8. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorisation applicant/holder who should ensure oversight by someone with the appropriate scientific background within the company.

Objectives of a risk management plan

- 3.9. The RMP must contain the following elements which:

- a. Identify or characterise the safety profile of the medicinal product(s) concerned;
 - b. Indicate how to characterise further the safety profile of the medicinal product(s) concerned;
 - c. Document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
 - d. Document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.
- 1.10. There is an implicit requirement that to fulfil these obligations a RMP should also:
- a. Describe what is known and not known about the safety profile of the concerned medicinal product(s);
 - b. Indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);
 - c. Include a description of how the effectiveness of risk minimisation measures will be assessed.
- 1.11. The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products.

Structure of the risk management plan

- 3.12. The RMP consists of seven parts:
- a. Product(s) overview
 - b. Safety specification
 - c. Pharmacovigilance plan
 - d. Plans for post-authorisation efficacy studies
 - e. Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
 - f. Summary of the risk management plan
 - g. Annexes

Product overview

- 3.13. This should provide the administrative information on the RMP and an overview of the product(s) covered within it. The information should include:
- a. Active substance information:
 - i. Active substance(s);
 - ii. Pharmacotherapeutic group(s) (ATC code);

- iii. Name of marketing authorisation holder;
- iv. Date and country of first authorisation worldwide (if applicable);
- v. Date and country of first launch worldwide (if applicable);
- vi. Number of medicinal product(s) to which this RMP refers.
- b. 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.
- c. For each medicinal product included in the RMP:
 - i. Authorisation number;
 - ii. Trade mark/brand name(s);
 - 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. Indications:
 - Current (if applicable);
 - Proposed (if applicable);
 - v. Dosage:
 - Current (if applicable);
 - Proposed (if applicable);
 - vi. Pharmaceutical forms and strengths:
 - Current (if applicable);
 - Proposed (if applicable);
 - vii. Whether the product is the subject of additional monitoring.

Safety specification

- 3.14. The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s). It should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information. 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-authorisation period. In the RMP, the safety specification will form the basis of the pharmacovigilance plan, and the risk minimisation plan.

- 3.15. The safety specification consists of eight elements:
- a. Epidemiology of the indication(s) and target population(s)
 - b. Non-clinical part of the safety specification
 - c. Clinical trial exposure
 - d. Populations not studied in clinical trials
 - e. Post-authorisation experience
 - f. Additional requirements for the safety specification by the Agency
 - g. Identified and potential risks
 - h. Summary of the safety concerns
- 1.16. It is recommended that marketing authorisation holders follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme. Elements which might need to be incorporated 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 with a medical device.

Epidemiology of the indications and target population

- 3.17. The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and 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.
- 3.18. 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.

- 3.19. 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.

Non-clinical part of the safety specification

- 3.20. This should present a summary of the important non-clinical safety findings, for example:
- a. Toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
 - b. General pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);
 - c. Drug interactions;
 - d. Other toxicity-related information or data.
- 3.21. 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. Also 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. For other special populations depending upon the indication and target population, consideration should be given to whether specific non-

clinical data needs exist.

Clinical trial exposure

- 3.22. 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, e.g. 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.
- 3.23. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:
- a. Age and gender;
 - b. Indication;
 - c. Dose;
 - d. Racial origin.
- 3.24. 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.
- 3.25. The categories above 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/immunisations or repeat administrations may be important categories to be added.
- 3.26. 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. Paediatric 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+, although the age strata should reflect that of the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

- 3.27. Unless clearly relevant, data should not be presented by individual trial 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.
- 3.28. 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.

Populations not studied in clinical trials

- 3.29. Limitations of the clinical trials should also 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 in the overall development programme in relation to the target population should be provided.
- 3.30. The implications, with respect to 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 with regard to the detection of adverse reactions due to:
- Number of patients studied;
 - Cumulative exposure (e.g. specific organ toxicity);
 - Longterm 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.
- 3.31. Populations to be considered for discussion should include (but might not be limited to):
- 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. taking into account 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 particular 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 effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular 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 medical 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 carrying known and relevant genetic polymorphism:***the extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme has been in patients with a specific mutation, the marketing authorisation holder should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern.If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and pharmacovigilance plan.Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.
- j. *Patients of different racial and/or ethnic origins:information on racial origin*** may be relevant and valuable for evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population.The experience of drug use in patients with different racial and/or ethnic origins should bediscussed including the implications on efficacy and safety, based on pharmacokinetics andpharmacodynamics, in the target population. If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP. Consideration should also be given as to whether post-authorisation efficacy and/or safety studies are necessary.

POST-AUTHORISATION EXPERIENCE

- 3.32. The purpose is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP. It should also include brief information on the number of patients included 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/or marketing authorisation holders for safety reasons

- 3.33. List any significant regulatory action (including those initiated by the marketing authorisation holder), in any market, taken in relation to a safety concern. 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 marketing authorisation.
- 3.34. 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.
- 1.35. 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. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations.

Non-study post-authorisation exposure

- 3.36. Where marketing of the medicinal product has occurred, the marketing authorisation holder should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables. These may include age, sex, indication, dose and region. Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment.
- 3.37. 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 kilogrammes 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.

- 3.38. If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. The Agency may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, marketing authorisation holders should consider routinely providing such data where possible.
- 3.39. A more accurate breakdown of drug exposure based on market research should be provided where possible.
- 3.40. If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real world setting, should be provided.

Post-authorisation use in populations not studied in clinical trials

- 3.41. Where there are data on post-authorisation use in the special populations identified in RMP as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label.
- 3.42. 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.

Post-authorisation off-label use

- 3.43. 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, marketing

authorisation holders should attempt to quantify such use along with a description of the methods used to arrive at these figures.

Epidemiological study exposure

- 3.44. Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

ADDITIONAL REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for harm from overdose

- 3.45. Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP and appropriate risk minimisation proposed in RMP.

Potential for transmission of infectious agents

- 3.46. The marketing authorisation holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed.

Potential for misuse for illegal purposes

- 3.47. The potential for misuse for illegal purposes should be considered. Misuse, as defined in Chapter 5, refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicinal product to cause an effect in another person.
- 3.48. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault. If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the risk minimisation plan.

Potential for medication errors

- 3.49. For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They fall broadly into 4 categories:
- a. Wrong medication;
 - b. Wrong dose (including strength, form, concentration, amount);
 - c. Wrong route of administration;
 - d. Wrong patient
- 3.50. Marketing authorisation holders should consider routinely the likelihood of medication errors. In particular, they should assess, prior to marketing, common sources of medication errors.
- 3.51. 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.
- 3.52. 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.

- 3.53. 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.
- 3.54. Consideration should be given to the prevention of accidental ingestion or other unintended use by children.
- 3.55. 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.
- 3.56. 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.
- 3.57. If the formulation or strength of a product is being changed, where appropriate, medication error should be included as a safety concern and the measures that the marketing authorisation 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.
- 3.58. If the product is to be administered with a medical device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medical device malfunction).

Potential for off-label use

- 3.59. The potential for off-label use should be discussed. Off-label use relates to situations where the medicinal product is intentionally used for a medical 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 area should also be considered where this is likely.
- 3.60. Where appropriate, use could be made of data on actual use versus authorised use in other markets.

Specific paediatric issues

- 3.61. This section deals with aspects of paediatric use not covered in sections 3.29 to 3.31.

Issues identified in paediatric investigation plans

- 3.62. Any recommendations for long term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be detailed here. This section should clarify if, and how, this had been taken into account in sections 3.67 to 3.75. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.
- 3.63. Proposals for specific long term paediatric studies should be considered at the time of application for a paediatric indication and if felt not to be necessary justification should be provided. If an indication in adults precedes an application for paediatric use, any registries established to provide data on use of the product in real medical practice should avoid age related exclusion criteria so that any potential off-label use in the paediatric population can be included.
- 3.64. In some circumstances, the safety concern identified in the paediatric investigation plan may be applicable to the whole population being treated. In these cases, consideration should be given as to whether some of the pharmacovigilance activities and/or risk minimisation activities from the paediatric investigation plan are appropriate for, and should be extended to cover, the whole population. For these safety concerns, this RMP section should also include details of how the specific paediatric aspects will be addressed and all paediatric investigation plan recommendations considered.
- 3.65. Cross-reference may be made to sections 3.29 to 3.31 and section 3.67 to 3.75.

Potential for paediatric off-label use

- 3.66. If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed. If there are limited treatment options it should not be assumed that clinicians will adhere to the labelled indication so it is important that potential paediatric issues are discussed. Any actual use should be discussed in sections 3.36 to 3.40 “Non-study post-authorisation exposure” and in section 3.41 to 3.42 “Post-authorisation use in populations not studied in clinical trials”.

IDENTIFIED AND POTENTIAL RISKS

- 3.67. This provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.
- 3.68. Newly identified safety concerns.
Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).
- 3.69. 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 other sections of the safety specification as appropriate
- 3.70. Details of important identified and potential risks from clinical development and post-authorisation experience

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 which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here.

- 3.71. 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, but 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 sections 3.76 to 3.79 “Summary of the safety concerns.”

Identified and potential risks (ATMP version)

- 3.72. Advanced therapy medicinal products (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products.
- 3.73. Newly identified safety concerns (ATMP)
- 3.74. Recent study reports with implications for safety concerns (ATMP)
- 3.75. Details of important identified and potential risks (ATMP)

SUMMARY OF THE SAFETY CONCERNS

- 3.76. At the end of the RMP part “Safety specification” a summary should be provided of the safety concerns.
- 3.77. A safety concern is:
- An important identified risk;
 - An important potential risk; or
 - Missing information (see Annex I).
- 3.78. For RMPs covering multiple products where there may be significant differences in the important identified and important 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:

- a. Safety concerns relating to the active substance;
 - b. Safety concerns related to a specific formulation or route of administration;
 - c. Safety concerns relating to the target population;
 - d. Risks associated with switch to non-prescription status.
- 3.79. 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.

Pharmacovigilance plan

- 3.80. The purpose of the pharmacovigilance plan is to discuss how the marketing authorisation holder plans to identify and/or characterise the risks identified in the safety specification.
- 3.81. It provides a structured plan for:
- a. The identification of new safety concerns;
 - b. Further characterisation of known safety concerns including elucidation of risk factors;
 - c. The investigation of whether a potential safety concern is real or not;
 - d. How missing information will be sought.
 - e. It does NOT include actions intended to reduce, prevent or mitigate risks
- 3.82. The pharmacovigilance plan should be based on the safety concerns summarised in section 3.76 to 3.79 of the safety specification. Early discussions between the Agency and the marketing authorisation holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all products.
- 3.83. Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the marketing authorisation holder 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.

Routine pharmacovigilance activities

- 3.84. Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for Pharmacovigilance Regulations of the Agency. The Pharmacovigilance System Master File (see Chapter 2) contains details of the system and processes each marketing authorisation holder has in place to achieve this.
- 3.85. 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 (see Chapter 1).

Specific adverse reaction follow-up questionnaires

- 3.86. Where a marketing authorisation holder is requested, or plans to use, specific questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. Marketing authorisation holders are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.
- 3.87. Use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine pharmacovigilance.

Additional pharmacovigilance activities

- 3.88. Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non-interventional studies. A safety concern may have no, or a number of, additional pharmacovigilance activities associated with it depending upon its nature, the degree to which it has already been characterised, and the feasibility of studying it. Marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long term

follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another example, when additional pharmacovigilance activities should be considered, is when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the “normal” incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with the Agency should be considered.

- 3.89. The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.
- 3.90. Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The marketing authorisation holder should include all studies designed to address the safety concern or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders, voluntarily, or pursuant to obligations imposed by the Agency
- 3.91. Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted with expert advice and in accordance with good pharmacoepidemiology practices. The responsibility for the scientific value of study protocols remains with marketing authorisation holders, even if they have been previously discussed with the Agency.
- 3.92. For some safety concerns, additional pharmacovigilance activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or further pre-clinical work.

Particular situations with post authorisation safety studies

- 3.93. This section should be read in conjunction with Chapter 7 on post-authorisation safety studies.

Studies to measure the effectiveness of risk minimisation measures

- 3.94. Post-authorisation safety studies (PASS) include in their definition studies which measure the effectiveness of risk management measures. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.

Drug utilisation studies

- 3.95. Drug utilisation studies may be requested by the Agency to monitor drug usage in the country. Although they may not be initiated to collect safety data, they can provide useful information on whether risk minimisation activities are effective and on the demographics of target populations.

Registries

- 3.96. 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).

Action plans for safety concerns with additional pharmacovigilance requirements

- 3.97. For safety concerns with additional pharmacovigilance activities only, the action plan for each safety concern should be presented according to the following structure:
- a. Safetyconcern;
 - b. Proposedaction(s);
 - c. Individualobjectives of proposed action(s) (i.e. what aspects of the safety concern they are intended to characterise); and for each action:
 - d. Detailsof individual action;
 - e. Steps; and
 - f. Milestones (including expected dates).

Summary table of additional pharmacovigilance activities

- 3.98. The summary table of the pharmacovigilance plan should provide clarity to all stakeholders as to which category an activity in the pharmacovigilance plan falls under, i.e.:
- Imposed obligations as a condition of the MA;
 - Specific Obligations in the framework of a MA under exceptional circumstances.
 - Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities;
 - Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities.

Plans for post-authorisation efficacy studies

- 3.99. Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months to 3 years). The benefit (efficacy of the medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.
- 3.100. For most medicines there will not be a need for post-authorisation efficacy studies.
- 3.101. Paediatric medicinal products and advanced therapy medicinal products need long term follow-up of efficacy as part of post-authorisation surveillance.

Summary of existing efficacy data

- 3.102. As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicinal product, the information should be provided by medicinal product to permit easy extraction for the summary of the RMP chapter. Similarly medicinal products with more than one indication should have a separate summary of efficacy for each indication.
- 3.103. The summary of efficacy (one page maximum per indication/population) should be in lay language and the following

- should be considered for inclusion:
- Current (gold) standards of treatment;
 - Where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.);
 - A brief statement of the standard against which the medicine was judged;
 - Number of patients in pivotal studies and treatment regimes;
 - Results in lay language.
- 3.104. The following areas should be discussed briefly and the need for further studies post authorisation evaluated:
- The robustness of the endpoints on which the efficacy evaluation is based;
 - Applicability of the efficacy data to all patients in the target population;
 - Factors which might affect the efficacy of the product in everyday medical practice;
 - Variability in benefits of treatment for sub-populations.
- 3.105. For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact on the benefits of the medicinal product discussed.

Tables of post-authorisation efficacy studies

- 3.106. A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex 8. Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should also be included in this part of the RMP.

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

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

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

Other efficacy/effectiveness studies

Risk minimisation measures

- 3.107. On the basis of the safety specification, a marketing authorisation holder should assess what risk minimisation activities are needed 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.
- 3.108. 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. Examples when multiple risk minimisation plans could be considered include:
- 3.109. An active substance where there are products with both prescription only and non-prescription legal status;
- 3.110. Medicinal products where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example an active substance which causes important QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;
- 3.111. Active substances where there are major risks which differ according to the target population.
- 3.112. 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.
- 3.113. All risk minimisation measures should be reviewed at regular intervals

and their effectiveness assessed (see sections 3.132 to 3.135).

Routine risk minimisation

- 3.114. Routine risk minimisation activities are those which apply to every medicinal product. These relate to:
- The summary of product characteristics;
 - The labelling;
 - The package leaflet;
 - The pack size(s);
 - The legal status of the product.
- 3.115. The summary of product characteristics (SmPC) and the package leaflet 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, and even the formulation itself, may play an important role in preventing medication error.

Pack size

- 3.116. Since every pack size is specifically authorised for a medicinal product, planning the number of “dosage units” within each pack, and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of “dosage units” should mean that patients will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.
- 3.117. A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

Legal status

- 3.118. Controlling the legal status under which a medicinal product may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal product may be prescribed, or the conditions under which a patient may receive a medicinal product.
- 3.119. When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the

medicinal product, including the conditions under which a medicinal product may be made available to patients. The conditions under which a medicinal product is made available is commonly referred to as the “legal status” of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medicinal prescription. It may also restrict where the medicinal product can be administered (e.g. in a hospital, but see below) or by whom it may be prescribed (e.g. specialist).

- 3.120. For medicinal products only available on prescription, additional conditions may be imposed by classifying medicinal products into those available only upon either a restricted medical prescription or a special medical prescription.

Restricted medical prescription

- 3.121. This may be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicine can be given or used. When considering classification of a medicinal product as subject to restricted medical prescription, the following factors should be taken into account:
- a. The medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
 - b. The medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere; or
 - c. The medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment.

Special medical prescription

- 3.122. For classification as subject to special medical prescription, the following factors should be taken into account:
- a. The medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971; or
 - b. The medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be

- misused for illegal purposes; or
- c. The medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure
- d. The majority of safety concerns may be adequately addressed by routine risk minimisation activities. However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary.

Additional risk minimisation activities

- 3.123. Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.
- 3.124. Many additional risk minimisation tools are based on communication which aims to augment the information in the summary of product characteristics (SmPC) and the package leaflet. Any communication material should be clearly focused on the risk minimisation goals, and should not be confused or combined with promotional material for marketing campaigns. MAH should discuss risk minimisation plans with the Agency as early as is feasible when it is likely that specific risk minimisation activities will need to be adapted to the health care system.
- 3.125. Where possible and appropriate, proposed risk minimisation activities should be discussed with patients and healthcare professionals if it is likely that risk minimisation activities will be directed towards them.

Educational material

- 3.126. Any 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, where appropriate, it is piloted before releasing for use.
- 3.127. The final version of the educational material will need to be approved by the Agency who will check that the material contains the key

- elements in an appropriate design and format and is not promotional.
- 3.128. For public health reasons, marketing authorisation holders for the same active substance may be required by the Agency to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorisation holders are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material.

Format of risk minimisation plan(s)

- 3.129. 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.
- 3.130. For each safety concern, the following information should be provided:
- a. Objectives of the risk minimisation activities
 - b. Routine risk minimisation activities;
 - c. Additional risk minimisation activities (if any), individual objectives and justification of why needed;
 - d. How the effectiveness of each (or all) risk minimisation activities will be evaluated in terms of attainment of their stated objectives;
 - e. What the target is for risk minimisation, i.e. what are the criteria for judging success;
 - f. Milestones for evaluation and reporting.
- 3.131. For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC), or a précis, should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

Evaluation of the effectiveness of risk minimisation activities

- 3.132. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall benefit-risk balance is optimised.
- 3.133. When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable.
- 3.134. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when

available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place. The marketing authorisation holder should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

- 3.135. In certain cases it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive benefit-risk balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks.

Gap analysis

- 3.136. Where the safety data for a specific product is obtained from a different region, the MAH should include a gap analysis 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.

Summary of risk minimisation measures

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

Summary of activities in the risk management plan by medicinal product

- 3.138. A summary of the RMP for each medicinal product should be made publically available. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.
- 3.139. 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.

Format and content of the summary of the RMP

- 3.140. This is a scientific summary, written for the lay reader to fulfil the requirements in the regulation. In situations where the RMP covers more than one product, a separate section 3.137 to 3.138 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.
- 3.141. The summary of the sections 3.137 to 3.138 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;
 - e. Summary of risk minimisation activities by safety concern;
 - f. Planned post authorisation development plan;
 - g. Studies which are a condition of the marketing authorisation (see sections 3.98 and 3.106);
 - h. Major Changes to the Risk Management Plan over time.
- 3.142. The information provided in each section should be brief, focussed and in accordance with the word limits in the templates.

Overview of disease epidemiology

- 3.143. The marketing authorisation holder should summarise the epidemiology of the disease/condition the medicinal product is intended to treat or prevent (as presented in section 3.17 to 3.19) 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 emphasised and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy.
- 3.144. 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.

Summary of treatment benefits

3.145. This should consist of very concise 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.

Unknowns relating to treatment benefits

3.146. 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, race

Risk and organ impairment	What is known	Preventability
Risk 1		
Risk 2 etc		

Summary of safety concerns

3.147. 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
Risk 1	For important potential risks the reasons why it is thought 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 studied 3,761 people”.
Risk 2 etc	

3.149. For 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, use with caution.

Summary of risk minimisation activities by safety concern

3.150. Details of routine risk minimisation measures will be provided in the published summary by a link to the product information. For each

safety concern which has additional risk minimisation 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

Planned post-authorisation development plan

Study	Objectives	Safety concerns/efficacy issues addressed	Status	Planned date for submission of interim and final results
Study 1				
Study 2 etc				

3.151. Data should be presented in the form of a submission of planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from sections 3.98 and 3.106. 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

Studies which are a condition of the marketing authorisation

3.152. 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 marketing authorisation.”

Summary of changes to the risk management plan over time

3.153. 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 minimisation activities and the associated dates these changes were agreed. Since changes to risk minimisation activities involve a variation, the date used for changes to risk minimisation 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.

Annexes to the risk management

3.164. The RMP should contain the annexes listed below. RMP annexes 1 to 3, 10 and 11 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 issues in sections 3.80 to 3.101 of

the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

- a. RMP annex 1: Interface between RMP and National Data Base(electronic only)
- b. RMP annex 2: Current (or proposed if product is not authorised) summary of product characteristics (SmPC) and package leaflet.
- c. RMP annex 3: Worldwide marketing authorisation status by country. This should include:
 - i. Current licence status (approved/refused/ under review/ suspended/expired/withdrawn);
 - ii. D a t e (s) o f 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 forsection3.80 to 3.101
- k. RMP annex 10: Details of proposed additional risk minimisation activities (if applicable).
- l. RMP annex 11: Mock up examples in English of the material provided to healthcare
- m. professionals and patients
- n. RMP annex 12: Other supporting data (including referenced material).

Principles for assessment of risk management plans

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

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 medical practice?

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

the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?

- p. Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

Plans for post-authorisation studies on efficacy

- q. 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?
- r. Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product?

Risk minimisation measures

- s. Does the product information adequately reflect all important identified risks and missing information?
- t. 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 authorisation 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 minimisation activities appropriate and adequate?
- y. Have additional risk minimisation 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 minimisation activities well described and appropriate?
- aa. Have criteria for evaluating the success of additional risk minimisation activities been defined a priori?

Summary of the Risk Management Plan

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

- ee. audience?
- ee. Have all required formats been provided?

When an update is being assessed

- ff. Have 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) is needed?

Quality systems and record management

- 3.156. Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies with the marketing authorisation holder. As such the qualified person responsible for pharmacovigilance in Nigeria (QPPV) should be aware of, and have sufficient authority over the content. The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in Chapter 1.
- 3.157. The marketing authorisation holder should maintain records of when RMPs were submitted to the Agency and the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by the Agency.

CHAPTER

4 SAFETY COMMUNICATION

- 4.1. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicinal products, preventing harm from adverse reactions and contributing to the protection of patients' and public health. This section provides guidance to marketing authorisation holders on how to communicate and coordinate safety information in Nigeria.
- 4.2. Safety communication is a broad term covering different types of information on medicinal products, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging) and public assessment reports. This section focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicinal product which has or may have an impact on a medicinal product's benefit-risk balance and its condition of use. Unless otherwise stated, the term 'safety communication' should be read as referring to emerging safety information. High levels of public interest are anticipated when new safety concerns arise and it is important that clear and consistent messages are provided in a timely manner. Communication of important new safety information on medicinal products should take into account, the views and expectations of concerned parties, including patients and healthcare professionals.

Objectives of safety communication

- 4.3. Safety communication aims at:
- Providing timely, evidence-based information on the safe and effective use of medicinal products;
 - Facilitating changes to healthcare practices (including self-medication practices) where necessary;
 - Changing attitudes, decisions and behaviours in relation to the use of medicinal products;
 - Supporting risk minimisation behaviour;

- e. Facilitating informed decisions on the rational use of medicinal products.
- 4.4. In addition to the above, effective high quality safety communication can support public confidence in the regulatory system.

Principles of safety communication

- 4.5. The following principles of safety communication should be applied:
- a. The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and should be part of risk assessment.
 - b. There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. the Agency, other public bodies and marketing authorisation holders).
 - c. Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
 - d. Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.
 - e. Information on risks should be presented in the context of the benefits of the medicinal product and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.
 - f. Safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while the Agency is conducting its evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.
 - g. Information on competing risks such as the risk of non-treatment should be included where appropriate.

- h. The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the benefit-risk balance may also be used.
- i. Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly on complex safety concerns.
- j. Where relevant, safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
- k. The effectiveness of safety communication should be evaluated where appropriate and possible.
- l. Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

Target audiences

- m. The primary target audiences for safety communication issued by the Agency and marketing authorisation holders should be patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products. As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time. Patient, consumer and healthcare professional organisations can play a role as multipliers as they can disseminate important safety information to target audiences.
The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare

professionals and the general public is a critical element for amplifying new and important information on medicinal products. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the Agency in addition to the information they receive from other sources, such as from the marketing authorisation holders.

Content of safety communication

- 4.6. Safety communication should contain:
- a. Important emerging information on any authorised medicinal product which has an impact on the medicinal product's benefit-risk balance under any conditions of use;
 - b. The reason for initiating safety communication clearly explained to the target audience;
 - c. Any recommendations to healthcare professionals and patients on how to deal with a safety concern;
 - d. When applicable, a statement on the agreement between the marketing authorisation holder and the Agency on the safety information provided;
 - e. Information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
 - f. A list of literature references, when relevant or a reference to where more detailed information can be found; where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.
- 4.7. The information in the safety communication should not be misleading and should be presented objectively. Safety information should not include any material or statement which might constitute advertising.

Means of safety communication

- 4.8. Communication tools and channels have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below:

Direct healthcare professional communication (DHPC)

- 4.9. A direct healthcare professional communication (DHPC) is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or the Agency, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimisation activities. The preparation of DHPCs involves cooperation between the marketing authorisation holder and the Agency. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder. The agreement will cover both the content of the information and the communication plan, including the intended recipients and the timetable for disseminating the DHPC. Where there are several marketing authorisation holders of the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered. Whenever possible, it is advised that healthcare professionals' organisations or learned societies are involved as appropriate during the preparation of DHPCs to ensure that the information they deliver is useful and adapted to the target audience. A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply. A DHPC may be an additional risk minimisation measure as part of a risk management plan.
- 4.10. A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:
- a. Suspension, withdrawal or revocation of a marketing authorisation for safety reasons;
 - b. An important change to the use of a medicinal product due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
 - c. A restriction in availability or discontinuation of a medicinal product with potential detrimental effects on patient care.
- 4.11. Other situations where dissemination of a DHPC should be considered are:
- a. New major warnings or precautions for use in the product information;

- b. New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- c. Substantiated knowledge that the medicinal product is not as effective as previously considered;
- d. New recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;
- e. Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimise the potential risk). The Agency may disseminate or request the marketing authorisation holder to disseminate a DHPC in any situation where the Agency considers it necessary for the continued safe and effective use of a medicinal product.

Documents in lay language

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. Lay language documents should contain the Agency's recommendations and advice for risk minimisation for patients and healthcare professionals in relation to the safety concern, and should be accompanied by relevant background information.

Lay language documents are generally useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference should be made to other communication materials on the topic to direct readers to where they can find further information.

Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience. Where the marketing authorisation holder needs to communicate to the general public, information should also be communicated in pidgin language and the 3 major Nigerian languages.

Press communication

4.12. Press communication includes press releases and press briefings which are primarily intended for journalists. The Agency may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent

with the Agency's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system. Press releases may also be prepared and published by marketing authorisation holders. Their press releases may reflect the position of the marketing authorisation holder on a safety topic but should also make reference to any regulatory action taken by the Agency. Relevant ongoing reviews should be mentioned in any communication by the marketing authorisation holder.

- 4.13. Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic. In cases where a DHPC is also prepared, healthcare professionals should ideally receive it prior to or around the same time of the publication or distribution of a press release so that they are better prepared to respond to patients.

Website

- 4.14. A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. Marketing authorisation holders should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

Other web-based communications

- 4.15. Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should take into account emerging communication tools used by the various target audiences.

Bulletins and newsletters

- 4.16. Bulletins and newsletters provide at regular intervals new information about medicinal products and their safety and effectiveness. MAHs can reach a large audience with these tools by using web- based and other available means.

Responding to enquiries from the public

- 4.17. Marketing authorisation holders should have systems in place for responding to enquiries about medicinal products from individual members of the public. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by the Agency. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

Other means of communication

- 4.18. In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.
- 4.19. Some tools and channels may be used in the context of risk management; risk minimisation measures often include specific programmes for risk communication.

Effectiveness of safety communication

- 4.20. Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Adequate mechanisms should be introduced in order to measure the effectiveness of the communication based on clear objectives. Measuring effectiveness allows lessons to be learned and helps in making decisions on prioritising and adapting tools and practices to meet the needs of the target audiences. A research-based approach will normally be appropriate in order to establish that safety communications have met the standard set out under the principles of safety communication. This approach may measure different outcomes, including behaviour, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication.
- 4.21. In the case of DHPCs, the marketing authorisation holder should be responsible for evaluating the dissemination of the DHPCs they prepare and should inform the Agency of the outcome and of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action should be taken as needed to correct the situation or prevent similar

problems in the future.

Quality system requirements for safety communication

- 4.22. In accordance with the quality system requirements, procedures should be in place to ensure that safety communications comply with the principles of safety communication as appropriate.
- 4.23. In particular, the communications should be subject to quality controls to ensure their accuracy and clarity. For this purpose review procedures with allocated responsibilities should be followed and documented.

CHAPTER

5 ADVERSE REACTION REPORTING

- 5.1. This chapter addresses the requirements for marketing authorisation holders as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in Nigeria. Non-serious reports are to be submitted to the Agency as ICSRs within 90 days.

Structures and processes

- 5.2. This section highlights the general principles in relation to the collection, recording and reporting of reports of suspected adverse reactions associated with medicinal products for human use as it concerns the marketing authorisation holders.

Collection of reports

- 5.3. The marketing authorisation holder should take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources. The pharmacovigilance system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.
- 5.4. The system should ensure the collection and recording of all reports of suspected adverse reactions brought to its attention by health care professionals or consumers or occurring in the context of post-authorisation study. Marketing authorisation holders should not refuse to consider reports of suspected adverse reactions received from patients and healthcare professionals.
- 5.5. Marketing authorisation holders should establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with data protection principles. Pharmacovigilance data and documents relating to individual authorised medicinal products should be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist.
- 5.6. With regards to the collection and recording of reports of suspected adverse reactions, marketing authorisation holders responsibilities apply to reports related to medicinal products for which ownership

cannot be excluded on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration.

- 5.7. The marketing authorisation holder shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products authorised in Nigeria, is brought to its attention by any company outside the country belonging to the same mother company (or group of companies). The same applies to the marketing authorisation holder when having concluded a commercial agreement with a company outside Nigeria for one of its medicinal product authorised in the country. The clock for reporting (see sections 5.61 to 5.64) starts when a valid ICSR is first received by one of these companies outside the country.
- 5.8. All notifications that contain pharmacovigilance data should be recorded and archived in compliance with the applicable data protection requirements of the Agency.

Unsolicited reports

Spontaneous reports

- 5.9. A spontaneous report is an unsolicited communication by a healthcare professional, or consumer that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection systems where adverse events reporting is actively sought.
- 5.10. Stimulated reporting that occurs consequent to a direct healthcare professional communication, publication in the press, questioning of healthcare professionals by company representatives, communication from patients' organisations to their members, or class action lawsuits should be considered spontaneous reports.
- 5.11. Unsolicited consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent “medical confirmation”.
- 5.12. Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside Nigeria, which are brought to their attention spontaneously by healthcare professionals, or consumers. In this context, marketing authorisation holders may consider utilising their websites to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details for direct communication.

Literature reports

- 5.13. The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the benefit-risk balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties. In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the Agency as appropriate.
- 5.14. Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by marketing authorisation holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorisation studies.
- 5.15. If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered by the concerned marketing authorisation holder(s).
- 5.16. One case should be created for each single patient identifiable based on characteristics provided in sections 5.74 to 5.80. Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).

Reports from other sources

- 5.17. If a marketing authorisation holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. The same reporting time frames should be applied as for other spontaneous reports.

Information on suspected adverse reactions from the internet or digital media

- 5.18. Marketing authorisation holders should regularly screen internet or digital mediasections 5.9 to 5.12) including VigiBase under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorisation holder. The frequency of the screening should allow for potential valid ICSRs to be reported to the Agency within the appropriate reporting timeframe. Marketing authorisation holders may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions.
- 5.19. If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting.
- 5.20. Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied (seesection5.61 to 5.64).
- 5.21. In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

Solicited reports

- 5.22. Solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous.
- 5.23. For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they refer to suspected adverse reactions and therefore meet the criteria for reporting.

MAH initiated post-authorisation studies

- 5.24. Marketing authorisation holders should record all reports of suspected adverse reactions originating from within or outside Nigeria, which occur in post-authorisation studies, initiated, managed, or financed by them. For all solicited reports (see sections 5.22 to 5.23), marketing authorisation holders should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, in order to allow meaningful assessment of individual cases and reporting of valid ICSRs (see sections 5.74 to 5.80) related to the studied (or supplied) medicinal product. Marketing authorisation holders should therefore exercise due diligence in establishing such system, in following-up those reports (see section 5.81 to 5.86) and in seeking the view of the primary source as regard the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the marketing authorisation holder should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR, which should be reported to the Agency. This requirement does not apply to study designs based on secondary use of data since reporting of ICSRs is not required.

Adverse Reaction Reports from Post-Registration Studies

- 5.25. MAHs should report all known serious suspected ARs occurring in post-registration studies undertaken in Nigeria, of which the MAH is aware, in accordance with reporting time frames for serious ARs. MAHs should have mechanisms in place to collect full and comprehensive case information and to evaluate that information in order to allow meaningful assessment of individual cases and reporting of valid ARs related to the studied (or supplied) medicine.
- 5.26. MAHs should therefore exercise due diligence in establishing such a system; in following up those reports; and in seeking the view of the primary source with regard to the causal role of the studied (or supplied) medicine in the notified AE. Where the primary source's opinion as to the causal role is missing, the MAH should exercise its own judgement based on the information available in order to decide whether the report is a valid AR that must be reported to the Agency in accordance with the requirements described in this document.
- 5.27. In instances where the post-registration study is conducted or initiated by an investigator, independent of the MAH of the medicine, the responsibility for reporting ARs to the Agency rests with the

investigator. However, if the MAH is aware of the study, the MAH should request that it is notified by the investigator of serious ARs that occur in the study. Where a MAH becomes aware of such ARs, they must ensure that the ARs are reported in accordance with the requirements described in this document.

Reports from other Post-Marketing Initiatives: Surveys, Registries etc.

- 5.28. MAHs may be involved in post-marketing initiatives that result in the collection of information related to their products such as patient support and disease management programs, surveys of patients or healthcare providers, information gathering on efficacy or patient compliance, market research programs and voluntary patient registries. These activities may involve the receipt of information on AEs.
- 5.29. MAHs should have in place a system to collect full and comprehensive case information and to evaluate that information in order to determine whether the collected AEs are possibly related to the studied (or supplied) medicine. If so, they should be classified and processed as suspected ARs and are subject to the reporting requirements described in this document.

Special situations

Use of a medicinal product during pregnancy or breastfeeding

Pregnancy

- 5.30. Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.
- 5.31. Not infrequently, pregnant women or healthcare professionals will contact either competent the marketing authorisation holder to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicinal product exposure to an embryo or foetus and to follow-up on the outcome of the pregnancy.
- 5.32. Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the

- exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.
- 5.33. Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in sections 5.61 to 5.64.
- 5.34. This especially refers to:
- Reports of congenital anomalies or developmental delay, in the foetus or the child;
 - Reports of foetal death and spontaneous abortion; and
 - Reports of suspected adverse reactions in the neonate that are classified as serious.
- 5.35. Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported since there is no suspected adverse reaction. These reports should however be collected and discussed in the periodic safety update reports (see Chapter 6).
- 5.36. However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be reported. This may be a condition of the marketing authorisation or stipulated in the risk management plan; for example pregnancy exposure to medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin).
- 5.37. A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the Agency.

Breastfeeding

- 5.38. Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported to the Agency.

Use of a medicinal product in a paediatric or elderly population

- 5.39. The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular

- population.
- 5.40. As regards the paediatric population, the guidance published by the Agency on the conduct of pharmacovigilance in this population should be followed.

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

- 5.41. For the purpose of these guidelines, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or consumer.
- 5.42. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable. When those reports constitute safety issues impacting on the benefit-risk balance of the medicinal product, they should be notified to the Agency in accordance with the recommendations provided in section 5.54.
- 5.43. Reports associated with suspected adverse reactions should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

Lack of therapeutic efficacy

- 5.44. Reports of lack of therapeutic efficacy should be reported within 15 calendar days and followed-up if incomplete unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product.
- 5.45. Clinical judgment should be used when reporting cases of lack of therapeutic efficacy. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be reported within 15 days.
- 5.46. For vaccines, cases of lack of immunogenic effect should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of immunogenic effect by a

healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate. General guidance regarding the monitoring of vaccine failure, provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, may be followed.

Suspected adverse reactions related to quality defect or falsified medicinal products

- 5.47. When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product or quality defect of a medicinal product, a valid ICSR should be reported. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions in accordance with the definitions provided in the glossary.
- 5.48. In addition, in order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product from the market. Therefore, marketing authorisation holders should have a system in place to ensure that reports of suspected adverse reactions related to falsified medicinal products or to quality defects of medicinal products are investigated in a timely fashion and that confirmed quality defects are notified separately to the Agency.

Suspected transmission via a medicinal product of an infectious agent

- 5.49. For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 days. This also applies to vaccines. If no other criterion is applicable, the seriousness of this ICSR should be considered as important medical event.
- 5.50. In the case of medicinal products derived from human blood or human plasma, haemovigilance procedures may also apply. Therefore the marketing authorisation holder should have a system in place to communicate suspected transmission via a medicinal product of an infectious agent to the manufacturer, the relevant blood establishment(s) and the Agency. Any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an

- infectious agent.
- 5.51. A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product. Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.
 - 5.52. In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g. injection/ administration) and the source (e.g. contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccinee).
 - 5.53. Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in 5.47-5.48 should be applied.

Emerging safety issues

- 5.54. Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known benefit-risk balance of a medicinal product and/or impact on public health. These events/observations, which may affect the benefit-risk balance of a medicinal product, are not to be submitted as ICSRs. They should be notified as emerging safety issues in writing to the Agency immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the concerned medicinal product. Those safety issues should also be analysed in the relevant sections of the periodic safety update report of the authorised medicinal product.

Period between the submission of the marketing authorisation application and the granting of the marketing authorisation

- 5.55. In the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, information (quality, non-clinical, clinical) that could impact on the benefit-risk balance of the medicinal product under evaluation may

become available to the applicant (see section 5.54). It is the responsibility of the applicant to ensure that this information is immediately submitted to the Agency.

Period after suspension, revocation or withdrawal of marketing authorisation

- 5.56. The marketing authorisation holder shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorisation. Where a marketing authorisation is withdrawn or revoked, the former marketing authorisation holder is encouraged to continue to collect spontaneous reports of suspected adverse reactions originating within the country to facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

Period during a public health emergency

- 5.57. A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Federal Ministry of Health. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the Agency website.

Reports from patient support programmes and market research programmes

- 5.58. A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imbursment schemes.
- 5.59. A market research programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.
- 5.60. Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (see sections 5.22 to 5.23) to manage that information and

report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product.

Reporting of Individual case safety reports (ICSRs)

- 5.61. Only valid ICSRs (see sections 5.74 to 5.80) should be reported. The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero. It is the first day when a receiver gains knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. Reporting timelines are based on calendar days.
- 5.62. Where the marketing authorisation holder has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the marketing authorisation holder and the person/organisation to ensure that the marketing authorisation holder can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the Agency.
- 5.63. For ICSRs described in the scientific and medical literature (see sections 5.13 to 5.16), the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organisation to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the marketing authorisation holder can comply with the reporting obligations.
- 5.64. When additional significant information is received for a previously reported case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow-up information. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case or could change its seriousness criteria; non-significant information includes updated comments on the case assessment or

corrections of typographical errors in the previous case version.

Reporting time frames

Serious Adverse Reactions

- 5.65. The marketing authorization holder (MAH) and other persons authorized to distribute medicinal products should keep records of all suspected serious adverse reactions which have occurred in Nigeria and brought to his attention and report same to the Agency not later than fifteen (15) days following the receipt of information.
- 5.66. All serious ARs must be reported as soon as possible and in no case later than fifteen (15) calendar days from receipt by the MAH. The clock for serious ARs starts (as day 0) on the day that the four minimum data elements in relation to the AR report are received.
- 5.67. The reporting time clock is considered to begin again when a MAH receives additional clinical or medically relevant information for a previously reported serious AR. This information must be reported as soon as possible and in no case later than fifteen (15) calendar days after receipt of the additional information.
- 5.68. If MAH receives additional information about a case initially classified as non-serious that indicates the case should be re-classified (e.g. from non-serious to serious), the MAH must report the case as soon as possible, and in no case later than 15 calendar days after receipt of the information that led to the change in classification.
- 5.69. For suspected serious AR cases occurring in Nigeria that are identified through screening the worldwide literature, the clock starts (day zero) when the MAH becomes aware of a publication containing the four minimum data elements. It is preferable that a copy of the relevant published article (in English or an English summary/translation) is provided to the Agency at the time the initial AR report is made. However, if the article is not available at this time, it must be provided to the Agency within 15 calendar days of submission of the AR report. Where difficulty is experienced in meeting the 15 calendar days requirement for submission of the article, the Agency must be notified in writing prior to the 15 day period ending.
- 5.70. The marketing authorization holder (MAH) should report to the Agency any action relating to their product safety that has been taken by a regulatory authority outside Nigeria, including the basis for such action, not later than three (3) working days of first knowledge.

Reporting timeframes for significant safety issues

- 5.71. Any significant safety issues identified by the MAH must be reported to the Agency within 72 hours. The 72-hour clock starts from the time of awareness of the issue by any personnel of the MAH. This is considered to have occurred when the MAH's review and analysis has been completed and a conclusion is drawn that a significant safety issue, or when the MAH becomes aware of the actions of an overseas regulatory authority.
- 5.72. These situations are different from the reporting of individual ARs, where the MAH is allowed up to 15 days to confirm and follow-up details before submitting an individual serious AR report to the

Type of ADR Report	Time frame for reporting	Format
TABLE 5.1 SUMMARY OF REPORTING REQUIREMENTS		
Post-Registration ADR Reports (registered medicinal products)		
Update (spontaneous/ published/ study): Serious (expected and unexpected)	15 days	ADR form #
Non serious (unexpected)	15 days	ADR form #
Non serious (expected)	Within 90 days	ADR form #
Foreign Reports (spontaneous/ published/ study): Serious	On request or relating to specific safety issue	As appropriate
Notification of Change in Nature, Severity or Frequency or Risk factors	15 days	Detailed report (including publications)
New information impacting on benefit-risk profile of product including international regulatory decisions	3 days	Detailed report (including publications)

Applicant's in-house ADR report form or NAFDAC/NPC ADR report form.

Reporting format

- 5.73. All adverse reactions should be reported using the adverse reaction reporting form available from the Agency. The MAH may use their in-house reporting forms, provided all the necessary data elements are included in the form in a legible format. Discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data should be attached.

- 5.74. Electronic submissions may also be required by the Agency using the ICH-E2B format for electronic reporting or any other format prescribed by the Agency.

Validation of reports

- 5.75. Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the Agency to make sure that the minimum criteria for reporting are included in the reports (see ICH-E2D). These are:
- a. One or more identifiable reporter (primary source), characterised by qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional) name, initials or address. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid providing the organisation who was informed of the case was able to confirm it directly with the reporter. All parties providing case information or approached for case information should be identifiable, not only the initial reporter.
 - b. One single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible.
 - c. One or more suspected substance/medicinal product (see the glossary).
 - d. One or more suspected adverse reaction (see the glossary). If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the MAH agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete. The report does not also qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information provided on the type of adverse reaction experienced. Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing

authorisation holder is made aware that a patient was hospitalised or died, without any further information. In this particular situation, medical judgment should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and reported.

- 5.76. The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. The marketing authorisation holder is required to exercise due diligence in following up the case to collect the missing data elements. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.
- 5.77. When collecting reports of suspected adverse reactions via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient (see sections 5.18 to 5.21).
- 5.78. When the marketing authorisation holder is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR.
- 5.79. A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) disagrees with the consumer's suspicion. In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR.
- 5.80. For solicited reports of suspected adverse reactions (see section 5.22 to 5.23), where the receiver disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of non-related adverse event. The opinions of both, the primary source and the receiver, should be recorded in the ICSR.
- 5.81. The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the MAH disagrees with the seriousness reported by the primary source.

Follow-up of reports

- 5.82. When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information (see section 5.74 to 5.80). Any attempt to obtain follow-up information should be documented.
- 5.83. Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern. The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy.
- 5.84. When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer, has been confirmed (totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR.
- 5.85. For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number.
- 5.86. Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.
- 5.87. Staff directly performing pharmacovigilance activities, should be appropriately trained in applicable pharmacovigilance legislation and

guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

Data management

- 5.88. Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence.
- 1.17. In order to ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorised personnel only. This security extends to the complete data path. In this aspect, procedures should be implemented to ensure security and non-corruption of data during data transfer.
- 5.89. When transfer of pharmacovigilance data occurs within an organisation or between organisations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.
- 5.90. Correct data entry, including the appropriate use of terminologies, should be verified by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed.
- 5.91. Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it.
- 5.92. Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.
- 5.93. A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports.

Quality management

- 5.94. The marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving (see Chapter I). Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (e.g. letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.
- 5.95. Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.
- 5.96. Personnel directly performing pharmacovigilance activities, should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

CHAPTER

6 PERIODIC SAFETY UPDATE REPORTS

- 6.1. Periodic safety update reports (PSURs) are pharmacovigilance documents providing evaluation of the **benefit-risk balance** of a medicine. Marketing-authorisation holders must submit PSURs at defined time points following a medicine's authorisation. PSURs summarise data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine, both in its authorised uses and in unauthorised uses.
- 6.2. The Agency uses the information in PSURs to determine if there are **new risks identified** for a medicine or whether the balance of benefits and risks of a medicinal product has changed. It can then decide if further investigations need to be carried out or can take action to protect the public from the risks identified, such as updating the information provided for healthcare professionals and patients.

The scope, objectives, format and content of the PSUR

- 6.3. The dates of submission according to the specified frequency shall be calculated from the date of the authorisation. Periodic safety update reports shall be submitted to the Agency immediately upon request or in accordance with the following:
 - 6.1.4. Where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;
 - 6.5. Where a medicinal product has been placed on the market, the following periodicity shall apply;
 - 6.6. For new drug molecules, at least every six (6) months for the first two (2) years, annually for the following three (3) years, and every five (5) years, at the time of renewal of license.
 - 6.7. For products already being marketed elsewhere, existing periodic safety update reports shall be submitted to the Agency not later than thirty (30) days after submission of documents requesting for marketing authorization in Nigeria.
 - 6.8. For listed medicinal products (provisional registration), the marketing authorization holder shall submit a periodic safety update report every six (6) months for the two (2) year listing period.

- 6.9. Each marketing authorisation holder should be responsible for submitting PSURs for its own products to the Agency according to the following timelines:
 - a. Within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
 - b. Within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;
- 6.10. The timeline for the submission of ad hoc PSURs requested by the Agency will normally be specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar days of the data lock point.
- 6.11. The obligations imposed in respect of PSURs should be proportionate to the risks posed by the medicinal product. PSUR reporting should therefore be linked to the risk management systems of a medicinal product (see chapter 3).
- 6.12. The holder of marketing authorisation for the following medicinal products shall only submit periodic safety update reports for such medicinal products in the following cases:
 - a. A reference medicinal product which is or has been authorised for not less than eight years in Nigeria
 - b. The active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety
 - c. Homeopathic medicinal products
 - d. Herbal medicinal products
 - e. Where such obligation has been laid down as a condition in the marketing authorisation
 - f. When requested by the Agency on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

Structures and processes

Objectives

- 6.13. The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the benefit-risk balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. The PSUR is

- therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.
- 6.14. For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicinal product in everyday medical practice and long term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trial. A different benefit-risk balance may emerge as pharmacovigilance reveals further information about safety. The marketing authorisation holder should therefore re-evaluate the benefit-risk balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management (see Chapter 3) to facilitate optimisation of the benefit-risk balance through effective risk minimisation.
- 6.15. Urgent safety information should be reported through the appropriate mechanism. A PSUR is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide the means by which new safety issues are detected. It is acknowledged that the review of the data in the PSUR may lead to new safety issues being identified.

Principles for the evaluation of the benefit-risk balance within PSURs and scope of the information to be included

Principles

- 6.16. Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimisation.
- 6.17. After a marketing authorisation is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long term use, to confirm that the benefit-risk balance remains favourable.
- 6.18. The analysis of the benefit-risk balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available, with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.
- 6.19. The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorised indications and use which is not in line with the product information. If use of the medicinal product is

identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation data, information from spontaneous reports and publications in the literature.

Scope:

- 6.20. The scope of the benefit information should include both clinical trial and real world data in authorised indications.
- 6.21. The integrated benefit-risk evaluation should be performed for all authorised indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorised indications).
- 6.22. The evaluation should involve:
 - a. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.
 - b. Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the benefit-risk balance of the medicinal product.
 - c. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information.
 - d. Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation actions that are planned to be implemented.
 - e. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

Principles for the preparation of PSURs

- 6.23. Unless otherwise specified by the Agency, the marketing authorisation holder should prepare a single PSUR for all its medicinal products

containing the same active substance with information covering all the authorised indications, route of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, should be presented in a separate section of the PSUR and any safety concerns should be addressed accordingly. There might be exceptional scenarios where the preparation of separate PSURs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the Agency preferably at the time of authorisation.

- 6.24. Case narratives should be provided in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern. In this context, the term “case narratives” refers to clinical evaluations of individual cases rather than the CIOMS narratives.
- 6.25. When data received at the marketing authorisation holder from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorisation holder's product information, these data should be included and discussed in the PSUR.
- 6.26. The format and table of contents of all PSURs should be as described in (sections 6.38 to 6.46). Each report should include interval as well as cumulative data.

Reference information

- 6.27. Risk minimisation activities evaluated in the PSUR include updates to the product information.
- 6.28. The reference product information for the PSUR should include “core safety” and “authorised indications” components. In order to facilitate the assessment of benefit and benefit-risk balance by indication in the evaluation sections of the PSUR, the reference product information document should list all authorised indications.
- 6.29. The basis for the benefit evaluation should be the important baseline efficacy and effectiveness information summarised in the PSUR sections 6.145 to 6.147 (“Important baseline efficacy and effectiveness information”).
- 6.30. Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.

- 6.31. The following possible options can be considered by the marketing authorisation holders when selecting the most appropriate reference product information for a PSUR:
- 6.32. Company core data sheet (CCDS)
- a. It is common practice for marketing authorisation holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorised indications for which benefit is evaluated.
 - b. When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR.

Other options for the reference product information

- 6.33. When no CCDS or CCSI exist for a product (e.g. established/generic products on the market for many years), the marketing authorisation holder should clearly specify the reference information being used.
- 6.34. Where the reference information for the authorised indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR (see sections 6.168).
- 6.35. The marketing authorisation holder should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PSUR section 6.55 (“Changes to the reference safety information”) and where relevant, discussed in PSUR section 6.115 (“Signal and risk evaluation”). These changes may include:
- a. Changes to contraindications, warnings/precautions sections;
 - b. Addition to adverse reactions and interactions;
 - c. Addition of important new information on use in overdose; and

- d. Removal of an indication or other restrictions for safety or lack of efficacy reasons.
- 6.36. The marketing authorisation holder should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) as an appendix to the PSUR (see 6.169). The reference product information should be dated and version controlled.
- 6.37. Where new information on safety that could warrant changes to the authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section 6.103 (“Late-breaking information”).

Format and contents of the PSUR

- 6.38. The PSUR should be based on all available data including those generated from within Nigeria and should focus on new information which has emerged since the data lock point of the last PSUR. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment.
- 6.39. Because clinical development of a medicinal product frequently continues following marketing authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate.
- 6.40. The PSUR should provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation.
- 6.41. Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:
- a. Non-clinical studies;
 - b. Spontaneous reports (e.g. on the marketing authorisation

- holder's safety database);
 - c. Active surveillance systems (e.g. sentinel sites);
 - d. Investigations of product quality;
 - e. Product usage data and drug utilisation information;
 - f. Clinical trials, including research in unauthorised indications or populations;
 - g. Observational studies, including registries;
 - h. Patient support programs;
 - i. Systematic reviews and meta-analysis;
 - j. Marketing authorisation holders sponsored websites;
 - k. Published scientific literature or reports from abstracts, including information presented at scientific meetings;
 - l. Unpublished manuscripts;
 - m. Licensing partners, other sponsors or academic institutions and research networks;
 - n. Competent authorities (worldwide).
- 6.42. The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorisation holder to present safety, efficacy and effectiveness information in the PSUR and to evaluate the benefit-risk balance, as appropriate to the product and its known and emerging important benefits and risks. A list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.
- 6.43. The PSUR should be prepared following the format in section 6.38.
- 6.44. Sources of information include data regarding the active substance(s) included in the medicinal product, or the medicinal product that the marketing authorisation holder may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or benefit-risk balance. It is therefore recognised that while the same format should be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the marketing authorisation holder. For example, for a marketing authorisation holder sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the marketing authorisation holder, only the published report may be accessible.
- 6.45. The level of detail provided in certain sections of the PSUR should depend on known or emerging important information on the

medicinal product's benefits and risks. This approach is applicable to those sections of the PSUR in which there is evaluation of information about safety, efficacy, effectiveness, safety signals and benefit-risk balance.

- 6.46. When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on Periodic Benefit-Risk Evaluation Report (PBRER) should also be applied. Guidance on the titles, order and content of the PSUR sections is provided in sections 6.47 to 6.168. When no relevant information is available for any of the sections, this should be stated.

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Part 1

Title page

- 1.1. The title page should include the following;
 - a. Name of the medicinal product(s) and substance;
 - b. International birth date (IBD) (the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world);
 - c. Date of first registration in Nigeria
 - d. Reporting interval;
 - e. Date of the report;
 - f. Marketing authorisation holder details;
 - g. Statement of confidentiality of the information included in the PSUR.
 - h. Signature of QPPV.

Part 2

Executive summary

- 1.2. An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR and should contain the following information:
 - a. Introduction and reporting interval;
 - b. Medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
 - c. Estimated cumulative clinical trials exposure;
 - d. Estimated interval and cumulative exposure from marketing experience;
 - e. Number of countries in which the medicinal product is authorised;
 - f. Summary of the overall benefit-risk analysis evaluation (based on sections 6.158 to 6.161 “Benefit-risk analysis evaluation” of the PSUR);
 - g. Actions taken and proposed for safety reasons, (e.g. significant changes to the reference product information, or other risk minimisation activities);
 - h. Conclusions.

Part 3

Table of contents

- 1.3. The executive summary should be followed by the table of contents.

Introduction

- 1.4. The marketing authorisation holder should briefly introduce the product(s) so that the PSUR “stands alone” but it is also placed in perspective relative to previous PSURs and circumstances. The introduction should contain the following information:
- a. International birth date (IBD), and reporting interval;
 - b. Medicinal product(s), therapeutic class(es), mechanism(s) of action, authorised indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
 - c. Brief description of the population(s) being treated and studied;

Worldwide marketing authorisation status

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

Actions taken in the reporting interval for safety reasons

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

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

Changes to reference safety information

- 1.9. This PSUR section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR.

Estimated exposure and use patterns

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

Cumulative subject exposure in clinical trials

- 1.13. This section of the PSUR should contain the following information on the patients studied in clinical trials sponsored by the marketing authorisation holder, if applicable presented in tabular formats:
 - a. Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the Development International Birth Date (DIBD). It is recognised that for “old products”, detailed data might not be available;
 - b. More detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex,

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

1.14. Provide examples in a tables for the estimated exposure in clinical trials.

Cumulative and interval patient exposure from marketing experience

1.15. Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR). Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may

be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

- 1.16. The data should be presented according to the following categories:
- a. Post-authorisation (non-clinical trial) exposure:
 - i. An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment. When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.
 - b. Post-authorisation use in special populations:
 - i. Where post-authorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include for instance non-interventional studies designed to obtain this information, including registries. Other sources of information may include data collection outside a study environment including information collected through spontaneous reporting systems (e.g. information on reports of pregnancy exposure without an associated adverse event may be summarised in this section). Populations to be considered for discussion include, but might not be limited to:
 - Paediatric population;
 - Elderly population;
 - Pregnant or lactating women;
 - Patients with hepatic and/or renal impairment;
 - Patients with other relevant co-morbidity;
 - Patients with disease severity different from that studied in clinical trials;
 - Sub-populations carrying relevant genetic polymorphism(s);
 - Populations with specific racial and/or ethnic origins.
 - c. Other post-authorisation use:
 - I. If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data,

provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without reference to adverse reactions should be summarised in this section as applicable. Such information may be received via spontaneous reporting systems, medical information queries, customer's complaints, screening of digital media or via other information sources available to the marketing authorisation holder. If quantitative information on use is available, it should be provided.

- ii. If known, the marketing authorisation holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information may be linked to clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorisation holder should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR (e.g. authorised indication, route of administration, contraindications).
- iii. Signals or risks identified from any data or information source should be presented and evaluated in the relevant sections of the PSUR.

1.17. Insert tables for the estimated exposure from marketing experience.

Data in summary tabulations

1.18. The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, the competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the marketing authorisation holder graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

- 1.19. When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations.
- 1.20. The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A9. When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSURs.

Reference information

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

Cumulative summary tabulations of serious adverse events from clinical trials

- 1.22. This PSUR section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorisation holder's clinical trials, from the DIBD to the data lock point of the current PSUR. The marketing authorisation holder should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables.
- 1.23. This section should not serve to provide analyses or conclusions based on the serious adverse events.
- 1.24. The following points should be considered:
 - a. Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the

summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.

- b. In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.
 - c. The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and marketing authorisation holders should not unblind data for the specific purpose of preparing the PSUR.
 - d. Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).
- 1.25. Provide tables of the summary of serious adverse events from clinical trials.

Cumulative and interval summary tabulations from post-marketing data sources

- 1.26. This section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The

table should be organised by MedDRA SOC (listed in the internationally agreed order).

- 1.27. For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.
- 1.28. As described in ICH-E2D11 guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.
- 1.29. Analysis or conclusions based on the summary tabulations should not be provided in this PSUR section.
- 1.30. Provide summary tables of adverse drug reactions from post-marketing data sources.

Summaries of significant findings from clinical trials during the reporting interval

- 1.31. This PSUR section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the marketing authorisation holder's sponsored clinical trials during the reporting interval, from the sources specified in the sections listed below. When possible and relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and region should be presented.
- 1.32. Signals arising from clinical trial sources should be tabulated in PSUR section 15 (“Overview on signals: new, ongoing or closed”). Evaluation of the signals, whether or not categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR section 6.122 to 6.127 (“Signal evaluation”). New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in PSUR sections 6.128 to 6.134 (“Evaluation of risks and new information”) and sections 6.135 to 6.138 (“Characterisation of risks”) respectively.
- 1.33. Findings from clinical trials not sponsored by the marketing authorisation holder should be described in the relevant sections of the PSUR.
- 1.34. When relevant to the benefit-risk evaluation, information on lack of

efficacy from clinical trials for treatments of non-life-threatening diseases in authorised indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness should be summarised in section 6.102 (“Lack of efficacy in controlled clinical trials”).

- 1.35. Information from other clinical trials/study sources should be included in the PSUR section 6.93 (“other clinical trials”).
- 1.36. In addition, the marketing authorisation holder should include an appendix listing the sponsored post-authorisation interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal products that were completed or ongoing during the reporting interval. The listing should include the following information for each trial:
 - a. Study ID (e.g. protocol number or other identifier);
 - b. Study title (abbreviated study title, if applicable);
 - c. Study type (e.g. randomised clinical trial, cohort study, case-control study);
 - d. Population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);
 - e. Study start (as defined by the marketing authorisation holder) and projected completion dates;
 - f. Status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

Completed clinical trials

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

Ongoing clinical trials

- 1.38. If the marketing authorisation holder is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes

previously identified safety concerns, as well as evidence of new safety signals.

Long term follow-up

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

Other therapeutic use of medicinal product

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

New safety data related to fixed combination therapies

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

Findings from non-interventional studies

- 1.43. This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions.
- 1.44. The marketing authorisation holder should include an appendix listing

marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval. (see sections 6.77 to 6.82). for the information that should be included in the listing).

- 1.45. Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR (see section 6.168).
- 1.46. Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PSUR. As for other information sources, the marketing authorisation holder should present signals or risks identified from such information in the relevant sections of the PSUR.

Information from other clinical trials and sources

Other clinical trials

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

Medication errors

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

Non-clinical data

- 1.49. This PSUR section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or

immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns should be included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR.

Literature

- 1.50. This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.
- 1.51. Literature searches for PSURs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.
- 1.52. The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:
 - a. Pregnancy outcomes (including termination) with no adverse outcomes;
 - b. Use in paediatric populations;
 - c. Compassionate supply, named patient use;
 - d. Lack of efficacy;
 - e. Asymptomatic overdose, abuse or misuse;
 - f. Medication error where no adverse events occurred;
 - g. Important non-clinical safety results.
- 1.53. If relevant and applicable, information on other active substances of the same class should be considered. The publication reference should be provided in the style of the Vancouver Convention.

Other periodic reports

- 1.54. This PSUR section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the Agency. In general, the marketing authorisation holder should prepare a single PSUR for a single active substance (unless otherwise specified by the Agency); however if multiple PSURs are prepared for a single medicinal product, this section should also summarise significant findings from other PSURs if they are not presented elsewhere within the report.

- 1.55. When available, based on the contractual agreements, the marketing authorisation holder should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, other marketing authorisation holders or other contractual partners).

Lack of efficacy in controlled clinical trials

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

Late-breaking information

- 1.57. The marketing authorisation holder should summarise in this PSUR section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the marketing authorisation holder, a data monitoring committee, or any competent authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR (e.g. a well-documented case of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).
- 1.58. Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR (see sections 6.27 to 6.32).
- 1.59. The data presented in this section should also be taken into account in the evaluation of risks and new information (see sections 6.128-6.134).

Overview of signals: new, ongoing, or closed

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

evaluation at the end of the reporting interval. For the purposes of the PSUR, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorisation holder. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicinal product/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide).

- 1.61. Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data, which is presented in sections 6.115 to 6.117 “Signal and risk evaluation” of the PSUR.
- 1.62. A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR.
- 1.63. Examples of new signals would therefore include new information on a previously:
 - a. Close and refuted signal, which would result in the signal being re-opened.
 - b. Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well-documented case report of agranulocytosis with no presence of possible alternative causes is received).
 - c. Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
 - d. Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

- 1.64. Within this section or as an appendix the marketing authorisation holder should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:
- a. A brief description of the signal;
 - b. Date when the marketing authorisation holder became aware of the signal;
 - c. Status of the signal at the end of the reporting interval (close or ongoing);
 - d. Date when the signal was closed, if applicable;
 - e. Source of the signal;
 - f. A brief summary of the key data;
 - g. Plans for further evaluation; and
 - h. Actions taken or planned.
- 1.65. Provide tables of signals.
- 1.66. The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in sections 6.122 to 6.127 (“Signal evaluation”) of the PSUR.
- 1.67. Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in PSUR sections 6.128 to 6.134 (“Evaluation of risks and new information”).
- 1.68. When any competent authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR, the marketing authorisation holder should summarise the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sections 6.122 to 6.127 (“Signal evaluation”).

Signal and risk evaluation

- 1.69. The purpose of this section of the PSUR is to provide:
- a. A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report (sections 6.118 to 6.121).
 - b. An evaluation of all signals closed during the reporting interval (6.123 to 6.128)
 - c. An evaluation of new information with respect to previously recognised identified and potential risks (sections 6.128 to

- d. 6.134). An updated characterisation of important potential and identified risks, where applicable (section 6.135 to 6.138).
 - e. A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (sections 6.139 to 6.143).
- 1.70. The information on signals and risks should be mapped in a flow chart.
- 1.71. These evaluation sections should not summarise or duplicate information presented in previous sections of the PSUR but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided (see sections 6.23 to 6.26).

Summary of safety concerns

- 1.72. The purpose of this section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary that is current at the start of the reporting interval of the PSUR. It should provide the following safety information:
- a. Important identified risks;
 - b. Important potential risks; and
 - c. Missing information.
- 1.73. The following factors should be considered when determining the importance of each risk:
- a. Medical seriousness of the risk, including the impact on individual patients;
 - b. Its frequency, predictability, preventability, and reversibility;
 - c. Potential impact on public health (frequency; size of treated population); and
 - d. Potential for avoidance of the use of a medicinal product with a preventive benefit due to a disproportionate public perception of risk (e.g. vaccines).
- 1.74. For products without an existing safety specification, this section

should provide information on the important identified and potential risks and missing information associated with use of the product, based on pre- and post-authorisation experience. Important identified and potential risks may include, for example:

- a. Important adverse reactions;
 - b. Interactions with other medicinal products;
 - c. Interactions with foods and other substances;
 - d. Medication errors;
 - e. Effects of occupational exposure; and
 - f. Pharmacological class effects.
- 1.75. The summary on missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

Signal evaluation

- 1.76. This section of the PSUR should summarise the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this section are:
- a. Those signals that, following evaluation, have been refuted as “false” signals based on medical judgement and scientific evaluation of the currently available information.
 - b. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.
- 1.77. For both categories of closed signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the marketing authorisation holder.
- 1.78. It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:
- a. Closed and refuted signals.
 - b. Closed signals that are categorised as important potential risks.
 - c. Closed signals that are categorised as important identified risks.

- d. Closed signals that are potential risks not categorised as important.
 - e. Closed signals that are identified risks not categorised as important.
- 1.79. Where applicable the evaluations of closed signals can be presented by indication or population.
- 1.80. The description(s) of the signal evaluations can be included in this section of the PSUR or in an appendix. Each evaluation should include the following information as appropriate:
- a. Source or trigger of the signal;
 - b. Background relevant to the evaluation;
 - c. Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
 - d. Results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
 - e. Discussion;
 - f. Conclusion.
- 1.81. Marketing authorisation holder's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

Evaluation of risks and new information

- 1.82. This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in sections 6.122 to 6.127 (“Signal evaluation”).
- 1.83. New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the signals tabulation (see sections 6.106 to 6.154) and evaluated in sections 6.122 to 6.127 (“Signal evaluation”), if the signal is also closed during the reporting interval of the PSUR.
- 1.84. Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information which allows any other further characterisation of a previously recognised risk.
- 1.85. New information can be organised as follows:

- a. New information on important potential risks.
 - b. New information on important identified risks.
 - c. New information on other potential risks not categorised as important.
 - d. New information on other identified risks not categorised as important.
 - e. Update on missing information.
- 1.86. The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in sections 6.135 to 6.138 (“Characterisation of risks”) of the report. It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medical significance and public health relevance.
- 1.87. The evaluation(s) of the new information and missing information update(s) can be included in this section of the PSUR, or in an appendix. Each evaluation should include the following information as appropriate:
- a. Source of the new information;
 - b. Background relevant to the evaluation;
 - c. Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
 - d. Results – a summary and critical analysis of the data considered in the risk evaluation;
 - e. Discussion;
 - f. Conclusion, including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in sections 6.135 to 6.138 (“Characterisation of risks”)
- 1.88. Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

Characterisation of risks”

- 1.89. This section should characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information.

- 1.90. Depending on the nature of the data source, the characterisation of risk may include, where applicable:
- a. Frequency;
 - b. Numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
 - c. Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
 - d. Estimate of relative risk and precision of estimate;
 - e. Estimate of absolute risk and precision of estimate;
 - f. Impact on the individual patient (effects on symptoms, quality or quantity of life);
 - g. Public health impact;
 - h. Patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
 - i. Dose, route of administration;
 - j. Duration of treatment, risk period;
 - k. Preventability (i.e. predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
 - l. Reversibility;
 - m. Potential mechanism; and
 - n. Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.
- 1.91. When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.
- 1.92. For PSURs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:
- a. Risks relating to the active substance;
 - b. Risks related to a specific formulation or route of administration (including occupational exposure);
 - c. Risks relating to a specific population; and
 - d. Risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

Effectiveness of risk minimisation

- 1.93. Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).
- 1.94. The PSUR should contain the results of assessments of the effectiveness of risk minimisation activities relevant to the benefit-risk assessment.
- 1.95. Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section of the PSUR.
- 1.96. Insights into the effectiveness of risk minimisation activities in Nigeria that may have utility in other countries or regions are of particular interest.
- 1.97. When required for reporting in a PSUR, results of evaluations that became available during the reporting interval, should be provided in the PSUR.

Benefit evaluation

- 1.98. PSUR sections 6.145 to 6.147 (“Important baseline efficacy and effectiveness information”) and sections 6.148 to 6.150 (“Newly identified information on efficacy and effectiveness”) provide the baseline and newly identified benefit information that support the characterisation of benefit described in sections 6.151 to 6.155 (“Characterisation of benefits”) that in turn supports the benefit-risk evaluation in section 6.156 (“Integrated benefit-risk analysis for authorised indications”).

Important baseline efficacy and effectiveness information”

- 1.99. This section of the PSUR summarises information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information should relate to authorised indication(s) of the medicinal product listed in the reference product information (see section 6.67).

- 1.100. For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.
- 1.101. The level of detail provided in this section should be sufficient to support the characterisation of benefit in the PSUR sections 6.151 to 6.155 (“Characterisation of benefits”) and the benefit-risk assessment in section 6.156 (“Integrated benefit-risk analysis for authorised indications”).

Newly identified information on efficacy and effectiveness”

- 1.102. For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this section of the PSUR. For authorised indications, new information on efficacy and effectiveness under conditions of actual use should also be described in this section, if available. New information on efficacy and effectiveness in uses other than the authorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised indications.
- 1.103. Information on indications newly authorised during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in sections 6.151 to 6.155 (“Characterisation of benefits”) and the benefit-risk assessment in section 6.156 (“Integrated benefit-risk analysis for authorised indications”).
- 1.104. In this section, particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

Characterisation of benefits”

- 1.105. This section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorised indications.
- 1.106. The level of detail provided in this section should be sufficient to support the analysis of benefit-risk in section 6.156 (“Integrated benefit-risk analysis for authorised indications”).
- 1.107. When there are no new relevant benefit data, this section should provide a characterisation of the information in sections 6.145 to 6.147 (“Important baseline efficacy and effectiveness information”).

- 1.108. When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.
- 1.109. This section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:
- a. A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
 - b. New information that challenges the validity of a surrogate endpoint, if used;
 - c. Clinical relevance of the effect size;
 - d. Generalisability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
 - e. Adequacy of characterization of dose-response;
 - f. Duration of effect;
 - g. Comparative efficacy; and
 - h. A determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice.

Integrated benefit-risk analysis for authorised indications”

- 1.110. The marketing authorisation holder should provide in this PSUR section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. Whereas sections 6.135 to 6.138 (“Characterisation of risks”) and sections 6.151-6.155 (“Characterisation of benefits”) present the risks and benefits, this section should provide a critical analysis and integration of the key information in the previous sections and should not simply duplicate the benefit and risk characterisation presented in the sections mentioned above.

“Benefit-risk context - medical need and important alternatives”

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

“Benefit-risk analysis evaluation”

- 1.112. A benefit-risk balance is specific to an indication and population. Therefore, for products authorised for more than one indication, benefit-risk balances should be evaluated and presented by each indication individually. If there are important differences in the benefit-risk balance among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.
- 1.113. The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks and should take into account the following points:
- a. Whereas previous sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section should be carried forward for integration in the benefit-risk evaluation.
 - b. Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).
 - c. With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
 - d. With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorized indications or populations, off-label use, or misuse.
 - e. The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.
- 1.114. Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:
- a. The assumptions, considerations, and judgement or weighting

that support the conclusions of the benefit-risk evaluation should be clear.

- b. If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
 - c. Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.
- 1.115. When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis should be presented based on cumulative data. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

Conclusions and actions”

- 1.116. A PSUR should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.
- 1.117. Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder should assess the need for changes to the reference product information and propose changes as appropriate.
- 1.118. In addition and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance for further discussion with the Agency. This may include proposals for additional risk minimisation activities.
- 1.119. For products with a pharmacovigilance or risk management plan, the proposals should also be considered for incorporation into the pharmacovigilance plan and/or risk minimisation plan, as appropriate (see Chapter 3).
- 1.120. Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder should draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the product(s) for which the PSUR is submitted.
- 1.121. Proposed changes to the reference product information should be described in this section of the PSUR. The appendix should include proposals for summary of product information and package leaflet together with information on ongoing changes when applicable.

Appendices to the PSUR

- 1.122. A PSUR should contain the following appendices as appropriate, numbered as follows:
- a. Reference information (see sections 6.27 to 6.32).
 - b. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
 - c. Tabular summary of safety signals (if not included in the body of the report).
 - d. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.
 - e. List of the sources of information used to prepare the PSUR.
 - f. Appendix:

Mapping signals and risks to PSUR sections/sections

Quality systems for PSURs at the level of marketing authorisation holders

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

- ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross departmental input to PSUR preparation.
- 1.126. The PSUR should also contain the assessment of specific safety issues requested by the Agency in accordance with agreed timelines and procedures. The marketing authorisation holder should have mechanisms in place to ensure that the requests made by the Agency during the time of their PSUR assessment are properly addressed.
 - 1.127. The provision of the data included in the summary tabulations (see sections 6.64 to 6.66) should undergo source data verification against the marketing authorisation holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.
 - 1.128. An appropriate quality system should be in place in order to avoid failure to comply with PSUR requirements such as:
 - a. Non-submission: complete non-submission of PSURs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the Agency);
 - b. Unjustified omission of information required by sections 6.38 to 6.46;
 - c. Poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardised medical terminology and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;
 - d. Submission of a PSUR where previous requests from the Agency have not been addressed;
 - e. Failure to provide an explicit evaluation of the benefit-risk balance of the medicinal product;
 - f. Failure to provide adequate proposals for the local authorised product information.
 - 1.129. Any significant deviation from the procedures relating to the preparation or submission of PSURs should be documented and the appropriate corrective and preventive action should be taken. This

documentation should be available at all times.

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

Training of staff members related to the PSUR process

- 1.132. For all organisations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSURs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and Chapter 6). The appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR should be in place.
- 1.133. Training to update knowledge and skills should also take place as necessary.

Training should cover regulations, guidelines, scientific evaluation and written procedures related to the PSUR process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

7 POST AUTHORIZATION SAFETY STUDIES

- 7.1. A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. This includes studies that may have commenced prior to registration that are on-going after the product has been registered.
- 7.2. A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by the Agency.
- 7.3. This chapter concerns PASS which are clinical trials or non-interventional studies and does not address non-clinical safety studies.
- 7.4. A PASS is non-interventional if the following requirements are cumulatively fulfilled;
- 7.5. The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation
- 7.6. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- 7.7. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.
- 7.8. Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

- 7.9. The purposes of this chapter are to:
- a. Provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorisation holders voluntarily or pursuant to an obligation imposed by the Agency;
 - b. Describe procedures whereby the Agency may impose to a marketing authorisation holder an obligation to conduct a clinical trial or a non-interventional study, and the impact of this obligation on the risk management system;
 - c. Describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results and for changes to the marketing authorisation following results

Structures and processes

Scope

- 7.10. These guidelines apply to non-interventional PASS which are initiated, managed or financed by a marketing authorisation holder as well as those conducted by a third party on behalf of the marketing authorisation holder. It involves primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.
- 7.11. Legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to studies conducted voluntarily in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format of study protocols, abstracts and final study reports and communication of the study information to the Agency.

Principles

- 7.12. A post-authorisation study should be classified as PASS when the main aim for initiating the study includes any of the following objectives:
- a. To quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
 - b. To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or

- hepatic impairment);
 - c. To evaluate the risks of a medicinal product after long-term use;
 - d. To provide evidence about the absence of risks;
 - e. To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
 - f. To measure the effectiveness of a risk minimisation activity.
- 7.13. The PASS design should be appropriate to address the study objective(s), for example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.
- 7.14. Good Clinical Practice guidelines should be considered by marketing authorisation holders and investigators for the development of study protocols, conduct of studies and writing of study reports as evaluated by the Agency.
- 7.15. For studies that are funded by a marketing authorisation holder, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorisation holder and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process.
- 7.16. In the research contract, the marketing authorisation holder should consider and address the following aspects:
- a. Rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
 - b. Rights and obligations of the investigator(s) and marketing authorisation holder;
 - c. Clear assignment of tasks and responsibilities;
 - d. Procedure for achieving agreement on the study protocol;
 - e. Provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators;
 - f. Intellectual property rights arising from the study and access to study data;
 - g. Storage and availability of analytical data set and statistical programmes for audit and inspection;
 - h. Communication strategy for the scheduled progress and final reports;

- I. Publication strategy of interim and final results.
- 7.17. Non-interventional post-authorisation safety studies should not be performed where the act of conducting the study promotes the use of a medicinal product. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the marketing authorisation holder and by third parties on behalf of the marketing authorisation holder.
- 7.18. Payments to healthcare professionals for participating should be restricted to compensation for time and expenses incurred

Study registration

- 7.19. In order to support transparency on non-interventional PASS conducted voluntarily or pursuant to an obligation and to facilitate exchange of pharmacovigilance information between the Agency and marketing authorisation holders, the marketing authorisation holder should make study information, before the start of data collection, should be approved by the Agency. Updates of the study protocol in case of substantial amendments, progress reports where applicable, and the final study report should be submitted to the Agency preferably within 2 weeks.

Study protocol

- 7.20. All post-authorisation safety studies must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. The good clinical practice regulation and guidelines of the Agency should be followed for ensuring the well-being and rights of the participants. The marketing authorisation holder should obtain prior approval of the protocol from the Agency.
- 7.21. In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate should be involved in the review and sign-off of study protocols conducted in Nigeria.

Format and content of the study protocol

- 7.22. The study protocol should include the following information:
 - a. Title: informative title including a commonly used term

- indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version
- b. Marketing authorisation holder: name, address and contact details
 - c. Responsible parties: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for multiple centre study. A list of all collaborating institutions and principal investigators should be made available to the Agency upon request.
 - d. Abstract: stand-alone summary of the study protocol including the following sections:
 - i. Title with subtitles including version and date of the protocol and name and affiliation of main author
 - ii. Rationale and background
 - iii. Research question and objectives
 - iv. Study design
 - v. Population
 - vi. Variables
 - vii. Data sources
 - viii. Study size
 - ix. Data analysis
 - x. Milestones
- 7.23. Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
- 7.24. Milestones: table with planned dates for the following milestones:
- a. Start of data collection
 - b. End of data collection
 - c. Study progress report(s)
 - d. Interim report(s) of study results, where applicable, in line with phases of data analyses
 - e. Final report of study results; and
 - f. Any other important timelines in the conduct of the study
- 7.25. Rationale and background: short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of

available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.

- 7.26. Research question and objectives: research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.
- 7.27. Research methods: description of the research methods, including:
 - a. Study design: overall research design and rationale for this choice.
 - b. Setting: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.
 - c. Variables: outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.
 - d. Data sources: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.
 - e. Study size: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

- f. Data management: data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.
 - g. Data analysis: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.
 - h. Quality control: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.
 - i. Limitations of the research methods: any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.
 - j. Protection of human participant: safeguards in order to comply with the good clinical practice regulation requirements of the Agency for ensuring the well-being and rights of participants in non-interventional post- authorisation safety studies.
 - k. Management and reporting of adverse events/adverse reactions: procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.
 - l. Plans for disseminating and communicating study results, including any plans for submission of progress reports and final reports.
 - m. References
- 7.28. Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available to the Agency upon

- request.
- 7.29. Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.
- 7.30. An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

Substantial amendments to the study protocol

- 7.31. The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the Agency should be informed immediately and the study should subsequently be conducted in accordance with The Good Clinical Practice Regulation and Guidelines

Reporting of pharmacovigilance data to the Agency

Data relevant to the benefit-risk balance of the product

- 7.32. The marketing authorisation holder should monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned. Any new information that may affect the benefit-risk balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to the Agency. Information affecting the benefit-risk balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data.
- 7.33. This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSURs) and in RMP updates, where applicable.

Reporting of adverse reactions/adverse events

- 7.34. Adverse reactions/adverse events should be reported to the Agency in accordance with Good Pharmacovigilance Practice. Procedures for the collection, management (including a review by the marketing authorisation holder) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the

study protocol. If appropriate, reference can be made to the Pharmacovigilance System Master File but details specific to the study should be described in this section. For study designs where expedited reporting is not required, this should be stated in the study protocol.

Study reports

Progress reports

- 7.35. Progress reports may be requested by the Agency. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of benefit-risk information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.
- 7.36. The timing of the progress reports should be agreed with the Agency and specified in the study protocol when they have been agreed before the study commences. Study progress should also be reported in any periodic safety update reports (PSURs) and risk management plan (RMP), where applicable.
- 7.37. The content of the progress report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report of study results. After review of the report, additional information may be requested.

Final study report

- 7.38. The final study report should be submitted as soon as possible within 12 months of the end of data collection. If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.
- 7.39. The final study report should include the following information:
 - a. Title: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author.
 - b. Abstract: stand-alone summary in the format presented in section 7.54.
 - c. Marketing authorisation holder: name and address of the marketing authorisation holder
 - d. Investigators: names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of

the protocol, the principal investigator, a coordinating investigator for multiple centre study. A list of all collaborating institutions and principal investigators should be made available to the Agency upon request.

- e. Milestones: planned and actual dates for the following milestones:
 - i. Start of data collection
 - ii. End of data collection or date of early termination, if applicable, with reasons for termination
 - iii. Study progress report(s)
 - iv. Interim report(s) of study results, where applicable
 - v. Final report of study results
 - vi. Any other important milestone applicable to the study, including date of protocol approval by an Ethics Committee, and date of study registration in the Nigerian PASS Register.
- f. Rationale and background: short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
- g. Research question and objectives: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.
- h. Amendments and updates to the protocol: list of any substantial amendment and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.

Research methods:

- 7.40. Study design: key elements of the study design and the rationale for this choice.
- 7.41. Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.
- 7.42. Participants: any source population and eligibility criteria of study participants. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of and reasons for dropouts.
- 7.43. Variables: all outcomes, exposures, predictors, potential

- confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.
- 7.44. **Data sources and measurement:** for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.
- 7.45. **Bias:** any efforts to assess and address potential sources of bias.
- 7.46. **Study size:** study size, rationale for any sample size calculation and any method for attaining projected study size.
- 7.47. **Data transformation:** transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.
- 7.48. **Statistical methods:** description of:
 - Main summary measures
 - Statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
 - Any methods used to examine subgroups and interactions
 - How missing data were addressed
 - Any sensitivity analyses
 - Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.
- 7.49. **Quality control:** mechanisms to ensure data quality and integrity.
- 7.50. **Results:** presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sections:
 - Participants:** numbers of study participants at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.
 - Descriptive data:** characteristics of study participants, information on exposures and potential confounders and

number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

- c. Outcome data: numbers of participants across categories of main outcomes.
- d. Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.
- e. Other analyses: other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.
- f. Adverse events and adverse reactions: summary of all adverse events/adverse reactions reported in the study. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

7.51. Discussion:

- a. Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, impact of the results on the benefit-risk balance of the product.
- b. Limitations: limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.
- c. Interpretation: interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.
- d. Generalizability: the generalizability (external validity) of the study results.

7.52. References.

- 7.53. **Other information:** any additional or complementary information on specific aspects not previously addressed.

- 7.54. The abstract of the final study report should include a summary of the study methods and findings presented in the following format:
- a. Title, with subtitles including date of the abstract and name and affiliation of main author;
 - b. Keywords (not more than five keywords indicating the main study characteristics);
 - c. Rationale and background;
 - d. Research question and objectives;
 - e. Study design;
 - f. Setting;
 - g. Participants and study size, including dropouts;
 - h. Variables and data sources;
 - i. Results;
 - j. Discussion (including, where relevant, an evaluation of the impact of study results on the risk- benefit balance of the product);
 - k. Marketing authorisation holder;
 - l. Names and affiliations of principal investigators.

Publication of study results

- 7.55. For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

Regulatory submission of manuscripts accepted for publication

- 7.56. In order to allow the Agency to review in advance the results and interpretations to be published, the marketing authorisation holder should communicate to the Agency the final manuscript of the article within two weeks after first acceptance for publication.

Data protection

- 7.57. Marketing authorisation holders and investigators should follow relevant national legislation in Nigeria.
- 7.58. For PASS imposed as an obligation, the marketing authorisation holder should ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that

information and should ensure that the confidentiality of the records of the study subjects remains protected. This provision should also be applied to PASS voluntarily initiated, managed or financed by the marketing authorisation holder.

Quality systems, audits and inspections

- 7.59. The marketing authorisation holder should ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the marketing authorisation holder should ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision should also be applied to PASS voluntarily initiated, managed or financed by the marketing authorisation holder.

Impact on the risk management system

- 7.60. Non-interventional PASS imposed as an obligation or required to investigate a safety concern of the RMP should be described in the RMP. Protocols for studies in the pharmacovigilance plan should be provided in RMP (annex 6) until submission of the final study report to the Agency. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.
- 7.61. Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product should be listed in the RMP “Summary table of additional pharmacovigilance activities.

Conditions for imposing PASS on MAH

Request for a post-authorisation safety study during a post-authorisation regulatory procedure

- 7.62. The need for a PASS could be identified by the Agency during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation or a renewal procedure

Request for a post-authorisation safety study due to an emerging safety concern

- 7.63. After the granting of the marketing authorisation, the Agency may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are concerns about the risk of the authorised medicinal product, for example following evaluation of a safety signal

Joint post-authorisation safety studies

- 7.64. If safety concerns apply to more than one medicinal product, the Agency will, encourage the marketing authorisation holders concerned to conduct a joint PASS.
- 7.65. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and the elements of the study design that support a joint protocol. Upon request from the marketing authorisation holders, the Agency may organise a pre-submission meeting in order to provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the Agency may define, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorisation holder will have to implement in the study protocol to be submitted to the Agency.

Written observations in response to the imposition of an obligation

- 7.66. Within 30 days of receipt of the written notification of the obligation, the marketing authorisation holder may request the opportunity to present written observations in response to the imposition of the obligation. The Agency will specify a time limit for the provision of these observations. On the basis of the written observations submitted by the marketing authorisation holder, the Agency may withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorisation should be subject to variation to include the obligation as a condition and the risk management plan (RMP) should be updated accordingly.

Impact on the risk management system

- 7.67. All post-authorisation safety studies imposed as a condition to the marketing authorisation will be described in the RMP and their results provided in the PSUR following completion of the final report, where applicable.
- 7.68. All relevant sections of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by

the Agency should be provided as an annex in the RMP. When a RMP does not exist, a new RMP should be developed referring to the post-authorisation safety study.

Regulatory supervision of non-interventional post-authorisation safety studies

- 7.69. Non-interventional PASS conducted pursuant to obligations imposed by the agency are supervised and assessed by the Agency

Roles and responsibilities of the marketing authorisation holder

- 7.70. Following the imposing of the obligation to conduct a non-interventional PASS as a condition to the marketing authorisation, the marketing authorisation holder should develop a study protocol and submit it to the Agency for review.
- 7.71. The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial. If the study is a non-interventional study, the marketing authorisation holder should ensure that the study meets all the requirements applicable to non-interventional PASS. The marketing authorisation holder should ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.
- 7.72. The marketing authorisation holder should develop the study protocol.
- 7.73. The study may commence only when the written endorsement from the Agency has been issued.
- 7.74. Prior to submission of the protocol, the marketing authorisation holder may submit a request to the Agency for a pre-submission meeting with the Agency in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure and outcomes) and to facilitate the development of the protocol
- 7.75. After a study has been commenced, the marketing authorisation holder should submit any substantial amendments to the protocol to the Agency, before their implementation.
- 7.76. The marketing authorisation holder may be requested to submit study progress reports to the Agency
- 7.77. Upon completion of the study, the marketing authorisation holder should submit a final study report, including a public abstract, to the Agency as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted. The final study report should follow the format recommended earlier.
- 7.78. The marketing authorisation holder should submit the study protocol,

the abstract of the final study report and the final study report.

Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

- 7.79. The marketing authorisation holder should evaluate whether the study results have an impact on the marketing authorisation and should, if necessary, submit to the Agency an application to vary the marketing authorization. In such case, the variation should be submitted to the Agency with the final study report within 12 months of the end of the data collection.
- 7.80. Following the review of the final study report, the Agency may recommend variation or suspend or revoke the marketing authorization. In case a variation is agreed upon, the marketing authorisation holder should submit to the Agency an appropriate application for a variation, including an updated summary of product characteristics (SmPC) and package leaflet within the determined timetable for implementation.

CHAPTER

8 PHARMACOVIGILANCE AUDIT

- 8.1. This chapter provides guidance on planning and conducting the legally required audits and outlines the general structures and processes that should be followed to identify the most appropriate pharmacovigilance audit activities. The chapter further describes the steps which can be undertaken by marketing authorization holders to plan, conduct and report upon individual pharmacovigilance audit activities. It also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

Structures and processes

Pharmacovigilance audit and its objective

- 8.2. Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.
- 8.3. In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are, for each audit objective, the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in this document and the regulation.

The risk-based approach to pharmacovigilance audits

- 8.4. A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods. The risk-based approach to audits focuses

on the areas of highest risk to the organisation's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- a. Strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by the management;
 - b. Tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
 - c. Operational level audit planning resulting in an audit plan for individual audit activities, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations.
- 8.5. Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation.

Strategic level audit planning

- 8.6. The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.
- 8.7. The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:
- a. All pharmacovigilance processes and tasks;
 - b. The quality system for pharmacovigilance activities;
 - c. Interactions and interfaces with other departments, as appropriate;
 - d. Pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. MAH affiliates or third parties, such as contract organisations and other vendors).
- 8.8. This is a non-prioritised, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment:
- a. Major re-organisation or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically

- for marketing authorisation holders, this may lead to a significant increase in the number of products for which the system is used);
- b. Change in key managerial function(s);
 - c. Risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organisation, increase in volumes of work;
 - d. Significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;
 - e. First medicinal product on the market (for a marketing authorisation holder);
 - f. Medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;
 - g. Criticality of the process, e.g. for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorisation holder, in addition to considering the other factors included in this list;
 - h. Outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritised depending on criticality); if the area/process has previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;
 - i. Identified procedural gaps relating to specific areas/processes;
 - j. Other information relating to compliance with the regulation e.g. for marketing authorisation holders: information from compliance metrics from inspections, from complaints, from other external sources, e.g. audits;
 - k. Other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively

impact upon pharmacovigilance activities.

Tactical level audit planning

- 8.9. An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long term audit strategy. The audit programme should be approved by the management with overall responsibility for operational and governance structure.
- 8.10. The risk-based audit programme should be based on an appropriate risk assessment and should focus on:
- a. The quality system for pharmacovigilance activities;
 - b. Critical pharmacovigilance processes;
 - c. Key control systems relied on for pharmacovigilance activities;
 - d. Areas identified as high risk, after controls have been put in place or mitigating action taken.
- 8.11. The risk-based audit programme should also take into account historical areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.
- 8.12. The audit programme documentation should include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.
- 8.13. The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) should be performed at regular intervals, which are in line with the Agency's requirements.
- 8.14. Changes to the audit programme may happen and will require proper documentation.

Operational level audit planning and reporting

Planning and fieldwork

- 8.15. The MAHs should ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit should be settled in the relevant audit related procedures, and the MAHs should ensure that audits are conducted in accordance with the written procedures.

Reporting

- 8.16. The findings of the auditors should be documented in an audit report and should be communicated to the Agency in a timely manner. The audit process should include mechanisms for communicating the audit

findings and receiving feedback, and reporting the audit findings to the Agency. Audit findings should be reported in line with their relative risk level and should be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below:

- a. **Critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.
 - b. **Major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.
 - c. **Minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.
- 8.17. Issues that need to be urgently addressed should be communicated to the Agency in an expedited manner.

Actions based on audit outcomes and follow-up of audits

- 8.18. Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. Corrective and preventive actions to address critical and major issues should be prioritised. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on nature of findings and the planned action(s).
- 8.19. The MAHs should be responsible for ensuring that a mechanism is in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis

- of identified audit findings and preparation of a corrective and preventive action plan.
- 8.20. The MAHs should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to the Agency. Evidence of completion of actions should be recorded in order to document that issues raised during the audit have been addressed.
- 8.21. Capacity for follow-up audits should be foreseen in the audit programme. They should be carried out as deemed necessary, in order to verify the completion of agreed actions.

QUALITY SYSTEM AND RECORD MANAGEMENT PRACTICES

Competence of auditors and quality management of audit activities

Independence and objectivity of audit work and auditors

- 8.22. The MAHs should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The MAHs should ensure this independence and objectivity in a structured manner and document this.
- 8.23. Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results. The main reporting line should be to the management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion. Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires auditors not to subordinate their judgement on audit matters to that of others.

Qualifications, skills and experience of auditors and continuing professional development

- 8.24. Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:

- a. Audit principles, procedures and techniques;
- b. Applicable laws, regulations and other requirements relevant to pharmacovigilance;
- c. Pharmacovigilance activities, processes and system(s);
- d. Management system(s);
- e. Organisational system(s).

f. *Evaluation of the quality of audit activities*

- g. Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance, audit programme, and audit procedures).

Audits undertaken by outsourced audit service providers

- 8.25. Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the MAHs. Where the MAH decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of these guidelines and perform pharmacovigilance audits:
- 8.26. The requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
- 8.27. The scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;
- 8.28. The organisation should obtain and document assurance of the independence and objectivity of outsourced service providers;
- 8.29. The outsourced audit service provider should also follow the relevant parts of these GVP guidelines.

Retention of audit reports

- 8.30. Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in these guidelines.

***Pharmacovigilance audit policy framework and organisational structure
Requirement to perform an audit***

- 8.31. The marketing authorisation holder is required to perform regular risk-based audit(s) of their pharmacovigilance system, including audit(s) of its quality system to ensure that it complies with the quality system requirements. The dates and results of audits and follow-up audits should be documented.

The qualified person responsible for pharmacovigilance (QPPV)

- 8.32. The QPPV should receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions.
- 8.33. The QPPV should be notified of any audit findings relevant to the pharmacovigilance system irrespective of where the audit was conducted.

Requirements for audit reporting***Reporting by the marketing authorisation holder***

- 8.34. The marketing authorisation holder should place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). Based on the audit findings, the marketing authorisation holder should ensure that an appropriate plan detailing corrective and preventive action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file.
- 8.35. The marketing authorisation holders should ensure that a list of all scheduled and completed audits is kept in the annex to the pharmacovigilance system master file and that they comply with reporting commitments in line with the Agency's requirements. The dates and results of audits and follow-up audits should be documented.

Confidentiality

- 8.36. Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion.

GLOSSARY

Abuse of a medicinal product	Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
Advanced therapy medicinal product (ATMP)	A medicinal product for human use that is either a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered product.
Adverse event (AE); synonym: Adverse experience	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse reaction, Adverse effect, Undesirable effect	A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors. <i>See also Adverse event, Serious adverse reaction, Unexpected adverse reaction, Off-label use, Overdose, Misuse of a medicinal product, Abuse of a medicinal product, Occupational exposure to a medicinal product</i>
Audit	A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011(3.1)2).
Audit finding(s)	Results of the evaluation of the collected audit evidence against audit criteria (see ISO19011 (3.4)3). 1. In the context of clinical trials, an adverse reaction is defined as all untoward and unintended responses to an investigational medicinal product related to any dose administered. 2. International Organization for Standardization (ISO); www.iso.org Audit evidence is necessary to support the auditor's results of the evaluation, i.e. the auditor's opinion and report. It is cumulative in nature and is primarily obtained from audit procedures performed during the course of the audit. <i>See also Audit</i>
Audit plan	Description of activities and arrangement for an individual audit (see ISO19011 (3.12)4). <i>See also Audit</i>
Audit programme	Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (see ISO 19011 (3.11)5). <i>See also Audit</i>
Audit recommendation	Describes the course of action management might consider to rectify conditions that have gone awry, and to mitigate weaknesses in systems of management control. Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them. <i>See also Audit</i>

Benefit-risk balance	An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks i.e.any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health. <i>See also Risks related to use of a medicinal product</i>
Clinical trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy. <i>See also Ongoing clinical trial, Completed clinical trial, Investigational medicinal product</i>
Closed signal	In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval.
Company core data sheet (CCDS)	For medicinal products, a document prepared by the marketing authorisation holder containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product. <i>See also Company core safety information</i>
Company core safety information (CCSI)	For medicinal products, all relevant safety information contained in the company core data sheet prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where the company markets the product, except when the Agency specifically requires a modification.
Compassionate use of a medicinal product Completed clinical trial Study for which a final clinical study report is available. <i>See also Clinical trial</i>	Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product (the medicinal product concerned must either be subject of an application for a marketing authorisation or must be undergoing clinical trials).
Consumer	For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient.
Data lock point	For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date. For a development safety update report (DSUR), the date designated as the cut-off date for data to be included in a DSUR, based on the development international birth date. Date includes day and month (see ICH-E2F Guideline). <i>See also Periodic safety update report, Development safety update report, International birth date, Development international birth date</i>
Development international birth date (DIBD)	Date of first approval (or authorisation) for conducting an interventional clinical trial in any country.
Direct healthcare	A communication intervention by which important information is delivered directly

professional communication (DHPC)	to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals.
Generic medicinal product	A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
Good pharmacovigilance practices (GVP)	A set of guidelines for the conduct of pharmacovigilance drawn up by the Agency, which apply to marketing authorisation holders in the country.
Healthcare professional	For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners.
Herbal medicinal product	Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binominal system. Herbal preparations are preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include: <ul style="list-style-type: none">an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group on a parameter of interest suggests a causal relationship;an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions. In a clinical trial, the comparator may be placebo, an active substance or non-exposure. <i>See also Risks related to use of a medicinal product, Important identified risk and Important potential risk, Missing information, Unexpected adverse reaction.</i>
Illegal purposes	<i>See Misuse for illegal purposes</i>
Immunisation	This is a process of making a person immune. For the context of Considerations P.I, immunisation refers to the process of making a person immune to an infection. <i>See also Vaccination.</i>

Individual case safety report (ICSR); synonym: Adverse (drug) reaction report	Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time. <i>See also Minimum criteria for reporting</i>
International birth date (IBD)	The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world.
Investigational drug	Experimental product under study or development. This term is more specific than investigational medicinal product, which includes comparators and placebos. <i>See also Investigational medicinal product</i>
Investigational medicinal product	An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. <i>See also Clinical trial</i>
Labelling	Information on the immediate or outer packaging.
Management	Group of persons in charge of the highest executive management of an organisation. Membership of this group is determined by the governance structure of the organisation. While it is envisaged that the management usually is a group, the head of the organisation is the one person at the top of the organisation with ultimate responsibility for ensuring that the organisation complies with relevant legislation.
Marketing Authorization Holder	A person authorized by the Agency to manufacture, import, receive as donation, distribute or sell a medicinal product in the country.
Medicinal product	Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
Minimum criteria for reporting	For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product. <i>See also Individual case safety report.</i>
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant. It is noted that there is an ICH definition for important missing information, which is: critical gaps in knowledge for specific safety issues or populations that use the marketed product.
Misuse of a medicinal product	Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. <i>See also Misuse of a medicinal product for illegal purposes.</i>
Misuse of a medicinal product for illegal purposes	Misuse for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault. <i>See also Misuse of a medicinal product</i>
Name of the medicinal product	The name which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorization holder. The common name is the international non-proprietary name (INN) recommended by the World Health Organization, or, if one does not exist, the usual common name. The complete name of the medicinal

	product is the name of the medicinal product followed by the strength and pharmaceutical form.
Natural person	A natural person is a real human being, as distinguished from a corporation which is often treated at law as a fictitious person.
Newly identified signal	In periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions or evaluation. This definition could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation. This definition is also applicable to periodic safety update reports. <i>See also Signal, Closed signal</i>
Non-interventional trial; synonym: Non-interventional study	<p>A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures should be applied to the patients and epidemiological methods should be used for the analysis of collected data. Thus, a trial is non-interventional if the following requirements are cumulatively fulfilled:</p> <ul style="list-style-type: none"> The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation; the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data. <p>Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice.</p>
Occupational exposure to a medicinal product	For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.
Off-label use	Situation where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. Off-label use includes use in non-authorised paediatric age categories.
Ongoing clinical trial	Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available (see ICH-E2F Guideline). <i>See also Clinical trial, Completed clinical trial</i>
Ongoing signal	In periodic benefit-risk evaluation reports, a signal that remains under evaluation at the data lock point. This definition is also applicable to periodic safety update reports. <i>See also Signal, Data lock point</i>
Overdose	Administration of a quantity of a medicinal product given per administration or

	cumulatively which is above the maximum recommended dose according to the authorised product information, Clinical judgment should always be applied.
Package leaflet	A leaflet containing information for the user which accompanies the medicinal product.
Periodic safety update report (PSUR)	Format and content for providing an evaluation of the risk-benefit ratiobenefit-risk balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.
Pharmacovigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO). In line with this general definition, underlying objectives of Pharmacovigilance are: preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.
Pharmacovigilance system	A system used by the marketing authorisation holder to fulfill the tasks and responsibilities and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit ratiobenefit-risk balance. In general, a pharmacovigilance system is a system used by an organisation to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit ratiobenefit-risk balance.
Pharmacovigilance system master file (PSMF)	A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products. <i>See also Pharmacovigilance system</i>
Post-authorisation safety study (PASS)	Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non- interventional study design. <i>See also Clinical trial, Non-interventional trial</i>
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the Medicinal product of interest but where this association has not been confirmed (see ICH-E2F Guideline, Volume 10). Examples include: non-clinical toxicological findings that have not been observed or resolved in clinical studies; adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship; a signal arising from a spontaneous adverse reaction reporting system;

	an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product. <i>See also Adverse event, Signal</i>
Quality assurance	<i>See Quality control and assurance</i>
Quality control and assurance	Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out. This applies for the purpose of fulfilling quality requirements. <i>See also Quality requirements</i>
Quality objectives	<i>See Quality requirements</i>
Quality of a pharmacovigilance system	All characteristics of the pharmacovigilance system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance. <i>See also Pharmacovigilance system, Quality system of a pharmacovigilance system</i>
Quality requirements	Those characteristics of a system which are likely to produce the desired outcome, or quality objectives. <i>See also Pharmacovigilance system, Quality system of a pharmacovigilance system</i>
Quality system of a pharmacovigilance system	The organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management. The quality system is part of the pharmacovigilance system. <i>See also Pharmacovigilance system</i>
Reference safety information	In periodic benefit-risk evaluation reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the marketing authorisation holder and which the marketing authorisation holder is listed in the country. It is a subset of information contained within the marketing authorisation holder's reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information. <i>See also Company core data sheet, Company core safety information</i>
Registry	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.
Risk management plan (RMP)	A detailed description of the risk management system. To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterise further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation. <i>See also Risk management system, Risk minimisation activity.</i>
Risk management system	A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.
Risk minimisation activity; synonym: Risk minimisation measure	An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur. These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimization activities (e.g. healthcare professional or patient communications/educational materials).
Risks related to use	Any risk relating to the quality, safety or efficacy of the medicinal product as regards

of a medicinal product	patients' health or public health and any risk of undesirable effects on the environment.
Safety concern	An important identified risk, important potential risk or missing information. It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information, i.e. includes the qualifier "important" in relation to missing information. The ICH-E2E Guideline uses the terms safety issue and safety concern interchangeably with the same definition for safety concern as defined in the ICH-E2C (R2) Guideline.
Serious adverse reaction	An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see ICH-E2D Guideline). Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. <i>See also Adverse reaction</i>
Signal	Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action. <i>See also Newly identified signal, Closed signal, Ongoing signal, Adverse reaction</i>
Spontaneous report, synonym: Spontaneous notification	An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme. In this context, an adverse reaction refers to a suspected adverse reaction. Stimulated reporting can occur in certain situations, such as after a direct healthcare professional communication (DHPC), a publication in the press or questioning of healthcare professionals by company representatives, and adverse reaction reports arising from these situations are considered spontaneous reports, provided the report meets the definition above. Reporting can also be stimulated by invitation from patients' or consumers' organisations to their members. Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting. <i>See also Adverse reaction</i>
Stimulated reporting	<i>See Spontaneous report</i>
Substance	Any matter irrespective of origin which may be human (e.g. human blood and human blood products), animal (e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (e.g. micro-organisms, plants, part of plants, vegetable secretions, extracts), chemical (e.g.

	elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis).
Summary of product characteristics (SmPC)	Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics.
Target population (treatment); synonym: Treatment target population	The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.
Target population (vaccine); synonym: Vaccine target population	Persons who might be vaccinated in accordance with the indication(s) and contraindications in the authorised product information and official recommendations for vaccinations.
Traditional herbal medicinal product	A herbal medicinal product that fulfills these conditions i.e. (a) it has (an)indication(s) exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment; (b) it is exclusively for administration in accordance with a specified strength and posology; (c) it is an oral, external and/or inhalation preparation; (d) the period of traditional use as laid down which has elapsed; (e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience. Regarding (d), the product must have been in medicinal use within the Agency's specified time.
Unexpected adverse reaction	An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics. This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product. <i>See also Summary of product characteristics.</i>
Vaccination	The administration of a vaccine with the aim to produce immune response. <i>See also Immunisation</i>
Vaccine	<i>See Immunological medicinal product</i>
Vaccine failure	Confirmed or suspected vaccine failure, Confirmed clinical vaccine failure occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation. For investigational medicinal products, an unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the investigator's brochure for an unauthorized investigational product or the summary of product characteristics for an authorised product). Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance).

	<p>Suspected clinical vaccine failure: Occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. disease of unknown serotype in a fully vaccinated person (based on CIOMS-WHO).</p> <p>Confirmed immunological vaccine failure: failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, as demonstrated by having tested or examined the vaccinated person at an appropriate time interval after completion of immunisation (based on CIOMS-WHO).</p> <p>Suspected immunological vaccine failure: failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, but with the testing or examination of the vaccinated person done at an inappropriate time interval after completion of immunisation (based on CIOMS-WHO). For interpreting what means appropriately vaccinated, consider the explanatory note for Immunisation error-related reaction. <i>See also Vaccination failure</i></p>
Valid individual case safety report	<i>See Individual case safety report</i>
VigiBase	The name of the WHO global ICSR database. It consists of reports of adverse reactions received from member countries.