EAC HARMONIZED COMPENDIUM ON SAFETY AND VIGILANCE OF MEDICAL PRODUCTS AND HEALTH TECHNOLOGIES

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FOREWORD

The East African Community (EAC) is home to 150 million citizens, of which 22% is an urban population. With a land area of 1.82 million square kilometers and a combined gross domestic product (GDP) of US$146 billion (EAC Statistics for 2016), the integration is of great strategic and geographical significance and prospects for a renewed and reinvigorated EAC.

The work of the EAC is guided by its Treaty, which established the Community. The Treaty entered into law on July 7, 2000, following its ratification by the original three Partner States of Kenya, United Republic of Tanzania, and Uganda. The Republic of Rwanda and the Republic of Burundi acceded to the EAC Treaty on June 18, 2007, and became full members of the Community effective July 1, 2007. The Republic of South Sudan acceded to the Treaty on April 15, 2016, and became a full member on August 15, 2016.

This compendium on pharmacovigilance has been developed to provide guidance to the National Medicines Regulatory Authority (NMRA) in carrying out pharmacovigilance activities in the EAC. It was compiled by the Expert Working Group on Pharmacovigilance of the EAC Medicines Regulatory Harmonization (MRH) Programme. The group relied on their experiences with and knowledge on pharmacovigilance in their individual countries as well as literature from the World Health Organization (WHO), International Council on Harmonization (ICH) of Technical Requirements for Regulation of Human Medicinal Products, European Union (EU), and other sources.

EAC Secretariat is highly indebted to United States Agency for International Development–Kenya East Africa (USAID/KEA) for financial support; African Medicines Regulatory Harmonization (AMRH) Programme partners, namely WHO, for their technical support; Bill and Melinda Gates Foundation for financial support; the World Bank for establishing the AMRH trust fund and financial management; the USAID Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program for their financial and technical assistance; and the African Union New Partnership for Africa's Development (AU-NEPAD) for its policy and advocacy role.

We also acknowledge the regional coordination and commitment for implementation of the East African MRH Programme. In addition, we highly appreciated the progressive monitoring of the project by the regional steering committee to ensure milestones were achieved.

Finally, I would like to acknowledge all key stakeholders who participated in the development and validation of the compendium from Ministries of Health and EAC Affairs, pharmaceutical industry, healthcare facilities, national and regional public health programs, research institutions, consumer associations, and academia for their valuable inputs and contributions to this compendium.

Amb. Liberat Mfumukeko
Secretary General
EAC Secretariat

RESPONSIBILITY FOR IMPLEMENTATION OF THE COMPENDIUM OF GUIDELINES, PROCEDURES, AND TOOLS FOR PHARMACOVIGILANCE SYSTEM IN THE EAST AFRICAN COMMUNITY

The EAC Sectorial Council of Ministers of Health recognizes the work done by the EAC Secretariat in collaboration with the lead EAC Partner States NMRA, Pharmacy and Poisons Board for coordinating the development of harmonized pharmacovigilance guidelines, procedures, and tools. The harmonized guidelines will facilitate uniformity in procedures for carrying out pharmacovigilance activities; bring together regional expertise; promote learning, reliance and convergence; and reduce duplication of efforts and resources between Medicines Regulatory Authorities in the region

The EAC Sectorial Council of Ministers of Health approves the use of these guidelines by partners in accordance with the existing regional legal framework. Implementation of these documents will facilitate mutual recognition of regulatory decisions and attestation of the quality and safety of medicines, cosmetics, medical devices, and diagnostics manufactured, produced, imported, exported, or traded in the EAC.

The EAC Partner States Ministries of Health shall be responsible for the enforcement of this pharmacovigilance compendium in the EAC through the respective NMRAs.

SIGNED on this …….....Day of ……by the EAC Sectorial Council of Ministers of Health

Hon. Sarah Opendi	Hon. Dr. Diane Gashumba	Hon. Dr. Thadee Ndikumana	Hon. Sicily Kariuki	Hon. Dr. Riek Gai Kok	Hon. Ummy Ally Mwalimu
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Republic of Uganda	Republic of Rwanda	Republic of Burundi	Republic of Kenya	Republic of South Sudan	The United Republic of Tanzania

ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
AE	adverse event
AEFI	adverse event following immunization
AU	African Union
BCG	Bacillus Calmette-Guérin
CAPA	corrective and preventive action
CEM	cohort event monitoring
CIOMS	Council for International Organizations of Medical Sciences
DEC	drug event combination
DHPC	direct healthcare professional communication
DIBD	development international birth date
DLP	data lock point
DME	designated medical event
DSUR	development safety update report
DUS	drug utilization study(-ies)
EAC	East African Community
eCTD	electronic common technical document
EMA	European Medicines Agency
EMEA	Europe, Middle East, and Africa
EPI	Expanded Programme on Immunization
EU	European Union
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practices
HLT	high-level term (in MedDRA)
IBD	international birth date
ICH	International Council on Harmonization
ICSR	individual case safety report
IME	important medical event
INN	international nonproprietary name
IR	inspection report
IT	information technology
IVD	in vitro diagnostic
KEA	Kenya East Africa
LTR	local technical representative
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRH	Medicines Regulatory Harmonization
NEPAD	New Partnership for Africa's Development
NMRA	National Medicines Regulatory Authority
NPC	National Pharmacovigilance Center
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report
PHP	public health program

PIL	package information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	pharmacovigilance system master file
PSUR	periodic safety update report
PSAC	Pharmacovigilance Scientific Advisory Committee
PT	preferred term
QPPV	qualified person responsible for pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SDA	signal detection algorithm
SDR	signal of disproportionate reporting
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
USAID	US Agency for International Development
WHO	World Health Organization
WHO-UMC	World Health Organization-Uppsala Monitoring Center

GLOSSARY OF TERMS

In the context of these guidelines the following words/phrases are defined as follows.

Abnormal use: Act or omission of an act by the operator or user of a medical device as a result of conduct that is beyond any reasonable means of risk control by the manufacturer.

Active surveillance: Active measures are taken to find adverse events (e.g., cohort event monitoring).

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found.

Adverse drug reactions (ADRs): A response to a medicine which is noxious and unintended, and which occurs at a dose normally used in human for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function. The term "adverse drug reaction" should be considered for harmful or seriously unpleasant effects occurring at doses intended for therapeutic, prophylactic, or diagnostic effect and which calls for reduction of dose or withdrawal of the medicine and/or forecast hazard from future administration.

Adverse event: Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the product whether or not related to the product. For the purposes of this compendium, adverse events will cover adverse drug reactions, adverse events following immunizations, and incidences following the use of a medical device.

Adverse event following immunization (AEFI): Any untoward medical occurrence that follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. AEFIs are grouped into five categories:

Cause-specific type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product and occurs even when the vaccine has been prepared, handled, and administered correctly (e.g., pain, swelling, redness following Bacillus Calmette-Guérin [BCG] vaccination).
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer (e.g., failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio).
Immunization error-related reaction (formerly "program error")	An AEFI that is caused by in appropriate vaccine handling, prescription, or administration and thus by its nature is preventable (e.g., transmission of infection by contaminated multidose vial, deaths associated with the reconstitution of vaccines with an incorrect diluent or a drug).
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization. These reactions are not related to the vaccine but rather to fear of the injection itself (e.g., vasovagal syncope or fainting in an adolescent during/following vaccination).
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error, or immunization anxiety, but a temporal association with immunization exists (e.g., a fever occurs at the time of the vaccination that is in fact caused by malaria).

Analytical sensitivity: Analytical sensitivity measures a test's ability to detect a low concentration of a given substance. Sometimes used interchangeably as limit of detection or detection limit.

Become aware: Manufacturers are considered to have "become aware" of a reportable event when: (1) any employee becomes aware of are portable event, or (2) any employee who is a person with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable event, from any source, including any trend analysis, necessitates remedial action to prevent an unreasonable risk of substantial harm to public health.

Case-control studies: Studies used to validate signals and to identify risk factors for adverse events (establishing association between medicine and one specific rare adverse event). These compare two groups: those with a condition (event) under study (cases) and a similar group that do not have the condition (controls) by looking backward in time (retrospectively) to measure the exposure status of the two groups (to the medicine) and compare the relative risk of developing the condition in the two groups.

Causal association: A cause-and-effect relationship between a causative factor and a disease with no other factors intervening in the process.

Clinical sensitivity: The number of true positive specimens identified by a given assay as positive divided by the number of specimens identified by the reference assays as positive, expressed as a percentage.

Clinical specificity: The number of true negative specimens identified by a given assay as negative, divided by the number of specimens identified by the reference assays as negative, expressed as a percentage.

Cluster: Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered. National Program managers may decide upon a more precise definition.

Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error, or immunization anxiety.

Conformity: Fulfillment of a requirement.

Conformity assessment: The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the National Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of Safety and Performance of Medical Devices.

Component complaint: Any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

Corrective action: Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. Complaints may be administrative (i.e., contractual) in nature or technical.

Correction: Action to eliminate a detected nonconformity.

Corrective action: Action to eliminate the cause of a detected nonconformity or other undesirable situation and to prevent recurrence.

Cohort event monitoring (CEM): A system created to actively monitor drug events in a population. Healthcare providers are requested to report all clinical events, regardless of whether they are suspected adverse reactions, for identified patients receiving a specified drug.

Data mining: A field at the intersection of computer science and statistics that attempts to discover in apparent patterns in large data sets. Data mining utilizes methods at the intersection of artificial intelligence, machine learning, statistics, and database systems. The overall goal of the data mining process is to extract information from a data set and transform it into an understandable structure for further use.

Drug utilization studies: Studies designed to describe how a medicine is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. They can be used to determine rates and to describe the effect of regulatory actions and media attention on the use of medicines, as well as to develop estimates of the economic burden of the cost of medicines as well as compare recommended and actual clinical practice.

External quality assessment: Monitoring of performance through either direct observation and supervision or inter-laboratory comparisons made possible by participation in an external quality assessment scheme (sometimes known as proficiency testing).

Falsified vaccines: Vaccines that deliberately/fraudulently misrepresent their identity, composition, or source

Field safety corrective action: Action taken by the manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market.

Field safety notice: A communication sent out by the manufacturer or its representative to device users in relation to a field safety corrective action.

Hemovigilance: The WHO defines hemovigilance as set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components through to their provision and transfusion to patients, and including their follow-up. Adverse events include all reactions, incidents, near misses, errors, deviations from standard operating procedures, and accidents associated with blood donation and transfusion.

Harm: Physical injury or damage to the health of people or damage to property or the environment.

Hazard: Potential source of harm.

Healthcare providers: For the purposes of reporting suspected adverse reactions, healthcare providers are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses, assistant medical officers and clinical officers, pharmaceutical technicians, pharmaceutical assistants, and traditional medicine practitioners.

Herbal medicines: Includes herbs (e.g., crude plant materials such as leaves, flowers, fruit, seed), herbal materials (e.g., fresh juices, gums, fixed oils, essential oils, dry powders), herbal preparations (e.g., comminuted or powdered herbal materials; extracts, tinctures, and fatty oils of herbal materials), and finished herbal products (e.g., preparations made from one or more herbs, may contain excipients).

Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization.

Immunization error-related reaction (formerly programmatic error): An AEFI that is caused by inappropriate vaccine handling, prescribing, or administration and thus, by its nature, is preventable.

Immunization safety: The public health practices and policies dealing with various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration.

Importer: The individual, firm, or legal entity that brings articles of trade/goods or services from a foreign source into domestic market in the course of trade.

International birth date (IBD): The date of the first marketing approval for a company's new medicinal product in any country in the world.

In vitro diagnostic (IVD): A device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring, or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Lack of efficacy: Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigations.

Local technical representative (LTR): A local person or local legal entity representing one or more manufacturers in an area and who gives technical advice on application, installation, operation, and maintenance of their products in addition to selling their products.

Lot: Defined amount of material—either starting material, intermediate, or finished product—which is uniform in its properties and has been produced in one process or series of processes.

Manufacturer: The natural or legal person responsible for design, production, assignment of intended purpose, packaging, and labeling of the diagnostic product, whether these tasks are performed by that person or on their behalf, and who represent themselves as the manufacturer on the diagnostic product labeling.

Marketing authorization holder (MAH): An individual or a corporate entity responsible for placing a pharmaceutical product in the market.

Medical device: Any instrument, apparatus, appliance, software, material, or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment, or alleviation of disease, diagnosis, monitoring, treatment, alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap
- Investigation, replacement, or modification of the anatomy or of a physiological process
- Control of conception

Additionally, by definition it does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

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.

Medication error: Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

National Medicines Regulatory Authority (NMRA): EAC partner states bodies or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement actions to ensure that medical products marketed within its jurisdiction comply with legal requirements.

National Pharmacovigilance Center (NPC): A single, governmentally recognized center (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze, and give advice on all information related to drug safety.

National Reference Laboratory: A testing laboratory that, in agreement with a specified laboratory community or through appointment by a competent organization, provides reference values in a specific technical field, (i.e., property values of materials or products to which test results can be related or traced back and whose quality is fit for the purpose).

Nonconformity: Non-fulfillment of a requirement.

Overdosage: A drug overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than is normally used.

Periodic safety update report (PSUR): An update of the worldwide safety experience of a product obtained at defined times post-marketing authorization. A PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points post-authorization.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible medicine-related problems.

Pharmacovigilance stakeholders: All those persons, individual or group, or parties that have an interest in, are impacted upon, or have concern about medication effects or any possible medicine-related problems.

Pharmacovigilance zonal/regional office: Pharmacovigilance offices other than the central/National Pharmacovigilance Center, pertaining to a specific geographical region or district and are part of the central office.

Pregnancy exposure registry: A prospective observational study that collects information on medicinal product exposure during pregnancy and the associated outcomes.

Preventive action: Action to eliminate the cause of a potential nonconformity or other undesirable situation and to prevent occurrence.

Requirement: Need or expectation that is stated, generally implied, or obligatory.

Risk: Combination of the probability of occurrence of a harm and the severity of that harm.

Risk-benefit 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).

Risk management system: A risk management system comprises a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

Risks related to use of a medicinal product: Any risk relating to the quality, safety, or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.

Sample: One or more units of product, either components or finished devices, drawn from a lot without regard to the quality of the units.

Sample size: Number of units of product in the sample.

Serious adverse event (SAE) or serious adverse drug reaction (serious ADR): Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; or is 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. Medical and scientific judgment 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 hospitalization but might jeopardize 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 hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Side effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug.

Signal: Reported information on a possible causal relationship between an adverse event and a drug, with the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Signal management process: A set of activities performed to determine whether, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, scientific literature information, or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications, and tracking.

Spontaneous reporting: An unsolicited communication of suspected adverse reactions by a healthcare provider or consumer to a company, EAC, or other organization that fulfills the following three conditions:

- It describes one or more suspected adverse reactions in a patient.
- The patient was given one or more medicinal products.
- It does not derive from a study or any organized data collection scheme.

Substandard vaccines: Authorized vaccines that fail to meet either their quality standards or specifications.

Summary of product characteristics (SmPC): Product information as approved by the EAC NMRA. The SmPC serves as the basis for production of information for healthcare providers as well as for consumer information on labels and leaflets of medicinal products.

Surveillance: Continuous systematic collection, analysis, and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice.

Test kit: Commercially prepared reagent sets, with accessory devices, containing all of the major components and literature necessary to perform one or more designated diagnostic test(s) or procedure(s).

Testing algorithm: Any computation, formula, look-up table, statistical survey, or nomogram that's used in an examination of the characteristics of something (e.g., the combination and sequence of specific HIV assays).

Testing strategy: A description of a testing approach for a specific need (e.g., blood transfusion and transplantation safety, HIV surveillance, and/or diagnosis of HIV infection in both client-initiated and provider-initiated testing and counseling), taking into consideration the disease factors, patient factors and endpoint of the test.

Toxicity: Cell damage from a direct action of the medicine, often at a high dose (e.g., liver damage from paracetamol overdose).

Trend reporting: A reporting type used by the manufacturer when a significant increase in the events not normally considered to be incidents occurred and for which pre-defined trigger levels are used to determine the threshold for reporting.

Unexpected adverse drug reaction: An adverse reaction in which the nature, severity, or outcome is not consistent with domestic labeling, marketing authorization, or the SmPC. This includes class-related reactions which are mentioned in the SmPC, but which are not specifically described as occurring with this product.

Unanticipated: A death or serious injury is considered unanticipated if the condition leading to the event was not considered in a risk analysis performed during the design and development phase of the device. There must be documented evidence in the design file that such analysis was used to reduce the risk to an acceptable level.

Vaccination failure: Vaccination failure is based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Vaccination failure can be due to vaccine failure (either "primary" when immune response is inadequate or "secondary" when the immune response wanes) or failure to vaccinate (i.e., when an indicated vaccine was not administered appropriately for any reason).

Vaccine pharmacovigilance: The science and activities relating to the detection, assessment, understanding, and communication of AEFI and other vaccine or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

Vaccine product: All components of a given vaccine formulation, including the immunogen (part of the vaccine that stimulates an immune response) and others that may be present such as the adjuvant, preservative, and other additives used during the manufacturing process to confirm product quality/stability (e.g., potassium or sodium salts, albumin, gelatin), support growth and purification of specific immunogens (e.g., egg or yeast proteins, antibiotic), or inactivate toxins (e.g., formaldehyde).

Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g., adjuvant, preservative, or stabilizer).

Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.

Verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

Vigiflow: A web-based data management tool used to manage the ADR database. All data are stored on a database server in Uppsala, Sweden.

CHAPTER 1 INTRODUCTION

BACKGROUND

Evidence of the risks and benefits of drugs and vaccines continue to emerge over the lifecycle of the product. The post-market uncertainties concerning the benefits and risks of a drug or vaccine extend beyond its inherent properties. The incidence, risk factors, and severity of reactions to a drug or vaccine in one population may differ significantly from another based on environmental and genetic reasons that can be difficult to predict. Programmatic errors occur in prescribing, preparing, administering, or taking medicines.

Pharmacovigilance is an arm of patient care and aims at identifying new information about hazards, preventing harm to patients, and getting the best outcome of treatment with medicines and other products. The science allows for identification, assessment, and understanding of risks, including risk factors when medicines are used after marketing authorization, and enables measures to be taken to prevent adverse reactions to patients.

There are two major approaches in pharmacovigilance: 1) spontaneous or passive reporting and 2) active surveillance systems. Passive reporting means that no active measures are taken to find adverse effects other than the encouragement of healthcare providers and others to report safety concerns. Passive reporting is voluntary and depends on the initiative and motivation of the reporter(s). Active (or pro-active) surveillance means that active measures are taken to find adverse events.

Information from spontaneous ADRs post-authorization clinical trials, case-control studies, and other post-market studies are used to aid decision-making. The information from these sources may lead to changes in product labels, restriction on product use, strengthening of specific warning, or product withdrawal.

Pharmacovigilance systems have been implemented in EAC Partner States since 1993. The systems are still being strengthened under the mandate of NMRAs.

However, the current existing pharmacovigilance system in the Partner States are at different levels of development and with varying requirements. Very few reports have been collected. Following the ongoing efforts in the EAC to harmonize medicines regulation, it is paramount that other NMRA functions such as pharmacovigilance be harmonized.

This guidelines provide the requirements, procedures, roles, and activities in pharmacovigilance, for marketing authorization holders, health workers, NMRAs, and other stakeholders. The guidelines therefore outline the reporting requirements for these different stakeholders, data management, communication, training requirements, as well as monitoring and evaluation of pharmacovigilance systems. They further highlight the requirements for expedited reporting, reporting of and unusual failure in efficacy, medication errors, patient reporting, and reporting of overdoses.

Various tools for collection of data, including reporting forms, have been appended with these guidelines for ease of referencing.

CHAPTER 2 MEDICINES POLICY, LEGAL ASPECTS, AND APPROACHES OF PHARMACOVIGILANCE IN EAC PARTNER STATES

Harmonization of pharmacovigilance guidelines is an explicit policy priority under Chapter 21 (Article 118) of the EAC Treaty and is vital in enabling the free movement of goods in line with the EAC Common Market Protocol. Streamlining pharmacovigilance requirements and practices will have a positive impact on public health by increasing access to good quality, safe, and efficacious medicines in the region.

All the NMRAs have a legal basis for the implementation of pharmacovigilance. The existing legal framework, in five of the seven NMRAs, also mandates the MAHs, LTRs, and/or pharmaceutical manufacturers to continuously monitor and report safety of products for which they are responsible on the market.

There are different approaches for reporting and monitoring adverse events and/or reactions. Among these are the spontaneous reporting system, active surveillance system (e.g., CEM, pregnancy exposure registry, case-control studies, drug utilization studies). In EAC Partner States NMRAs, both systems are being used.

CHAPTER 3 PHARMACOVIGILANCE SYSTEMS

The pharmacovigilance system is composed of structures, processes, resources, documentation, and outcomes of pharmacovigilance activities and is designed to monitor the safety of medical products and health technologies. The aim is to promote safe and effective use of the products and timely provision of safety information to ensure that consumers of medical products are prevented from any harm that may arise from product use. The pharmacovigilance system is used by NMRAs, manufacturers, MAHs, health facilities, public health programs, suppliers, Ministry of Health, Contract Research Oganisations, professional bodies/councils, academia, distributors, and other stakeholders of regulated products to fulfill their obligations toward patient and public safety.

PRINCIPLES FOR GOOD PHARMACOVIGILANCE PRACTICES (GVP)

Stakeholders are expected to adhere to the following principles of good pharmacovigilance practices to guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

1. The needs of patients, healthcare professionals, and the public in relation to the safety of medical products and health technologies should be met.
2. Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
3. All persons within the organization 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.
4. All persons within the entire organization should engage in continuous quality improvement
5. Resources and tasks should be organized as structures and processes in a manner that will support the proactive, risk-proportionate, continuous, and integrated conduct of pharmacovigilance.
6. All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact the risk-benefit balance and the use of a product, should be considered for decision-making.
7. Good cooperation should be fostered between MAHs, NMRAs, public health program patients, healthcare professionals, communities, and other relevant bodies in accordance with the applicable legal provisions in each Partner State.

FACILITIES AND EQUIPMENT FOR PHARMACOVIGILANCE

Appropriate facilities and equipment shall be allocated to support pharmacovigilance processes and their outcomes. These shall include but not limited to office space, information technology (IT) systems, and (electronic) storage space.

The facilities should be located, designed, constructed, adapted, and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance. Facilities and equipment that are critical for the conduct of pharmacovigilance should be subject to periodic appropriate checks, qualification, and/or validation activities to prove their suitability for the intended purpose.

QUALITY SYSTEMS

The pharmacovigilance system requires a robust quality control and assurance system that covers the organizational structure, responsibilities, procedures, processes, and resources. This system is essential for monitoring and evaluation as well as appropriate resource management, compliance management, and record management as required by the current international quality standard.

The pharmacovigilance stakeholders shall be required to establish a quality system for all pharmacovigilance activities to produce desired outcomes and quality objectives. The pharmacovigilance quality system shall involve quality planning, adherence, control, assurance, and improvements.

A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance. This shall include: quality documentation, record management, training of personnel in pharmacovigilance, communication within EAC, and continuous improvement.

QUALITY DOCUMENTATION AND RECORD MANAGEMENT

Implementation of pharmacovigilance activities shall follow quality system documentation in accordance with each Partner State NMRA's quality management system which should be in line with the technical requirements of the compendium for quality management system on technical documents for harmonization of medicine regulation in the EAC.

Pharmacovigilance information shall be recorded, handled, and stored so as to allow accurate reporting, interpretation, and verification. A record management system shall be established for all documents used for pharmacovigilance activities to ensure that they are easily retrievable and traceable. The records shall include measures taken to investigate safety concerns, timelines taken for the investigations, and the decision-making process.

A pharmacovigilance records management system shall ensure that the data is complete, accurate, and of high integrity. The data shall be timely and accessible. The retention of pharmacovigilance data and documents relating to registered medicinal products shall be for at least 10 years after the marketing authorization has ceased to exist.

All elements, requirements, and provisions adopted for the quality system shall 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.

The retention of minimum elements of the pharmacovigilance system master file (PSMF) shall be as long as the system described in the PSMF exists and for at least another 5 years after it has been formally terminated by the MAH and/or LTR. Measures shall exist to ensure that confidentiality of the data is maintained, access to the data is restricted, and data is protected from destruction.

TRAINING OF PERSONNEL FOR PHARMACOVIGILANCE

Institutions shall ensure availability of a sufficient number of competent and appropriately qualified and trained personnel to perform pharmacovigilance activities. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. The institution shall also establish a training system on vigilance with adequate documentation such as training plans, training records, curricula vitae, and job descriptions.

COMMUNICATIONS WITHIN EAC PARTNER STATES

A communication system shall be established to facilitate timely interaction among pharmacovigilance stakeholders.

CHAPTER 4 PHARMACOVIGILANCE PROCESSES, ROLES, AND RESPONSIBILITIES

PHARMACOVIGILANCE PROCESSES

EAC Partner States have established a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medical products and health technologies in accordance with the EAC medicines and health technologies policy. The EAC NMRAs shall continuously monitor the safety profile of the products marketed in East Africa, take appropriate action where necessary, and monitor the compliance of MAHs with their obligations with respect to pharmacovigilance. The EAC Partner States should ensure that all stakeholders implement risk management plans, where appropriate, to effectively monitor and manage risks associated with the safety of medicinal products.

For a functional pharmacovigilance system, the following processes are critical:

- Continuous safety profile monitoring and risk-benefit evaluation of authorized medical products and health technologies.
- Establishing, assessing, and implementing risk management systems and evaluating the effectiveness of risk minimization.
- Collecting, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation, and timely electronic transmission of safety reports from any source.
- Signal management.
- Scheduling, preparation (including data evaluation and quality control), submission, and assessment of periodic safety update reports.
- Meeting commitments and responding to requests from NMRAs, including provision of correct and complete information.
- Interaction between the pharmacovigilance and product quality defect systems.
- Communication about safety concerns between MAHs and competent authorities, notifying changes to the risk-benefit balance of medicinal products.
- Communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products.
- Keeping product information up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable NMRA.
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required.

ROLES AND RESPONSIBILITIES

NMRAS/NPC

The NMRAs/NPC shall be responsible for:

a) Coordinating pharmacovigilance activities in the country.
b) Planning and budgeting for national pharmacovigilance activities.
c) Developing, reviewing, and distributing adverse event forms and collecting reports of suspected adverse reactions to medicines and other products from the market.
d) Acknowledging receipt of adverse event reports from healthcare providers, zonal/regional pharmacovigilance centers, MAHs/LTRs, and EAC Partner State NMRA offices.
e) Conducting causality assessment and analyzing adverse reactions reports.
f) Generating hypotheses or identifying signals and taking appropriate regulatory action(s) based on signals generated.

g) Collecting and communicating relevant safety information to all stakeholders.
h) Linking with WHO program for international drug monitoring and sharing information on adverse reactions.
i) Providing feedback to reporters (e.g., issuing ADR bulletins/newsletters) including alerting prescribers, health facilities, MAH/manufactures/LTR, and the public to new risks of adverse reactions. Conducting pharmacovigilance inspection at the MAHs/manufacturing facilities.
j) Conducting pharmacovigilance inspection at the MAHs/local manufacturers/LTR facilities, health facilities, public health programs.
k) Monitoring and evaluating all pharmacovigilance activities in the country.
l) Conducting trainings and sensitization of different stakeholders.
m) Taking regulatory action on a medicine/medical product with serious adverse reaction.
n) Receiving information, responding to queries, and providing information related to pharmacovigilance to the relevant stakeholders.
o) Reviewing ADR reports and feeding information into the data management tool—Vigiflow/any other—where accessible and send them to EAC Partner State NMRAs for further action.
p) Receiving safety alerts from national and international sources and sharing them with healthcare providers and patients.
q) Collaborating with the respective pharmacovigilance stakeholders in implementing pharmacovigilance activities.
r) Reviewing risk management plans.
s) Ensuring compliance with the good pharmacovigilance practices.
t) Collaborating with medical training institutions to incorporate a pharmacovigilance module in the curriculum.

PHARMACOVIGILANCE ZONAL/REGIONAL OFFICES

The zonal/regional office shall be responsible for:

a) Coordinating pharmacovigilance activities in the zone/region.
b) Planning and budgeting for zonal/regional pharmacovigilance activities.
c) Distributing safety reporting forms and collecting reports of suspected adverse reactions to medicines and other products from the market.
d) Acknowledging receipt of safety reports from healthcare providers, patients, and the public/caregivers.
e) Conducting causality assessment and analyzing adverse reactions reports.
f) Generating hypotheses or identifying signals and taking appropriate regulatory action(s) based on signals generated.
g) Providing feedback to reporters (e.g., issuing ADR bulletins/newsletters) including alerting prescribers, health facilities, manufactures, and the public to new risks of adverse reactions.
h) Monitoring and evaluating all pharmacovigilance activities in the region.
i) Conducting trainings and sensitization of different stakeholders.
j) Receiving information, responding to queries, and providing information related to pharmacovigilance to the relevant stakeholders.
k) Reviewing ADR reports and feeding information into the data management tool—Vigiflow—where accessible or send them to EAC Partner State NMRAs for further action.
l) Receiving safety alerts from national and international sources and sharing them with healthcare providers and patients.
m) Collaborating with the respective pharmacovigilance stakeholders in implementing pharmacovigilance activities.
n) Ensuring compliance with the good pharmacovigilance practices.

o) Conducting active surveillance on safety issues within the region.

HEALTH FACILITIES

The healthcare providers are the link between patients, MAHs, and NMRAs. They play an important role in pharmacovigilance. The health facilities are required to establish a facility-based pharmacovigilance system.

The health facilities shall:

a) Receive and distribute ADR reporting forms to healthcare providers.
b) Detect, investigate, manage, and report ADRs and take appropriate action to prevent ADRs.
c) Conduct preliminary identification of signals and other risk factors.
d) Communicate appropriate safety information to health management teams and the community, including patients.
e) Organize and conduct staff training and sensitization on matters related to pharmacovigilance.
f) Set aside a budget for pharmacovigilance activities.
g) Identify focal person to coordinate pharmacovigilance activities within their health facilities.
h) Integrate pharmacovigilance concept into relevant committees (e.g., hospital therapeutic committees)
i) Maintain a register of suspected ADRs including medication errors, pregnancy registry, prescription registers, drug interactions, etc.

PUBLIC HEALTH PROGRAMS (PHPS)

Public health programs (PHPs) in EAC Partner States shall be actively engaged in pharmacovigilance activities. Such programs encompass HIV and AIDS, malaria, tuberculosis and leprosy, vaccines/immunization, and reproductive health programs, among others. The public health programs shall:

a) Include and budget for pharmacovigilance activities in their strategic plan.
b) Have a focal person, who has a minimum of a Bachelor of Pharmacy degree to coordinate pharmacovigilance activities in collaboration with NMRAs.
c) Collect data using national ADR reporting forms.
d) Distribute ADR forms in program sites.
e) Collaborate with NMRAs on active surveillance of their products.
f) Develop risk management plans and follow up with patients.
g) Train healthcare providers in reporting adverse drug events, including other aspects of pharmacovigilance.
h) Promote rational and safe use of medicines by healthcare providers.
i) Educate and inform patients on the importance of reporting adverse drug events.
j) Assess and communicate risks and effectiveness of medicines used in the specific PHP in collaboration with NMRAs.
k) Develop protocols and conduct active surveillance of the program medical products.
l) Monitor and evaluate the impact of interventions.

PATIENTS, CAREGIVERS, AND CONSUMERS

Patients, caregivers, and consumers should report any suspected adverse reaction or event associated with the use of medical products and technologies immediately to the nearest health facility, healthcare provider, MAH, or directly to EAC Partner State NMRA.

MAHS, MANUFACTURERS, AND LTRS

The MAHs, manufacturers, and LTRs shall ensure that there are appropriate pharmacovigilance and risk management systems in place to assure responsibility for their products on the market.

LTRs operate pharmacovigilance activities at the level of each EAC-PS, under the supervision of the qualified person responsible for pharmacovigilance (QPPV) of the MAH/manufacturer. In the EAC country where the QPPV is located, the LTR may be the QPPV her/himself. In other countries, the LTR may be an employee of the MAH or a person with adequate qualification appointed by the MAH among the personnel of the company or institution distributing the product.

The MAHs/Manufacturers/LTRs shall:

a) Continuously monitor pharmacovigilance data, examine options for risk minimization and prevention, and ensure that appropriate measures are taken by the MAH.
b) Carry out scientific evaluation of all information and report safety concerns arising from use of the product within or outside the terms/jurisdiction of its marketing authorization.
c) Submit accurate and verifiable data on serious and non-serious adverse reactions to the NMRAs within the legally required time limits.
d) Ensure quality, integrity, and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals.
e) Ensure effective communication with NMRAs including communication on new or changed risks, risk management systems, periodic safety update reports, and the update of product information by the MAH in light of new scientific knowledge.
f) Ensure appropriate communication of relevant safety information to healthcare professionals and patients.
g) The MAH shall appoint a QPPV who should be residing in at least one EAC Partner State.
h) Adequately support the QPPV and ensure that they have access to all resources relevant for the fulfillment of their responsibilities and tasks.
i) MAH ensures the QPPV is trained and well equipped to perform assigned tasks.
j) Establish and maintain a system to collect, collate, and evaluate pharmacovigilance data.
k) The MAHs and manufacturers will be required to establish documentation on the quality system, which shall include information relevant to their human resource management, job description, organizational chart, and instructions on critical processes and records on the PSMF.
l) Meet legal obligations for reporting of suspected adverse events and the preparation and the submission of periodic safety update reports.
m) Report to the NMRAs any published suspected ADRs/events related to their medicines and health technologies, occurring in and outside EAC Partner States. If more than one medicine is mentioned in the literature report, only the MAH whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s).
n) It is the responsibility of the MAH to provide evidence to the NMRA/NPC on compliance with sanctions or recommendations.
o) MAHs liaise with healthcare practitioners and public health institutions on updates on approved safety information and safety issues by NMRA/NPC (i.e., summary of product characteristics, patient information leaflet).

QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE (QPPV)

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance, in order to fulfill the responsibilities and tasks of the post.

A QPPV responsible for safety of medical products shall have at minimum a Bachelor of Pharmacy degree with appropriate training and knowledge in pharmacovigilance and be recognized/registered with any of the EAC NMRAs.

In case of other health technologies, a QPPV shall have a minimum of bachelor's degree in health sciences with appropriate training and knowledge in pharmacovigilance, and be recognized/registered with the relevant professional bodies.

The QPPV shall:

a) Provide information to EAC Partner State NMRAs on all adverse events.
b) Ensure submission of safety reports to the NMRA of each respective EAC Partner State.
c) Supervise the provision of individual case safety reports (ICSRs) from countries outside the EAC Partner State area whenever applicable.
d) Ensure submission of the PSURs/periodic benefit-risk evaluation reports (PBRERs)/development safety update reports (DSURs) to the NMRAs within the stipulated timeframes.
e) Inform the NMRA of the respective EAC Partner State about any significant safety issue(s) or action(s) taken by relevant foreign health authorities, including the rationale for the action taken; have oversight of the safety profile of the medicinal product under her/his scope; and be aware of the emerging safety concerns.
f) Have sufficient oversight of the content of risk management plans.
g) Be involved in the review and sign-off of protocols of post-authorization safety studies (PASS) conducted within the EAC Partner States or pursuant to a risk management plan agreed upon in the region.
h) Participate in PASS and provide results as requested by NMRAs.
i) Be involved in the design and approval process of PASS and provide results as requested by the NMRA of the EAC Partner State.
j) Ensure submission of all pharmacovigilance-related documents in accordance with the legal requirements and Good Pharmacovigilance Practices (GVP).
k) Ensure the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the NMRAs in EAC Partner States.
l) Ensure a full and prompt response to any request from NMRAs in EAC Partner States and the provision of additional information necessary for the benefit-risk evaluation of a medicinal product.
m) Provide input into the preparation of regulatory action in response to emerging safety concerns (e.g., variations, urgent safety restrictions, communication to patients and healthcare professionals).
n) Act as a single pharmacovigilance contact point for the NMRAs in Partner States.

Academia

a) Develop and incorporate the pharmacovigilance training modules in the curricula of health professionals.
b) Provide pre-service, in-service, and continuous professional development trainings on pharmacovigilance.
c) Actively participate in the development of pharmacovigilance training materials.
d) Carry out safety studies related to medical products and health technologies.
e) Collaborate with NMRAs, MAHs, and other relevant stakeholders in pharmacovigilance activities.
f) Share safety information and study findings related to medical products and health technologies with NMRAs.

Research institutions

a) Carry out safety studies related to medical products and health technologies.
b) Collaborate with NMRAs, MAHs, and other relevant stakeholders in pharmacovigilance activities.

c) Share safety information and study findings related to medical products and health technologies with NMRAs.

ADVISORY COMMITTEES

The advisory committees will assess scientific, safety, and pharmacovigilance documentation on individual medical products and health technologies, providing recommendations and advice on NMRA concerns. The roles and responsibilities of the advisory committees include the following:

a) Provide guidance on risk management of the use of medical products including the detection, assessment, minimization, and communication relating to the risk of adverse reactions, the design and evaluation of clinical trials, PASS, and pharmacovigilance audits/inspections.
b) Provide recommendations for urgent safety procedures.
c) Assess post-authorization safety studies protocols and issue recommendations.
d) Evaluate and issue recommendations on signals.
e) Provide advice for updating medical products list with safety concerns requiring additional monitoring.
f) Provide recommendations for risk management plans (RMPs).
g) Offer advice on safety consideration for the medical products, which undergo a renewal and/or for safety variations.
h) For NMRA's safety announcements and communications, the advisory committee shall issue advice on the timing and message content for individual safety cases.

DEVELOPMENT PARTNERS

Development partners, in collaboration with the EAC Secretariat, NMRAs, and other stakeholders, shall provide both financial and technical support during implementation of pharmacovigilance activities at all levels.

Ministry of Health

The Ministry shall have the following roles:

a) Develop and review policies, legal framework, and strategies to strengthen pharmacovigilance activities.
b) Oversee implementation of pharmacovigilance activities.
c) Ensure effective integration of pharmacovigilance activities within public health programs, pharmacovigilance zonal/regional offices, and health facilities.
d) Mobilize and provide resources for pharmacovigilance activities to health facilities and NMRAs.

EAC SECRETARIAT

The roles of EAC Secretariat in the process of strengthening pharmacovigilance activities in the region will include, but are not limited to:

a) Overall coordination of joint EAC regional pharmacovigilance-related activities.
b) Technical and financial resource mobilization to support implementation of the activities.
c) Coordinating and organizing technical capacity building sessions for the region.
d) Undertaking the lead in advocacy sessions at regional policy levels and international community in line with pharmacovigilance systems strengthening.
e) Providing guidance on the overall regional pharmaceutical policy framework and its implementation, including pharmacovigilance system strengthening.
f) Coordination of communication on safety messages with regional and international stakeholders.
g) Organizing regional public hearings for safety-related referral procedures.
h) Coordination and monitoring of post-authorization safety and efficacy studies in the region.

i) Coordination of regional development and drafting of any required standard operating procedures (SOPs) and tools in relation to the implementation of pharmacovigilance.
j) Sharing of safety information within EAC Partner State NMRAs.

CHAPTER 5 ADVERSE EVENTS REPORTING

SPONTANEOUS REPORTING

Submission of a report does not constitute an admission that the medical personnel or manufacturer or the product caused or contributed to the event. All reports submitted to NMRAs shall be treated with utmost confidentiality to protect both the reporter and the patient. In addition, no reporter shall be penalized for reporting on the adverse event, including medication errors. It is important that any adverse event is reported even when the reporter is not certain about the suspected medical product and health technology causing it.

Who should report adverse events?

Everyone is encouraged to report adverse events through the reporting structure. Reporters from both the public and private health sector are expected to submit reports to Partner State NMRAs. These shall include medical doctors, dentists, pharmacists, clinical officers, pharmaceutical technologists, nurses, public health programs, staff in medical laboratories, community health workers, pharmaceutical manufacturing companies, MAHs, importers, distributors, patients or patient representatives/guardians, researchers, and principal investigators.

Reports from patients are a potentially valuable source of information and should receive appropriate attention. A simplified reporting form (**Annex 2**, **Patient Reporting Form**) shall be used to collect information on adverse experience from patients. Patients are encouraged to report adverse events and seek medical attention through their healthcare providers. Further information on the report can be sought from the healthcare provider for serious and/or unknown reaction reported directly from patients. Patients who experienced a serious ADR should be given special cards (**Annex 5, Patient ADR Alert Card**) by the healthcare provider who diagnosed and managed the reaction.

The card will alert all healthcare providers that the bearer of the card had experienced serious reaction(s) (e.g., hypersensitivity reactions) or experienced a serious adverse reaction to a particular medicine. The card will be carried by the patient at all times and will be presented to healthcare provider at the time of consultation. This will help the healthcare provider identify the patient's medicines-related co-morbidity and prevent similar reactions.

What to report

It is important to report the following:

i. All local expected and/or unexpected suspected adverse reactions and events to conventional medicines, allopathic medicines, traditional/alternative/herbal medicines, biologicals, vaccines, X-ray contrast media, medical devices, diagnostics, and cosmetics.
ii. All medication errors.
iii. All suspected adverse events that may be associated with suspected or confirmed quality defects including adulteration or contamination or falsified medical products.
iv. Case reports of acute and chronic poisoning (toxicity).
v. Abuse, overdose, misuse, and off-label use of medical products.
vi. Adverse interactions of medicines with chemicals, other medicines, and food.
vii. Lack of therapeutic efficacy/therapeutic failure.
viii. Any adverse events observed in pregnancy or during breastfeeding.
ix. All SAEs and suspected unexpected adverse reactions (SUSARs) on exposure to investigational products.
x. Other patient or community safety concerns about medical products.

When to report

Any suspected adverse event should be reported as soon as possible to the NMRAs via telephone, email, or in writing using the following timelines:

Healthcare professionals/patients:

a) Fatal adverse events/adverse drug reaction shall be notified within 24 hours.
b) Other serious and non-serious cases shall be reported within 7 calendar days.

Marketing Authorization Holders:

a) Fatal cases shall be notified as soon as possible but not later than 7 calendar days.
b) Serious (non-fatal) reactions that have occurred in an EAC Partner State shall be reported within 15 calendar days.
c) Non-serious local reports shall be submitted within 30 calendar days.
d) All foreign fatal, serious (non-fatal), and non-serious adverse events/reactions to medicines and health technologies registered in an EAC Partner State shall be reported as per regular timelines within the PSUR/PBRER.

How and where to report

All the filled adverse event reporting forms (i.e., forms for reporting suspected ADRs/AEFIs, adverse event following use of a medical device) and forms for reporting suspected poor quality product (**Annex 1, Annex 3, and Annex 5, respectively**) shall be sent to the NMRAs either electronically, via email, or by post. The occurrence of adverse events can be communicated by telephone, fax, or email to the NMRAs. The MAHs shall report via the Council for International Organizations of Medical Sciences (CIOMS) I form-E2B -XML file via email or report directly by filling the relevant form on the NMRA's website. Reports originating from clinical trials shall be reported to the NMRAs via CIOMS form or trial specific forms.

Reporting of safety information at various levels shall be as described in the flow of information (**Annex 20**).

The NMRAs shall share the aggregate reports to the EAC Secretariat via the EAC regional shared portal.

Timelines for providing feedback:

a) The NMRA shall acknowledge receipt of safety reports as soon as possible but not later than 7 days.
b) NMRAs shall provide feedback within 60 calendar days.

BASIC PRINCIPLES OF EFFICIENT REPORTING OF SUSPECTED ADVERSE EVENTS

In-time reporting:

i. Report the suspected adverse events as soon as it occurs/as per the timelines in sec 5.2.3.
ii. Send the report quickly to the NMRAs.

Strong suspicion on both initial and follow-up reports:

i. Closely monitor for signs and symptoms that may enhance or exclude the possibility of a drug-induced event.
ii. All follow-up/supplementary information should be documented and submitted to the NMRA with "FOLLOW-UP REPORT" clearly indicated.
iii. Make sure that the patient names and patient unique identifier numbers are the same on both initial and follow-up reports.
iv. It is very important that follow-up reports are accurately identified and linked to the initial report.

Accuracy and completeness:
Ensure that each suspected adverse events reporting form is filled in accurately and contains all the necessary information, as much as is available. This is very important for the determination of causality (i.e., of the medicines and health technology causing the event).

IMPORTANT INFORMATION TO BE PROVIDED WHEN REPORTING ADVERSE EVENTS

The following minimum information is required to make a report valid.

Patient details

For Partner State cases, this includes the initials of the patient's name, age/date of birth, sex, weight, height, pregnancy status, inpatient/outpatient, patient address, any known allergy, and the ward/clinic where the patient was seen. It is also important to fill in the name, address, location (county), and contacts of the institution to assist in contacting the patient for follow-up when necessary.

Details on the adverse reaction/event

A brief description of the reaction/event, date of onset, severity (e.g., mild, severe, fatal), action taken (e.g., drug withdrawn, dose reduced), outcome (e.g., whether the patient is recovering, recovered), and causality (e.g., certain, possible) should be filled in and checked on the form as appropriate.

Details on the suspected product

This includes the name (generic and brand), dose, route and frequency, date the medicine was started and stopped, and the indication. It is very important to provide details of any other medicines that the patient is on that may not be necessarily responsible for the reaction. The additional information required includes batch number, manufacture date, and expiry date.

Details of the reporter

For Partner States cases, it is important to provide contact details as a reporter in case there is a need for any clarification or additional information about the report. The reporter details include name, email address, designation, and phone number.

If the above information is missing the report may not be useful. Remember to fill in all information accurately and in clear, legible writing when using the manual forms.

VIGILANCE OF HEALTH TECHNOLOGIES

The NMRA recognizes that various PHPs will have reporting requirements that do not fit well with the aforementioned requirements. These PHPs and medical technologies include, but are not limited to, vaccines, medical devices, herbal and traditional medicines, nutraceuticals, blood products, veterinary products, and biopharmaceuticals. The minimal pharmacovigilance requirements are specified herein.

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine safety monitoring is a collaborative process that involves the National Vaccines and Immunization Programs, NMRAs, healthcare providers, consumers, partners, and other stakeholders. These incidents shall be reported using the ADR/AEFI form (**Annex 1**).

AEFIs are grouped into five categories: vaccine product-related reaction, vaccine quality defect-related reaction, immunization errors-related reaction, immunization anxiety-related reaction, and coincidental event.

What AEFIs to report

Healthcare providers and caregivers should report any AEFI that is of concern. Both minor and serious AEFI cases should be reported. This includes:

i. Serious AEFIs, including adverse events or reactions that result in death, hospitalization (or prolongation of existing hospital stay), persistent or significant disability or incapacity (e.g., paralysis), or are potentially life threatening
ii. Signals and events associated with a newly introduced vaccine
iii. AEFIs caused by immunization error (e.g., injection site abscesses, severe local reaction, high fever or sepsis, BCG toxic shock syndrome, clusters of AEFIs)
iv. Allergic reaction (e.g., anaphylaxis, hives, bronchospasm, edema)
v. Clusters of events (> 2 cases of same event in same month from the same facility), apart from fever
vi. Seizures
vii. Any events causing significant parental/caregiver or community concern
viii. Swelling, redness, soreness at the site of injection if it lasts more than 3 days or swelling extends beyond nearest joint, inability to move the limb

CONDUCTING AN AEFI INVESTIGATION

1. Additional investigation on some AEFIs may be required to ascertain the underlying cause of the AEFI. The purpose of the investigation is to:
    i. Confirm the reported diagnosis and timing of AEFI
    ii. Identify details of vaccine(s) administered
    iii. Determine the cause of AEFI
    iv. Document the outcome of the reported adverse event
    v. Determine whether the reported event is a single incident or part of a cluster
    vi. Identify and address the operational aspects of the immunization program that may have led to immunization errors

2. The AEFIs that require further investigation include:
    i. Serious AEFIs
    ii. Clusters of minor AEFIs
    iii. Occurrence of events above the expected rate or of unusual severity
    iv. Signals and events associated with old or newly introduced vaccines
    v. AEFI that may have been caused by immunization error (e.g., bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock, clusters of AEFIs)
    vi. Significant events of unexplained cause occurring within 30 days after a vaccination (not listed in the product label)
    vii. Events causing significant parental or community concern

3. The Partner State NMRA Vaccine Safety Advisory Committee then reviews all reported serious AEFIs presented to them for expert opinion, carries out causality assessment, draws conclusions, and makes recommendations to improve the immunization program and promote the safety of vaccines.
4. For comprehensive guidance on vaccine vigilance, cross-reference the WHO global manual on surveillance of AEFI and causality assessment of AEFI, and user manual for the revised WHO classification (second edition).

REPORTING SUSPECTED ADVERSE EVENTS WITH FOLLOWING USE OF MEDICAL DEVICES AND DIAGNOSTICS

An event/incident due to a medical device that meets the following criteria is subject to reporting to NMRAs.

An event has occurred. It may include but not limited to:

1. A malfunction or deterioration in the characteristics or performance
2. For IVDs where there is a risk that an erroneous result would either:

    i. Lead to a patient management decision resulting in an imminent life-threatening situation to the individual being tested, or to the individual's offspring.
    ii. Cause death or severe disability to the individual or fetus being tested, or to the individual's offspring. All false positive or false negative test results shall be considered as events. For all other IVDs, false positive or false negative results falling outside the declared performance of the test shall be considered as events.

3. Unanticipated adverse reaction or unanticipated side effect
4. Interactions with other substances or products
5. Degradation/destruction of the device (e.g., fire)
6. Inappropriate therapy
7. An inaccuracy in the labeling, instructions for use, and/or promotional materials. Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.
8. The medical device is considered to be the contributing cause of the incident

The incident caused or could have caused one of the following outcomes:

1. Death of patient, user, or another person
2. A serious deterioration in the state of health of a patient, user, or other person in the form of:

    i. Life-threatening disease/illness
    ii. Permanent damage, injury, or impairment of a body function
    iii. Necessary medical or surgical treatment to prevent life-threatening illness, permanent injury
    iv. Any indirect harm caused by incorrect diagnostic or IVD device test results or caused by the use of in vitro fertilization/assisted reproductive technology equipment used in accordance with the manufacturer's instructions for use
    v. Fetal death, fetal injury, or congenital abnormalities

Any incident must be reported, whether the fault is due to technical faults or defects in the equipment, instruction manual, marking, or use or maintenance of the equipment. Events due to the intervention of healthcare professionals regardless of the serious outcome must also be reported.

On identifying a significant increase or trend of events or incidents that are usually excluded from individual reporting, the manufacturer or the MAH must report to the NMRAs. The manufacturer should have suitable systems in place for proactive scrutiny of trends in complaints and incidents occurring with their devices. Field safety notices and field safety corrective actions, including those based on incidents occurring outside EAC Partner State, must be reported to the NMRAS.

The MAH may be requested by the NMRA to conduct a concise critical analysis of the safety and performance of the medical device or IVD and submit results within a specified timeframe. In addition, anyone can report

incidents; however, healthcare professionals and manufacturers as well as MAHs, distributors, and importers of medical devices are obliged to report incidents. Moreover, manufacturers must report field safety corrective actions for marketed products.

The following timelines apply for the reporting of incidents that have occurred in EAC Partner States:

i. Serious public health threat: Immediately (without any delay that could not be justified) but not later than 24 hours after awareness of this threat.
ii. Death or unanticipated serious deterioration in state of health: Immediately (without any delay that could not be justified) after the manufacturer has established a link between the device and the event but not later than 10 elapsed calendar days following the date of awareness of the event.
iii. Others: Immediately (without any delay that could not be justified) after the manufacturer established a link between the device and the event but not later than 30 elapsed calendar days following the date of awareness of the event.

Conditions where reporting is not required include:

i. Deficiency of a device found by the user prior to its use
ii. Adverse event caused by patient conditions
iii. Service or shelf life of the medical device is exceeded
iv. Protection against a fault functioned correctly
v. Expected and foreseeable side effects
vi. Negligible likelihood of occurrence of death or serious injury

The periodic summary reports should include the full details of vigilance issues, including the status of any field safety corrective actions or notices. All adverse events related to medical devices should be reported to NMRAs using the suspected adverse event/incidence reaction reporting form (**Annex 3**).

REPORTING OF ADVERSE EVENTS DUE TO TRADITIONAL/HERBAL MEDICINES

Adverse events, case reports of acute and chronic poisoning (toxicity), and adverse interactions with other medical products and food related to herbal products shall be reported to the NMRA using the suspected adverse event reporting form (**Annex 1**). In addition, any other factors affecting product safety should also be reported using the form for reporting poor quality medicinal products (**Annex 4**).

REPORTING OF ADVERSE EVENTS FROM INVESTIGATIONAL PRODUCTS IN CLINICAL TRIALS

The following apply to reporting of adverse events in clinical trials by investigators and sponsors.

1. Fatal or life-threatening unexpected SAEs (local) shall be sent as a notification as soon as possible (within 24 hours) but no later than 7 days after first knowledge of reaction followed by complete report within the next 8 calendar days.
2. All other serious non-fatal adverse events shall be filed as soon as possible but not later than 15 calendar days.
3. Any frequent adverse event to the product shall receive immediate medical attention and be reported to NMRAs within 7 calendar days.
4. Foreign NMRA decisions that affect the safety or use of the product under study shall be reported to NMRAs within 7 calendar days through a detailed report.
5. Literature reports that affect the safety of the product under study shall be submitted within 15 days through a detailed report and a copy of the publication.
6. The SUSARs to be reported include those that occur within and outside the concerned trial.
7. Before the trial starts, sponsors should ensure that processes are in place for expedited reporting of any SUSARs to NMRAs.

8. The investigator should ensure that all serious adverse events are reported promptly to the NMRA within timelines.

REPORTING OF POOR QUALITY MEDICINES AND HEALTH TECHNOLOGIES

All healthcare providers in the private and public sector can alert NMRAs on product quality issues. The poor-quality issues may include color change, separation of components, powdering, crumbling, caking, molding, change of odor, mislabeling, incomplete pack, suspected contamination, questionable stability, defective components, poor packaging/poor labelling, therapeutic failures, and receiving expired medicines. This can be reported to NMRAs using the form for reporting poor quality medicinal products (**Annex 4**).

EXPEDITED REPORTING

All ADRs that are both serious and unexpected are subject to expedited reporting. The same respective reporting forms (Annex 1–4) shall be used to report these reactions. The expedited reports shall be submitted immediately and not later than 14 calendar days after first knowledge by the reporter. In addition, the report shall have the minimum information required, such as an identifiable patient, suspected medical product or health technology, reaction/event that can be identified as serious and unexpected, and identifiable reporter information.

CHAPTER 6 RISK MANAGEMENT SYSTEMS

Medicines and health technologies are authorized on the basis that in the specified indication(s) at the time of authorization, the risk-benefit balance is judged to be positive for the target population. Generally, medicines and health technologies will be associated with adverse reactions/events and these will vary in terms of severity, likelihood of occurrence, effect on individual patients, and public health impact. However, not all adverse reactions/events and risks will have been identified at the time an initial marketing authorization is granted, and some will only be discovered and characterized in the post-authorization phase.

The aim of an RMP is to document the risk management system considered necessary to identify, characterize, and minimize important risks that could be posed by medicines and health technologies.

The medicines RMP shall contain:

i. The identification or characterization of the safety profile of the medicines and health technologies, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the "safety specification").
ii. The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks and to identify new adverse reactions/events (the "pharmacovigilance plan").
iii. The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the "risk minimization plan").

GENERAL PRINCIPLES OF RISK MANAGEMENT

The MAH shall have an RMP for their medicines and health technologies throughout the life cycle of the product(s). An RMP shall be proportionate to the identified and potential risks of the medicines and health technologies.

The RMP is a dynamic document that should be updated throughout the life cycle of the product(s). This includes the addition of safety concerns where required, but also, as the safety profile is further characterized, the removal or reclassification of safety concerns to include new concerns.

The safety concerns in the RMP will be reduced in the following circumstances.

i. It may be that important potential risks can be removed from the safety specification in the RMP in cases where:

    a) Accumulating scientific and clinical data do not support the initial supposition, the impact to the individual has been shown to be less than anticipated resulting in the potential risk not being considered important, or when there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk.
    b) They need to be reclassified due to "important identified risks" (e.g., if scientific and clinical data strengthen the association between the risk and the product).

ii. In certain circumstances, where the risk is fully characterized and appropriately managed, important identified risks may be removed from the safety specification (e.g., for products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimization activities recommending specific clinical measures to address the risk have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines).

iii. Given the overall aim of obtaining more information regarding the risk-benefit balance in certain populations excluded in the pre-authorization phase, it is expected that as the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information.

The overall aim of risk management is to ensure that the benefits of a particular medicines and health technologies exceed the risks by the greatest achievable margin. The primary aim and focus of the RMP remains that of appropriate risk management planning throughout a medicinal product's life cycle. The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorization safety data.

Applicants/MAHs shall be required to comply with legislation on risk management in each Partner State as well as international standards. Product information, medical treatment guidelines, and any materials produced by MAHs or NMRAs shall guide healthcare professionals and patients in the management of both benefits and risks.

RISK MANAGEMENT PLAN FORMAT

The RMP consists of seven parts. The submitted RMP shall follow the format of Table 1, as shown below. Part II of the RMP safety specification is subdivided into sections, so the content can be tailored to the specifics of the medicinal product. This part generally follows the section titles in the safety specification of ICH E2E. The modular structure aims to facilitate the update of the RMP. In addition, in specific circumstances, certain RMP sections may have reduced content requirements. However, the RMP document is expected to be submitted as one single document including all sections and annexes, as relevant.

Table 1. Overview of RMP parts and sections

Part I Product(s) overview
Part II Safety specification
Section SI Epidemiology of the indication(s) and target population(s)
Section SII Non-clinical part of the safety specification
Section SIII Clinical trial exposure
Section SIV Populations not studied in clinical trials
Section SV Post-authorization experience
Section SVI Additional EAC requirements for the safety specification
Section SVII Identified and potential risks
Section SVIII Summary of the safety concerns
Part III Pharmacovigilance plan (including post-authorization safety studies)
Part IV Plans for post-authorization efficacy studies
Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
Part VI Summary of the risk management plan
Part VII Annexes

The amount of information, particularly in RMP Part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its lifecycle.

It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/MAH containing the same active substance(s) (i.e., the RMP is an active substance-based document).

Information in the RMP should be provided in enough detail while avoiding unnecessary text that distracts from the key issues to be considered for the risk management of the product. However, the safety specifications in the RMP should not be a duplication of data submitted elsewhere in the dossier, unless the sections are intended to be common sections with other documents such as the PSUR. Where applicable, the information in the RMP should provide an integrated overview/discussion focusing on the most important risks that have been identified or are anticipated based on pre-clinical, clinical, and post-marketing data presented in other modules of the electronic Common Technical Document (eCTD). Any data included in the RMP should be consistent with other sections of the dossier. Links or references to relevant sections of the non-clinical and clinical overviews and summaries should be included in the RMP. For new RMP submissions for nationally authorized products with limited safety data in the dossier, the RMP may contain the relevant safety data and discussion.

To aid consistency between the information provided in the dossier and the RMP, Table 2 below indicates where information from the eCTD is likely to be discussed in the RMP. The eCTD data refers to the submission containing the RMP (e.g., initial marketing authorization applications and major variations) or to historical data already included in the dossier with previous submissions.

In the context of a centralized procedure, the RMP should be submitted as part of an eCTD submission; however, for non-centralized procedures, the RMP submission might still be part of a CTD submission. eCTD data/submissions in this section should be read as eCTD or CTD data/submission, corresponding to the type of submission to the NMRAs.

Table 2. Mapping between RMP modules and information in eCTD

RMP	**CTD**
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the target population	Module 2.5 Clinical overview
Module SII Non-clinical part of safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary briefly Module 5 Clinical study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorization experience	Module 2.5 Clinical overview briefly
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SmPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IIV Plans for post-authorization efficacy studies (including presentation of efficacy data)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimization measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

Only key literature referenced in the RMP should be included in RMP (**Annex 6**). This should be in the format of electronic links or references, if already included elsewhere in eCTD

The description of the parts and sections of an RMP will provide guidance on the main topics to be addressed within each specific area. However, some sections may not be relevant to all medicinal products and there may be

additional topics that need to be included but are not mentioned in this guidance. The RMP is part of the scientific dossier of a product and as such should be scientifically based and should not include any element of a promotional nature. The preliminary section of the RMP should include the following administrative information about the RMP document:

i. Data lock point of the current RMP.
ii. Sign-off date and the version number of the RMP.
iii. List of all parts and modules. For RMP updates, modules version number and date of approval (opinion date) should be tabulated in this section. High level comment on the rationale for creating the update should be included for significant changes to each module.
iv. The evidence of oversight from the QPPV is not needed for versions submitted for assessment.

The QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalized approved version of the document; for eCTD submissions, this would be the RMP with the last eCTD sequence of the procedure (e.g., closing sequence). The evidence of QPPV oversight can take the form of a statement that the RMP has been reviewed and approved by the MAH/applicant's QPPV and that the electronic signature is on file.

RISK MINIMIZATIONS MEASURES

Risk minimization measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Planning and implementing risk minimization measures and assessing their effectiveness are key elements of risk management. Risk minimization measures may consist of routine risk minimization or additional risk minimization measures. Safety concerns of a medicinal product are normally adequately addressed by routine risk minimization measures in the RMP. In exceptional cases, however, routine risk minimization measures will not be sufficient for some risks and additional risk minimization measures will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product.

Risk minimization measures aim to facilitate informed decision-making to support risk minimization when prescribing, supplying, dispensing, and/or using a medicinal product. While routine measures are applied to every medicinal product, additional risk minimization activities should only be introduced when they are deemed to be essential for the safe and effective use of the medicinal product and should be developed and provided by suitably qualified people.

Routine risk minimization activities shall include the following:

1. **Summary of product characteristics (SmPC) and package leaflet**. The summary of product characteristics and the package leaflet are important tools for risk minimization as they constitute a controlled and standardized format for informing healthcare professionals and patients about the medicinal product. They provide information on undesirable effects of the medicinal product and specific clinical measures to address the risks as per the EAC compendium for registration.
2. **Pack size**. Since every pack size is specifically authorized for a medicinal product, planning the number of "dosage units" within each pack and the range of pack sizes available should be considered a form of routine risk management activity.
3. **Legal status**. Controlling the conditions under which a medicinal product may be made available can reduce the risks associated with its use or misuse. The marketing authorization 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. This is commonly referred to as the "legal status" of a medicinal product. This includes information on whether or not the medicinal

product is subject to medical prescription. It should also restrict where the medicinal product can be administered (e.g., in a hospital) or by whom it should be prescribed (e.g., specialist).

For medicinal products only available by prescription, additional conditions should be imposed by classifying them into those available only upon either a restricted medical prescription or upon a special medical prescription.

Restricted medical prescription. The following factors should be considered when classifying drug use as for restricted medical prescription:

i. The medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments that can only be followed in a hospital environment.
ii. The medicinal product is used in the treatment of conditions that must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere.
iii. The medicinal product is intended for outpatients, but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

1. **Special medical prescription.** For classification, as "subject to special medical prescription," the following factors shall be taken into account:

i. The medicinal product contains or is classified as a narcotic or a psychotropic substance within Partner States' regulations.
ii. If incorrectly used, the medicinal product is likely to present a substantial risk of medicinal abuse, lead to addiction, or be misused for illegal purposes.
iii. The medicinal product contains a substance which, by reason of its novelty or properties, could be considered to have potential for abuse.

2. Categorization at the Partner State level

a) There is the possibility of implementing sub-categories at the Partner State level, which permits the Partner States to tailor the above-mentioned classifications to their national situation. The definitions and, therefore, the implementation vary in those Partner States where sub-categories exist.
b) The introduction of additional risk minimization should be considered as a "program" where specific tools, together with an implementation scheme and evaluation strategy, are developed. The description of risk minimization measures—an integral part of the RMP—should therefore give appropriate consideration to the following points:

i. Rationale: When additional risk minimization measures are introduced, a rationale should be provided for those additional measures.
ii. Objectives: Each proposed additional risk minimization measure should include defined objective(s) and a clear description of how and which safety concern is addressed with the proposed additional risk minimization measure(s).
iii. Description: This section of the RMP should describe the selected additional risk minimization measures, including tools that will be used and key elements of content.
iv. Implementation: This section of the RMP should provide a detailed proposal for the implementation of additional risk minimization measures (e.g., setting and timing or frequency of intervention, details of the target audience, plan for the distribution of educational tools, how the action will be coordinated where more than one MAH is involved).

v. Evaluation: This section of the RMP should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimization measures in process terms and in terms of overall health outcome measures (e.g., reduction of risk).

Additional risk minimization measures that may be considered in addition to the routine measures, include:

1. Educational programs

i. The content of any educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and package information leaflet (PIL) and should add rather than duplicate SmPC and PIL information.
ii. The aim of an educational program is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients toward minimizing risk.
iii. Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimize selected safety concerns risks. The aim of an educational program is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients toward minimizing risk.
iv. In an educational program, the tools can have several different target audiences, can address more than one safety concern, and can be delivered using a combination of tools and media (e.g., paper, audio, video, web, in-person training).
v. Promotional elements, either direct or veiled (e.g., logos, product brand colors, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimization.

2. Educational tools

a) The educational tool should have a clearly defined scope and should include unambiguous statement(s) regarding the important risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s), and the specific steps to be taken by healthcare professionals and/or patients in order to minimize those risks. Elements for inclusion in an educational tool shall provide:

i. Guidance on prescribing, including patient selection, testing, and monitoring.
ii. Guidance on the management of such risks (to healthcare professionals and patients or caregivers).
iii. Guidance on how and where to report adverse reaction of special interest.

b) There are two categories of educational tools—those targeting healthcare professionals and those for patients and community.

Healthcare workers

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (e.g., how to manage an adverse reactions) associated with the medicine and the specific important risks needing additional risk minimization measures, including:

i. Selection of patients.
ii. Treatment management such as dosage, testing, and monitoring.
iii. Special administration procedures, or the dispensing of a medicinal product.
iv. Details of information that needs to be given to patients.
v. The format of a particular tool should depend upon the message to be delivered (e.g., brochure, poster, checklists).

Patients and community

The aim of tools targeting patients and/or caregivers should be to enhance their awareness of the patients or their caregivers on the early signs and symptoms of specific adverse reactions causing the need for additional risk minimization measures and on the best course of action to be taken should any of those sign or symptoms occur. This could provide information on dosing, diagnostic procedures, and patient alert cards.

Controlled access programs

A controlled access program consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimization measures (i.e., legal status). Controlled access should only be considered as a tool for minimizing an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a program where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Some of the requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme include (they may be included individually or in combination):

i. Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria.
ii. Prescriber, dispenser, and/or patient documenting their receipt and understanding of information on the serious risk of the product.
iii. Explicit procedures for systematic patient follow-up through enrollment in a specific data collection system (e.g., patient registry).
iv. Medicines made available for dispensing only by pharmacies that are registered and approved to dispense the product.

On occasion, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

Other risk minimization measures

This includes controlled distribution system, pregnancy prevention programs, and direct healthcare professional communication.

EFFECTIVENESS OF RISK MINIMIZATION MEASURES

Evaluating the effectiveness of additional risk minimization measures is necessary to establish whether an intervention has been effective or not, and, if not, why and which corrective actions are necessary. The evaluation should be performed for the additional risk minimization tools individually and for the risk minimization program as a whole. Effectiveness evaluation should be conducted at the most appropriate time, accounting for time required for launch of interventions, risk minimization measures, estimated use of the product in to by the healthcare system, and other relevant circumstances.

Periodic review of the effectiveness of one or more specific tools or the overall program, as appropriate, should be also planned. Time points of particular relevance are as follows:

i. After initial implementation of a risk minimization program (e.g., within 12-18 months) in order to allow the possibility of amendments, should they be necessary.
ii. In time for the evaluation of the renewal of a marketing authorization.

Effectiveness evaluation should address different aspects of the risk minimization, such as the process itself (i.e., to what extent the program has been implemented as planned), its impact on knowledge and behavioral changes in the target audience (i.e., the measure[s] in affecting behavioral change), and the outcome (i.e., to what extent the predefined objectives of risk minimization were met, in the short and long term).

To evaluate the effectiveness of additional risk minimization measures two categories of indicators should be considered.

a) **Process indicators**. These are necessary to gather evidence that the implementing steps of additional risk minimization measures have been successful. These process indicators should provide insight into what extent the program has been executed as planned and whether the intended impacts on behavior have been observed. Depending on the nature of the interventions, various process indicators can be identified for the assessment of their performance including reaching the target population, assessing clinical knowledge, and assessing clinical actions.
b) **Outcome indicators**. They provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place. The ultimate measures of success of a risk minimization program are the safety outcomes, including the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e., non-interventional setting) and those safety outcomes should be the outcome indicator(s). Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency, such as incidence rate or cumulative incidence of an adverse reaction, obtained, for example, in the context of PASS.

In addition to assessing the effectiveness of risk minimization measures in managing safety concerns, it is also important to monitor if the risk minimization intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term.

MEDICAL DEVICES, IN VITRO DIAGNOSTICS, AND OTHER HEALTH TECHNOLOGIES RISK MANAGEMENT

There are risks associated with every medical device and other health technologies that are on the market or in development. Manufacturers shall manage risks of their product throughout the entire lifecycle to monitor whether the risks continue to remain acceptable and whether any new hazards or risks of illness or injury associated with the use of the device for its intended uses and conditions of use are discovered. The risk management procedures shall be directly linked to the manufacturer's post-marketing surveillance procedures and shall focus on controlling and mitigating risks. Details on risk management activities shall be as described in the current International Organization for Standards guidelines (ISO 14971:2007).

Manufacturers shall plan and perform internal quality audits to verify whether risk management activities and related results comply with planned and established procedures. The internal audits should ensure the continued effectiveness of the risk management system. Risk management activities should begin as early as possible in the design and development phase, when it is easier to prevent problems.

If at any time, a risk is determined to be unacceptable, the existing risk analysis should be re-examined and appropriate action taken to meet the risk acceptability criteria. If a new hazard is identified, four phases of risk management shall be performed.

After release of the device to market, risk management activities should be linked to quality management processes, for example, production and process controls, corrective and preventive actions (CAPAs), servicing, and customer feedback.

RISK MANAGEMENT PLAN

1. Risk management planning shall be in the span of the entire lifecycle of a device. The plan shall include the following:

    i. Scope of the plan, device, and the lifecycle phases
    ii. Design development process
    iii. Risk management activities and methods
    iv. Verification plan for risk control measures
    v. Reviews
    vi. Allocation of responsibilities
    vii. Criteria for risk acceptability

2. The following risk management activities shall be included in the plan:

    i. Establishment of risk acceptability criteria
    ii. Risk analysis
    iii. Hazard identification
    iv. Risk analysis methods

3. The following tools shall be considered for analysis and validation risk management:

    i. Preliminary hazards analysis
    ii. Fault tree analysis
    iii. Failure mode effect analysis
    iv. Failure mode effect and criticality analysis
    v. Hazard and operability study
    vi. Hazard analysis and critical control point
    vii. Risk evaluation including risk-benefit analysis, assessment of risks, and assessment of benefits
    viii. Risk control and monitoring

4. Risk control activities may begin as early as design input and continue through the design and development process, manufacturing, distribution, installation, servicing, and throughout the medical device life cycle.
5. Risk control measures may be examined in the following order:

    i. Inherent safety by design
    ii. Protective measures in the device or its manufacture
    iii. Information for safety, such as warnings, etc.
    iv. Overall risk evaluation

USER-RELATED HAZARDS RISK MANAGEMENT

a) Manufacturers shall undertake efforts to control user-related hazards. The goal is to minimize use-related hazards and assure that intended users are able to use medical devices safely and effectively throughout the product life cycle. Risk management will help to identify, understand, control, and prevent failures that can result in hazards when people use medical devices.
b) The following hazards typically should be considered in risk analysis: chemical hazards (e.g., toxic chemicals), mechanical hazard (e.g., kinetic or potential energy from a moving object), thermal hazards (e.g., high temperature components), and electrical hazards (e.g., electrical shock, electromagnetic interference), radiation hazards (e.g., ionizing and non-ionizing), and biological hazards (e.g., allergic reactions, bio-incompatibility, infection).

c) Thorough consideration of use-related hazards in risk management, processes shall include the following tasks:

i. Identify and describe use-related hazards through analysis of existing information.
ii. Apply empirical approaches using representative device users to identify and describe hazards that do not lend themselves to identification or understanding through analytic approaches.
iii. Estimate the risk of each use-related hazard scenario.
iv. Develop strategies and controls to reduce the likelihood or mitigate the consequences of use-related hazard scenarios.
v. Select and implement control strategies.
vi. Ensure controls are appropriate and effective in reducing risk.
vii. Determine if new hazards have been introduced as a result of implementing control strategies.
viii. Verify that functional and operational requirements are met.
ix. Validate safe and effective device use.

Human factors shall be considered in user device risk management. Human factors engineering considerations and approaches should be incorporated into the design and risk management processes/activities in the following essential steps:

i. Identify anticipated (derived analytically) and unanticipated (derived empirically) user-related hazards.
ii. Describe how hazardous use scenarios occur (prioritize and assess risks of use-related hazards).
iii. Develop, mitigate, and verify strategies to control use-related hazards. Use-related hazards often require a combination of mitigation and control strategies.

Strategies to control or mitigate risks of use-related hazards shall include, but are not limited to, the following:

i. Modify device design to remove hazard or reduce its consequences.
ii. Make user interface, including operating logic, error tolerant (safety features).
iii. Alert users to the hazard.
iv. Develop written procedures and training for safe operation.
v. Determine if the risks related to device use are acceptable and determine if new hazards have been introduced.
vi. Demonstrate safe and effective device use (validation).

DOCUMENTATION OF RISK MANAGEMENT ACTIVITIES

Design and development activities targeted at controlling risks shall be supported by documentation. Documents or records resulting from risk management activities such as risk management procedures, reports, etc., shall be maintained or referenced in either a risk management file or other appropriate files (e.g., design history file, technical file/technical documentation, design dossier, device master record, device history record, or process validation file).

TRACEABILITY

Risk management data shall be utilized to define which devices, components, materials, and work environment conditions require traceability. Risk management activities shall be used to establish criteria for traceability. Points to be considered include:

i. Origin of components and materials
ii. Processing history
iii. Distribution and location of the device after delivery (to the first consignee)
iv. Intended use of the device (i.e., life sustaining, life supporting, or implantable)

v. Probability of failure
vi. Need for safety-related updates (i.e., recalls, advisory notices, field updates)
vii. Consequence of the failure for patients, users, or other persons

The records required for traceability shall consider all those devices, components, materials, and work environment conditions that could cause the medical device not to satisfy its specified requirements, including its safety requirements.

COORDINATION AND HARMONIZATION

If several products have the same active ingredient registered within a Partner State, there should be a consistent approach in the use of additional risk minimization measures coordinated by the NMRAs. In the case of medicinal products having the same active ingredients registered in at least three or more EAC Partner States, there should be a harmonized risk minimization measure that be instituted and coordinated by the EAC Secretariat and the lead NMRA.

CHAPTER 7 POST-AUTHORIZATION SAFETY STUDIES

A PASS is any study relating to an authorized medical product and health technology conducted with the aim of identifying, characterizing, or quantifying a safety hazard; confirming the safety profile of the medical product; or of measuring the effectiveness of risk management measures.

A PASS may be interventional or non-interventional. These guidelines will be for both interventional and non-interventional PASS, with a main focus on non-interventional studies. If a PASS is interventional, each Partner State-applicable guidelines for registration of clinical trials shall be followed.

GENERAL REQUIREMENTS

Partner State NMRAs shall require MAHs to conduct post-authorization studies on safety and on efficacy as a condition at the time of the granting of marketing authorization or later as/when required.

The obligation shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study. The request may also include recommendations on key elements of the study, such as study design, setting, exposure(s), outcome(s), and study population.

A marketing authorization may be granted subject to the conduct of a PASS. The need for a PASS could be identified by the NMRA during a post-authorization NMRA procedure, for example, an extension or a variation to a marketing authorization, a renewal procedure, or a PSUR procedure.

The non-interventional PASS can be imposed due to the following concerns.

i. Imposed as an obligation in accordance with RMPs stipulated in Chapter 6 (RMP) of these guidelines because they are key to the risk-benefit profile of the product (Category 1 studies in the pharmacovigilance plan).
ii. Imposed as a specific obligation in the framework of a marketing authorization granted under exceptional circumstances (Category 2 studies in the pharmacovigilance plan).
iii. Required in the RMP to investigate a safety concern or to evaluate the effectiveness of risk minimization activities (Category 3 studies in the pharmacovigilance plan). Such studies included in the pharmacovigilance plan are also legally enforceable.

A study shall be classified as a PASS when the main aim for initiating the study includes any of, but is not limited to, the following objectives:

i. To quantify potential or identified risks (e.g., to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal).
ii. Products as appropriate and investigate risk factors, including effect modifiers.
iii. To evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups, patients with renal or hepatic impairment, or other relevant comorbidity or co-medication).
iv. To evaluate the risks of a medical product after long-term use.
v. To provide evidence about the absence of risks.
vi. To assess patterns of drug utilization that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g., collection of information on indication, off-label use, dosage, co-medication, or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern).
vii. To measure the effectiveness of a risk management measures.

The classification of a post-authorization study as a PASS is not constrained by the type of design chosen. For example, a systematic literature review or a meta-analysis may be considered as PASS depending on its aim.

The MAH shall develop study protocols, conduct studies, and write study reports by considering relevant scientific guidance.

APPLICATION PROCEDURE FOR PASS

Safety studies to be conducted within a Partner State application shall be done according to the existing laws and regulations governing clinical research conduct in that country.

The application form to be used and registration procedures shall be as described in each Partner State applicable guidelines for registration of clinical trials. The MAH shall be required to state in the application form that the study is PASS and provide justification as to why it is not a clinical trial.

i. The MAH shall be required to submit to the NMRA the PASS study protocol for review and approval. The study protocol should be developed by individuals with appropriate scientific background and experience. Guidance for the format and content of the protocol of non-interventional PASS shall be as described in **Annex 7** of these guidelines.
ii. The QPPV or his/her delegate should be involved in the review and sign-off of study protocols required in the RMP to ensure compliance of the MAH with its pharmacovigilance obligations.
iii. An overview of study designs and databases frequently used in PASS has been provided in **Annex 1**.
iv. Information on studies conducted pursuant to an obligation imposed by NMRA shall be included in the RMP.
v. Non-interventional PASS shall be registered in the NMRA clinical trials registry or any WHO-recognized clinical trials registry before the study commences or at the earliest possible date, for example if data collection had already started for a study included in the RMP.
vi. Pre-submission meetings might be requested from the NMRA in order to clarify specific aspects of the requested study and to facilitate the development of the protocol in accordance with the objectives.
vii. NMRA shall, from time to time, conduct its own post-marketing surveillance studies if deemed relevant to determine safety, quality, and effectiveness of the products placed on the market.

STUDY CONDUCT

The study shall commence only when the written authorization from the NMRA has been issued.

Non-interventional PASS shall be initiated, managed, or financed by an MAH voluntarily or pursuant to imposed obligations by the NMRA.

The MAH shall ensure the fulfillment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected, and verified.

The conduct of the study shall follow the NMRA guidelines for Good Clinical Practice (GCP), ethical considerations for conducting biomedical research, and each Partner States' regulations on conducting clinical trials to ensure the protection of the well-being and rights of participants in the study.

Additionally, the code of conduct shall address:

i. Rationale, main objectives, and brief description of the intended methods of the research to be carried out by the investigator(s).

ii. Rights and obligations of the investigator(s) and MAH.
iii. Clear assignment of tasks and responsibilities.
iv. Procedure for achieving agreement on the study protocol.
v. Provisions for meeting the MAH's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable.
vi. Intellectual property rights arising from the study and access to study data.
vii. Storage and availability of analytical dataset and statistical programs for audit and inspection.
viii. Communication strategy for the scheduled progress and final reports.
ix. Publication strategy of interim and final results.

The MAH should ensure that the investigators are qualified by education, training, and experience to perform their tasks.

Agreements between the MAH and the investigators shall follow NMRA contractual requirements.

Non-interventional PASS shall not be performed where the act of conducting the study promotes the use of a medical product. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the MAH and by third parties on behalf of the MAH.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred.

SUBMISSION OF STUDY REPORTS

5.2.1 Biannual (every 6 months after commencement of study) progress reports on PASS studies shall be submitted to the NMRA in which the study is conducted, whether it was a requirement or conducted voluntarily.

5.2.2 If need arises, the NMRA might request a progress report (ad hoc) before the study commences or at any time during the study conduct depending on the communication of risk-benefit information arising from the study or the need for information about the study progress in the context of NMRA procedures or important safety communication about the product.

The progress report shall include relevant information to document the progress of the study, such as the number of patients who have enrolled in to 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 include an interim report of study results.

An interim report submitted shall include study results of any planned interim analysis of study data before or after the end of data collection.

A final study report including a public abstract shall be submitted to the NMRA as soon as possible and not later than 12 months after the end of data collection. The content of the final study report shall be as described in **Annex 7** and **Annex 8** of these guidelines.

REPORTING OF SAFETY AND RISK-BENEFIT BALANCE DATA

The MAH shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the product concerned.

Any new information that may affect the risk-benefit balance of the product shall be communicated within 14 calendar days in writing as an emerging safety issue to the NMRA. The reporting shall be as per expedited reporting requirements described in chapter 5(reporting of event) of these guidelines.

Information affecting the risk-benefit balance of the medical products and health technology may include an analysis of adverse reactions and aggregated data.

This communication is without prejudice of the information on the findings of studies which shall be provided by means of periodic safety update reports (PSURs/PBRERs), described in chapter 8.

Individual cases of suspected adverse reactions and SAEs that arise from the studies shall be reported to the Partner States' NMRAs according to the requirements set out and as stipulated in the applicable guidelines for registration of clinical trials and chapter 5.

Adverse events/reactions collected in studies with primary data collection shall be recorded and summarized in the interim safety analysis and in the final study report.

Adverse events/reactions collected in studies with secondary data collection shall be recorded and summarized in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification.

Procedures for the collection, management (including a review by the MAH, if appropriate), and reporting of suspected adverse reactions/events shall be put in place and summarized in the study protocol. If appropriate, reference can be made to the PSMF, but details specific to the study shall be described in the study protocol.

The NMRA shall recruit a risk assessment technical expert committee to assess the risk-benefit balance. If technical expertise is not available in the country, it can contract another committee available in a different country.

The role of the regulator to conduct risk-benefit assessment on receipt of safety information following the conduct of a PASS cannot be overstated and if the regulator does not have the capacity, the EAC can have the mandate to perform the role.

AMENDMENTS TO THE STUDY PROTOCOL

5.2.3 The study protocol shall be amended and updated as needed throughout the course of the study.

5.2.4 Any substantial amendments to the protocol after the study start shall be documented in the protocol in a traceable and auditable way including the dates of the changes.

5.2.5 If changes to the protocol lead to the study being considered an interventional clinical trial, the NMRA shall be informed immediately and approval shall be obtained.

5.2.6 Application for amendment shall be as prescribed in the NMRA regulations and guidelines for registration of clinical trials.

JOINT POST-AUTHORIZATION STUDIES CONDUCTED IN THE EAC PARTNER STATES

The MAH may apply for joint assessment of PASS if the study is to be conducted in EAC Partners States.

The application with protocols shall be submitted to the lead country as per EAC procedures.

The EAC Secretariat shall organize a joint assessment meeting. The EAC secretariat shall communicate the recommendation to MAH on behalf of the NMRAs. Recommendations from EAC shall be applied to register the PASS at each Partner State.

The assessors shall include the pharmacovigilance experts in the EAC expert working group from all seven NMRAs, with additional experts on a case-by-case basis.

If safety concerns apply to more than one medicinal product, the NMRAs, following consultation with the EAC advisory committee, may encourage the MAHs involved to conduct a joint PASS.

Requests to the MAHs shall contain the justification for the request of a joint study and may include core elements for the study protocol.

The lead NMRA shall support interactions between the concerned MAH and provide suggestions for the joint study proposal.

The EAC shall establish an electronic study register for registration, transparency, and sharing of information on PASS being conducted within the region.

The MAHs shall be required to register the approved PASS in the EAC PASS register and obtain an EAC PASS registration number before the study commences, or at the earliest possible date (e.g., if data collection had already started for a study included in the risk management plan).

The MAHs shall also enter in the EAC PASS register all non-interventional PASS required in the RMP agreed upon in the EAC or conducted voluntarily in the EAC region.

Other requirements such as reporting of safety data shall be as described in previous sections in this chapter.

OUTCOME OF THE PASS APPLICATION

After the application has been reviewed by the NMRA and technical committees, the following decisions shall be made within 60 working days.

Endorsement of the protocol. In case of endorsement, the assessment report may still include recommendations for amendments to the protocol. These recommendations are for consideration by the MAH and do not require resubmission of the protocol.

Objection to the protocol. In case of objection, resubmission of an amended protocol for reassessment will be required.

DATA PROTECTION, MANUSCRIPTS SUBMISSION, AND PUBLICATION OF STUDY RESULTS

DATA PROTECTION

a) Partner State rules and regulations regarding data transfer and publication shall be followed.
b) For non-interventional PASS imposed as an obligation, the MAH shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation, and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

PUBLICATION

a) The MAH and the investigator shall agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership.
b) The MAH shall be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

MANUSCRIPT SUBMISSION

The MAH initiating, managing, or financing a non-interventional PASS shall communicate to the NMRA of each Partner State in which the product is authorized the final manuscript of the article within 2 weeks after first acceptance for publication in order to allow the NMRA to review in advance the results and interpretations to be published.

Quality systems, audits, and inspections of PASS

a) The MAH shall ensure the fulfillment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected, and verified.
b) For PASS imposed as an obligation, the MAH shall ensure that the analytical dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.
c) For PASS required in the risk RMP agreed upon in the EAC or conducted voluntarily in the EAC, record management and data retention shall follow the regulatory provisions at regional levels and each Partner State level.

Changes following results from a non-interventional post-authorization safety study

The MAH shall evaluate whether the study results have an impact on the marketing authorization and shall, if necessary, submit to the NMRAs an application to vary the marketing authorization. The applications shall be as described in each Partner State's applicable guidelines for variation of registration. Following the review of the final study report, the NMRA may recommend variation, suspension, or revocation of the marketing authorization according to Partner State laws and regulations.

IMPACT ON THE RISK MANAGEMENT SYSTEM

Information on non-interventional PASS conducted pursuant to an obligation imposed by NMRA or required in the RMP shall be included in the RMP as described in these guidelines.

i. Pharmaco-epidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders, and other variables, through interview of appropriate subjects (e.g., patients, relatives) or by consulting the paper-based medical records.
ii. The advent of automated healthcare databases has remarkably increased the efficiency of pharmaco-epidemiological research. Generally, there are two main types of automated databases: those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters, and discharge reports; and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmaco-epidemiological studies or in their validation phase.
iii. MAHs should select the best data source according to validity (e.g., completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g., time span to provide results).
iv. Data sources that are selected shall ensure both internal and external validity.
v. With any data source used, the privacy and confidentiality regulations that apply to personal data should be adhered to.

CHAPTER 8 PERIODIC SAFETY UPDATE REPORTS (PSURS)/PERIODIC BENEFIT-RISK EVALUATION REPORTS (PBRERS) AND DEVELOPMENT SAFETY UPDATE REPORTS (DSURS)

PSURs and PBRERs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by MAHs at defined time points during the post-authorization phase.

There is a need for continuous and prompt analysis of safety, efficacy, and effectiveness information throughout the lifecycle of a medicinal product, to capture important findings that may occur and to allow for a periodic overall assessment of the accumulating data. This is important as, during approval, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Although most of the new information will be safety related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

PSURs provide a comprehensive picture of the safety of approved medicinal products, however, assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, and therefore PBRERs provide a greater emphasis on benefit than PSURs, particularly when changes in the risk estimates is important. PBRERs have therefore been extended to include benefits as well as safety and provide greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.

The scope, objectives, format, and content of the PSUR in the EAC are based on those for the PBRER described in the current ICH E2C guideline. The PBRER format replaces the PSUR format previously described in ICH E2C(R1).

It is recognized that a concise discussion of benefit will usually be enough, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals, benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.

The main objective of PBRERs/PSURs is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

SCOPE OF PBRERS/PSURS

The main focus of each PBRER/PSUR shall be the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information, that may have become available since the international birth date (IBD)—the date of the first marketing approval in any country in the world—or the development international birth date (DIBD)—the date of first authorization for the conduct of an interventional clinical trial. Any new safety and efficacy/effectiveness information discovered during the reporting period shall be discussed in the appropriate sections of the PBRERs/PSURs.

GENERAL PRINCIPLES

1. PBRERs for one active substance product.

The PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single data lock point (DLP). In some circumstances, it will be appropriate to present data by indication, dosage form, dosing regimen, or population (e.g., children vs. adults) within the relevant section(s) of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, the NMRAs should be notified and their agreement obtained, preferably at the time of approval.

2. PBRERs for fixed dose combination product.

For combinations of substances also marketed individually, information for the fixed combination may be reported either in a separate PBRER or included as separate presentations in the report for one of the individual substances, depending on the circumstances. Listing related PBRERs is considered important.

3. PBERs for products manufactured and/or marketed by more than one company.

Each MAH is responsible for submitting PBRERs for its own products. When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the NMRA authorities should be clearly specified in the written agreement.

When data received from a partner company(ies) might contribute meaningfully to the safety, benefit, and/or benefit-risk analyses and influence the reporting company's product information, these data should be included and discussed in the PBRER.

Standards for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) within the EAC region shall follow current ICH E2C (PBRER) guideline.

FORMAT AND CONTENT OF PBRERS/PSURS

The format, presentation, and content of a PBRER and an outline of points to be considered in its preparation and submission shall follow current ICH E2C (PBRER) guideline.

PBRERs/PSURs shall contain at a minimum the following:

i. 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 authorization.
ii. A scientific evaluation of the risk-benefit balance of the medicinal product.
iii. All data relating to the volume of sales of the medicinal product and any data in possession of the MAH relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.
iv. Collection of ADR information (i.e., serious ADRs, non-serious ADRs, case reports published on international or local literatures including academic conferences).
v. A comprehensive, concise, and critical analysis of product's known or emerging important risks and evidence of emerging important benefits.
vi. Summary of relevant new safety information that could have an impact on the benefit-risk profile of the product.
vii. Summary of any important new efficacy/effectiveness information that has become available during the reporting interval.
viii. Assessment of whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the product's benefit and risk profile.

ix. Conducting an integrated benefit-risk evaluation for approved indications in case a new safety information that has emerged.
x. Recommend action(s) to optimize the benefit-risk profile.

Timelines for submission of PBERs/PSURs to NMRA(s)

a) Foreign NMRA decisions that affect the safety or use of products marketed, donated, or imported, and/or for compassionate use within EAC Partner States shall be reported to NMRAs within 7 calendar days through a detailed report on the same.
b) It is the responsibility of the QPPV to ensure that PSURs are submitted according to this guideline.
c) The PSURs must be prepared by the MAH at the following intervals:

i. Immediately upon request
ii. Every 6 months from authorization until the product is placed in the market
iii. Every 6 months for the first 2 years on the market
iv. Annually for the next 2 years
v. Thereafter every 3 years

d) The following timelines apply for the submission of PSURs:

i. Within 70 calendar days of the DLP (Day 0) for PSURs covering intervals up to 12 months
ii. Within 90 calendar days of the DLP (Day 0) for PSURs covering intervals in excess of 12 months
iii. Ad hoc PSURs should be submitted upon request within 90 calendar days of the DLP, unless otherwise specified

e) The PSURs should emphasize the following:

i. Scientific evaluation of the benefit-risk profile
ii. Summaries of relevant scientific/clinical data including literature searches

The reaction terms used shall be in accordance with the Medical Dictionary for Regulatory Activities (MedDRA)terminology.

Inclusion of the signal in the periodic safety update report PBER/PSUR

i. If a PSUR is due to be submitted within 6 months of the completion, by the marketing authorization holder, the submission of a separate standalone signal notification is not required. If the data-lock point of the PBER/PSUR has elapsed by the time the marketing authorization holder has completed their assessment of the signal, it should be mentioned in the PBER/PSUR section 'Late breaking information' together with a proposal for further management of the signal.
ii. Regardless of their source, all validated signals and emerging safety issues for which the evaluation was concluded during the reporting interval of a PBER/ PSUR or are ongoing at the time of a PBER/PSUR data lock point, should be reported in that PBER/PSUR.

Development safety update reports (DSURs)

a) The DSUR is a common standard for periodic reporting on medical products under development (including marketed medical products that are under further study).
b) The focus of the DSUR shall be the data and findings from interventional clinical trials. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies shall also be included in the DSUR. A DSUR shall concentrate primarily on the

investigational product, providing information on comparators only where relevant to the safety of trial subjects.

c) The format, presentation, and content of a DSUR and an outline of points to be considered in its preparation and submission timelines shall follow current ICH E2F guideline on DSURs.
d) The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

   i. Clinical trials using an investigational product (i.e., human pharmacology, therapeutic exploratory, and therapeutic confirmatory trials [Phase I – III])
   ii. Clinical trials conducted using marketed medical products in approved indications (i.e., therapeutic use trials [Phase IV])
   iii. Therapeutic use of an investigational products
   iv. Clinical trials conducted to support changes in the manufacturing process of medicinal products
   v. Any significant other findings pertinent to the safety of the investigational products

Sponsors and MAHs shall be required to submit annual DSURs of their products to the NMRAs.

For products that are jointly registered in more than one Partner State, the MAH and sponsors shall be required to submit the relevant PSURs/PBRERs/DSURs to the EAC web-based portal.

CHAPTER 9 CAUSALITY ASSESSMENT & SIGNAL MANAGEMENT

The collected adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medical products in line with ICH E2D.

NMRAs and MAHs can use their preferred method for causality assessment, however, for products that require EAC joint assessment, Partner States will agree on the common method for causality assessment to be used such as the WHO-UMC System for Standardized Case Causality Assessment. For vaccines, causality assessment shall follow the WHO Causality Assessment of an AEFI: User Manual for the Revised WHO Classification.

A signal is any 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. New aspects of a known association may include changes in the frequency, distribution (e.g., gender, age, country), duration, severity, or outcome of the adverse reaction. A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form, or route of administration, whereas other signals may apply to a whole class of medicinal products.

Signal management is a set of activities performed to determine whether, based on an examination of ICSRs, aggregated data from active surveillance systems or studies, scientific literature information, or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications, and tracking. Management of signals is a requirement for MAHs, pharmacovigilance zonal centers, NMRAs, Partner States, and technical advisory committees.

SIGNAL MANAGEMENT

Signals can arise from a wide variety of data sources. Common sources for signals include spontaneous reporting systems, active surveillance systems, studies, and the scientific literature reporting such data. The process of signal management involves the following:

i. Signal detection
ii. Signal evaluation and validation
iii. Signal prioritization
iv. Signal communication

These same principles shall apply for signal management for medical devices and other health technologies.

SIGNAL DETECTION

1. Signal detection is the process of looking for and/or identifying signals using data from any source. Signal detection should follow a methodology that considers the nature of data and the characteristics (e.g., time on market, patient exposure, target population) as well as the type of medicinal product concerned (e.g., vaccines may require specific methodological strategies). Data from all appropriate sources should be considered. Clinical judgment should always be applied.
2. Signal detection may involve a review of ICSRs, statistical analyses, or a combination of both, depending on the size of the data set. When it is not relevant or feasible to assess each individual case (e.g., signals detected from published studies, healthcare record data), assessment of aggregated data should be considered.

3. Signal detection is often based on the periodic monitoring of databases of suspected adverse reactions, which can vary in size or remit (e.g., MAH databases, national databases, the database of the WHO Programme for International Drug Monitoring [VigiBase]).
4. Signal detection is done by either the qualitative or quantitative method:

    i. Review of individual case safety reports (qualitative methods). This is based on clinical evaluation by a research fellow who reviews data reported by the health worker for a single case or series of cases.
    ii. Statistical analyses in large databases/data mining (quantitative). This technique analyses large volume data.

5. Further guidance on statistical aspects of signal detection are found in **Annex 9** of these guidelines. The signal detection process should be adequately documented by each organization.

SIGNAL EVALUATION AND VALIDATION

1. The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. This evaluation should consider the strength of the evidence, clinical relevance, and previous awareness of the association. The extent of evaluation performed during signal validation versus further assessment may vary according to NMRA internal procedures.
2. The following elements should be considered when performing signal validation based on the review of ICSR data:

    i. Previous awareness, such as whether the information was included in the SmPC and PIL or whether the information has been assessed in the RMP, PSUR, and other NMRA procedure.
    ii. Strength of the evidence, taking into account the total number of cases (after exclusion of duplicates), number of cases in context of patient exposure, additional cases reported with related terms consistency of the evidence across cases, quality of the data and their documentation, cases matching internationally agreed case definitions if applicable, dose-reaction relationship, possible mechanism based on a biological and pharmacological plausibility, and disproportionality of reporting, if applicable.

3. Clinical relevance and context such as seriousness and severity of the reaction; outcome and reversibility of the reaction; additional insight on a known adverse reaction (e.g., in terms of its severity, duration, outcome, incidence, or management); reactions occurring in the context of drug-drug interactions; reactions occurring in vulnerable populations; patients with pre-existing risk factors; and other reactions such as overdose, abuse, misuse, off-label use, medication errors, or falsified products.
4. Additional sources of information may provide further evidence for or against a causal association, or a new aspect of a known association, and may be considered during further assessment of the signal, depending on their relevance to the signal and availability to each organization. These may include:

    i. Clinical trial data.
    ii. Findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products.
    iii. Information on the epidemiology of the adverse reaction or the underlying disease.
    iv. Experimental and/or non-clinical findings.
    v. Databases with larger datasets, when the signal was detected from national or MAH-specific databases.

vi. Healthcare databases that may provide information on characteristics of exposed patients and medicines utilization patterns.
vii. Information from other NMRA authorities worldwide and expert opinion.

5. A validated signal can be further evaluated by considering all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed. This review may include non-clinical and clinical data and should be as comprehensive as possible regarding the sources of information.

SIGNAL PRIORITIZATION

Signal prioritization aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay. Prioritization should be continuously performed throughout signal management process. The following should be considered when evaluating patients or public health impact:

a) The severity, seriousness, outcome, and reversibility of the adverse reaction and the potential for prevention
b) The patient exposure and estimated frequency of the adverse reaction
c) The patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate
d) The consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options
e) The expected extent of the NMRA intervention (e.g., addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation)
f) Whether the signal is likely to apply to other substances of the same class of medicinal product (e.g., in some circumstances, signals that could cause media attention and/or public concerns, such as adverse events following mass immunization, may deserve special attention)

Signal validation and communication within EAC

i. Partner States shall validate and prioritize signals they have detected or that have been brought to their attention from any source, including the EAC database. The affected NMRA Partner State shall take the lead on data monitoring, signal detection, validation, and confirmation. The Partner State NMRA shall be responsible for updating the EAC and pharmacovigilance database.
ii. The lead country and EAC Secretariat shall coordinate and communicate signal detection and validation to other Partner States and the public. Signals validated by a Partner State shall be confirmed and prioritized by the EAC Pharmacovigilance Scientific Advisory Committee (PSAC). The EAC Secretariat and the lead country shall be responsible for monitoring the safety data in the EAC pharmacovigilance database.

EMERGING SAFETY ISSUES

Emerging safety issues are considered by an MAH to require urgent attention by NMRAs because of the potential major impact on the risk-benefit balance of the medicinal product and/ or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals. This includes:

i. Major safety issues identified in the context of ongoing or newly completed studies (e.g., an unexpectedly increased rate of fatal or life-threatening adverse events).

ii. Major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contraindication, a restriction of use of the medical product, or its withdrawal from the market.
iii. Major safety-related regulatory actions outside the Partner States (e.g., a restriction of the use of the medical product or its suspension).

When the MAH in the EAC becomes aware of an emerging safety issue from any source, they should notify it in writing to the Partner State NMRA where the medical product is authorized. The notification shall be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

The notification shall describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and any relevant documentation available at the time of initial notification. Any further information relevant to the issue should be provided to the NMRA as soon as it becomes available.

For signals notified as emerging safety issues, a standalone signal notification is not required, unless it is considered appropriate to handle the issue within the EAC signal management process, in which case the MAH may be requested to complete and provide a standalone signal notification form (**Annex 17**).

Should the MAH, as a result of the emerging safety issue, decide to suspend, withdraw, or cancel marketing of their medicinal product, they shall notify the responsible NMRA.

STANDALONE SIGNAL NOTIFICATION

After signal assessment, if an MAH concludes that further analysis of the signal is required by the NMRA, they should complete the standalone signal notification form and send it to the NMRA where the medicinal product is registered. This should be done as soon as possible and no later than 30 days after the MAH has completed their assessment and concluded that further analysis by the competent authorities is required.

Standalone signal notifications are not required in case of signals included within PSURs or variation applications, as per the conditions outlined in **Annex 17**.

Signals refuted by MAHs should not be sent as standalone signal notifications but should be included in PSURs/PBRERs as applicable.

EXCHANGE OF INFORMATION

Validated signals that may have implications for public health and the benefit-risk profile of the product in treated patients should be immediately communicated to the Partner State NMRA, and, when appropriate, this should include proposals for action. The NMRA should also communicate results of signal assessments to MAHs.

An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively; that the roles, responsibilities, and required tasks are standardized; that these tasks are conducted by people with appropriate expertise and are clear to all parties involved; and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes.

CHAPTER 10 PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF)

The MAHs shall be required to maintain and make available a PSMF upon request by NMRAs.

The PSMF shall be located either at the site where the main pharmacovigilance activities of the MAH are performed or at the site where the QPPV operates.

The PSMF shall be continuously accessible to the QPPV and to the NMRA on request. The information shall be concise and accurate and shall 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.

MAHs should be aware that immediate access to the PSMF may also be required by the national NMRA authorities at the stated PSMF location or QPPV site (if different).

The PSMF shall describe the pharmacovigilance system for one or more medical products of the MAH. For different categories of medical products the MAH may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate PSMF.

Where a single MAH establishes more than one pharmacovigilance system, such as specific systems for particular types of products (e.g., vaccines, consumer health), or that the pharmacovigilance system may include products from more than one MAH, a specific PSMF shall be in place to describe each system. The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

Where a pharmacovigilance system is shared by several MAHs, each MAH is responsible for ensuring that a PSMF exists to describe the pharmacovigilance system applicable for their products. For a particular product(s), the MAH may delegate through written agreement (e.g., to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the MAH is responsible.

In this case, the PSMF of the MAH may cross refer to all or part of the PSMF 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 MAH and the authorities. Where applicable, a list of all PSMFs held by the same MAH shall be provided in the annex; this includes their location(s), details of the responsible QPPV(s), and the relevant product(s). Submission of summary information to NMRA authorities cannot contain multiple locations for a single PSMF.

When delegating any activities concerning the pharmacovigilance system and its master file, the MAH shall retain the ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF, and its provision to NMRA authorities upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions, and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs. Accessibility of the PSMF to all the applicable MAH(s) and its provision to NMRA authorities should be defined in written agreements. It is vital that MAH(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

OBJECTIVES

The objectives of PSMF are to provide an overview of the pharmacovigilance system, which may be requested and assessed by NMRAs during marketing authorization application(s) or post-market authorization. It shall also contribute to the appropriate planning and conduct of audits by the applicant or MAH(s), fulfillment of supervisory responsibilities of the QPPV, and inspections or other verification of compliance by NMRAs.

Through the development and maintenance of the PSMF, the MAH and QPPV shall be able to:

i. Gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements.
ii. Confirm aspects of compliance in relation to the system.
iii. Obtain information about deficiencies in the system, or non-compliance with the requirements.
iv. Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

STRUCTURES AND PROCESSES

PSMF is applicable for any medical products authorized in the EAC region, irrespective of the marketing authorization procedure.

The required content and management of the PSMF applies irrespective of the organizational structure of an MAH, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the QPPV's residence, the location at which he/she carries out his/her tasks, and the PSMF location must be within the EAC region. The content of the PSMF should reflect global availability of safety information (if available/applicable) for medical products authorized in the EAC, presenting information on the pharmacovigilance system applied at global, regional, and/or local levels.

DOCUMENT AND RECORD CONTROL

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents.

PROCEDURAL DOCUMENTS

i. The PSMF shall contain a general description of the types of documents used in pharmacovigilance (e.g., SOPs, work instructions); the applicability of the various documents at the global, regional, or local level within the organization; and the controls that are applied to their accessibility, implementation, and maintenance.
ii. Information about the documentation systems applied to relevant procedural documents under the control of third parties.
iii. A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions. Details of how the procedures can be accessed must be provided along with the detailed guidance.

AUDITING

Information about quality assurance auditing of the pharmacovigilance system shall be included in the PSMF. 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. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, and specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces, and should cover a rolling 5-year period.

The PSMF shall 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 PSMF, it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified, and the anticipated resolution date(s). Cross-referencing the audit report and the documented corrective and

preventative action plan(s), the PSMF should also describe the process for recording, managing, and resolving deviations from the quality system along with pharmacovigilance procedures, their impact, and management until resolved. The audit trail should also allow traceability of how validated signals have been investigated.

TRANSPARENCY WITHIN EAC

Information on the PSMF location should be made available to the public via the EAC medicines web portal.

MARKET AUTHORIZATION AND MAINTENANCE

A summary of the applicant's pharmacovigilance system shall be included in the marketing authorization application, which shall include the following in the dossier:

i. Proof that the applicant has a designated QPPV
ii. The Partner States in which the qualified person resides and carries out his/her tasks
iii. Contact details of the qualified person
iv. A statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities
v. A reference to the location where the PSMF for the medical product is kept
vi. Pharmacovigilance plan (**chapter 11**)

CHANGES TO AND TRANSFER OF RESPONSIBILITIES FOR THE PSMF

The pharmacovigilance system may change with time. Changes of activities concerning the master file shall be documented and managed to ensure that the marketing authorization holder fulfills their responsibilities. The QPPV shall be notified of any changes to the PSMF. The types of changes that should be routinely and promptly conveyed to the QPPV are:

i. Updates to the PSMF or its location that are conveyed to the NMRA authorities.
ii. The addition of corrective and/or preventative actions to the PSMF (e.g., following audits and inspections).
iii. Changes to content that fulfill the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning, and compliance).
iv. Changes in arrangements for the provision of the PSMF to NMRA authorities.
v. Transfer of significant services for pharmacovigilance to a third party (e.g., outsourcing of PSUR production).
vi. Inclusion of products into the pharmacovigilance system for which the QPPV is responsible.
vii. Changes for existing products that may require a change or increased workload in relation to pharmacovigilance activity (e.g., new indications, studies, or the addition of regions).

TRANSFER OR DELEGATION OF RESPONSIBILITIES

Following the transfer of responsibilities, the recipient QPPV shall explicitly accept the transfer of responsibility for a pharmacovigilance system in writing. The QPPV should be in a position to ensure and verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under his/her responsibility.

CONTENTS OF THE PHARMACOVIGILANCE SYSTEM MASTER FILE

The PSMF shall include documents to describe the pharmacovigilance system. Where there is no marketing authorization (and master file) previously existing in the EAC, there may be information that cannot be initially provided (e.g., compliance information). However, descriptions of what will be implemented shall be provided instead. The contents of the PSMF shall be as described in **Annex 10**.

CHANGE CONTROL, LOGBOOK, VERSIONS, AND ARCHIVING

The MAHs shall implement change control systems and have robust processes in place to continuously be informed of relevant changes in order to maintain the PSMF accordingly. The MAHs shall submit information about important changes to the pharmacovigilance system including:

i. 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.
ii. Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data.
iii. Organizational changes, such as takeovers, mergers, and the sites at which pharmacovigilance is conducted or the delegation/transfer of PSMF management.
iv. Changes to the PSMF should be recorded, such that a history of changes is available (specifying the date and the nature of the change), and changes to the PSMF must be recorded in the logbook. A record of the date and nature of notifications of the changes made available to the competent authorities, the QPPV, and relevant third parties should be kept to ensure that change control is fully implemented.
v. As a basis for audit and inspections, the PSMF provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

ACCESSIBILITY OF THE PHARMACOVIGILANCE SYSTEM MASTER FILE

i. The PSMF shall be kept up to date and be permanently available to the QPPV. It shall also be permanently available for inspection at the site where it is kept, irrespective of whether the inspection has been notified in advance or is unannounced.
ii. The MAH shall maintain and make available on request a copy of the PSMF. The MAH must submit the copy not later than 7 days after receipt of the request from an NMRA. The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.
iii. In the situation where the same PSMF is used by more than one MAH (where a common pharmacovigilance system is used), the concerned PSMF should be accessible to each, as any of the applicable MAHs shall be able to provide the file to the NMRA authorities within 7 days, upon request.
iv. The PSMF may be requested on an ad hoc basis, particularly if a new pharmacovigilance system is being implemented or if product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified.

ANNEX TO THE PSMF

An annex to the PSMF shall contain the following documents:

1. A list of medical products covered by the PSMF including the name of the medicinal product, international non-proprietary name of the active substance(s), and Partner States in which the authorization is valid. The list of medicinal products authorized in the EAC should also include the authorization number(s) including, per authorization:

    i. Type of procedure for authorization and procedure number (e.g., centrally authorized-EAC harmonized registration, nationally authorized products,).
    ii. Rapporteur country or reference Partner State.
    iii. Presence on the market in the EAC.

iv. Other (non-EAC) territories where the product is authorized or on the market.

2. The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (e.g., risk minimization measures contained in the RMP or laid down as conditions of the marketing authorization, non-standard PSUR periodicity). The monitoring information may be provided as a secondary list.
3. For marketing authorizations 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 PSMF(s) should also be provided as a separate list in the annexes, such that, for an MAH, the entire product portfolio can be related to the set of PSMFs.
4. Where pharmacovigilance systems are shared, all products that utilize 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, organized 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.
5. A list of written policies and procedures.
6. A list of contractual agreements covering delegated activities including the medicinal products.
7. A list of tasks that have been delegated by the QPPV.
8. A list of all completed audits, for a period of 5 years, and a list of audit schedules.
9. Where applicable, a list of performance indicators implementing regulation.
10. Where applicable, a list of other PSMFs held by the same MAH. This list should include the PSMF 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 an MAH, the name of the service provider should also be included.
11. Other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change, and the nature of the change.

CHAPTER 11 PHARMACOVIGILANCE PLANNING

This section describes methods for summarizing the important identified risks of medical products, important potential risks, and important missing information, including the potentially at-risk populations and situations where the products are likely to be used that have not been studied pre-approval. This section proposes a structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies.

SCOPE

Pharmacovigilance planning will be useful for new medical products and health technologies as well as for significant changes in established products (e.g., new dosage form, new route of administration, new manufacturing process for a biotechnology-derived product), for established products that are to be introduced to new populations, insignificant new indications, or where a new major safety concern has arisen.

SAFETY SPECIFICATIONS

The safety specifications shall provide a summary of the important identified risks of a drug, important potential risks, and important missing information. These specifications shall also address the potentially at-risk populations and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period.

The safety specification can be built initially during the pre-marketing phase and, at the time approval is sought, it shall reflect the status of issues that were being followed during development. The elements of the safety specifications shall be as prescribed in the ICH E2E pharmacovigilance planning guideline.

PHARMACOVIGILANCE PLAN

This section provides guidance on the structure of a pharmacovigilance plan. The plan shall be developed by the sponsor and will be discussed with NMRAs during product development prior to approval (i.e., when the marketing application is submitted) of a new product or when a safety concern arises post marketing.

STRUCTURE OF THE PHARMACOVIGILANCE PLAN

The structure for the pharmacovigilance plan can vary depending on the product in question and the issues identified in the safety specification. The structure shall contain the following:

i. Summary of ongoing safety issues
ii. Routine pharmacovigilance practice
iii. Action plan for safety issues
iv. Summary of actions to be completed, including milestones

The structure and details regarding the pharmacovigilance plan shall be as prescribed in the ICH E2E pharmacovigilance planning guideline.

PHARMACOVIGILANCE METHODS

The methods to address specific situations can vary, depending on the product, indication, population being treated, and issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors shall employ the most appropriate method to ensure the safety concern is adequately addressed.

The various PV methods are described in **Annex 11** of these guidelines. The list is not all-inclusive and sponsors/MAHs shall use the most up-to-date methods that are relevant and applicable.

CHAPTER 12 PHARMACOVIGILANCE INSPECTIONS AND SELF-AUDITS

To ensure that MAHs comply with pharmacovigilance obligations and to facilitate compliance, EAC NMRAs will conduct routine or "for cause" pharmacovigilance inspections. The results of an inspection will be routinely provided to the inspected MAH, which will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.

This chapter contains guidance on the planning, conducting, reporting, and follow-up of pharmacovigilance inspections by EAC Partner States and outlines the role of the different parties involved.

The objectives of pharmacovigilance inspections are:

1. To determine that the MAH has personnel, systems, and facilities in place to meet their pharmacovigilance obligations.
2. To identify, record, and address non-compliance, which may pose a risk to public health.
3. To use the inspection results as a basis for enforcement action, where considered necessary.

Inspections can be announced, announced on short notice, or unannounced. This will be determined by NMRAs on a case-by-case basis.

INSPECTION TYPES

PRE-AUTHORIZATION INSPECTIONS

Pre-authorization pharmacovigilance inspections will be determined by NMRAs on a case-by-case basis depending on the risk of the product.

POST-AUTHORIZATION INSPECTIONS

Post-authorization pharmacovigilance inspections are inspections performed after a marketing authorization is granted and are intended to examine whether the MAH complies with its pharmacovigilance obligations. The types of inspections are as follows:

1. Pharmacovigilance system and product-related inspections

i. Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with NMRA pharmacovigilance requirements. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

ii. Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g., the system used for that product).

2. Routine pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programs. These inspections are usually system inspections, but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, such as those raised by assessors, may also be included in the scope of a routine inspection in order to investigate the specific issues.

3. Investigative, or "for cause," inspections

For cause pharmacovigilance inspections are undertaken when a trigger is recognized and an inspection is considered an appropriate way to examine the issues; this should be conducted through national or regional mechanisms. These inspections shall focus on specific pharmacovigilance processes or include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. These inspections may arise when, for example, one or more of the triggers listed below are identified:

a) Risk-benefit balance of the product:

i. Change in the risk-benefit balance where further examination through an inspection is considered appropriate
ii. Delays or failure to identify or communicate a risk or a change in the risk-benefit balance
iii. Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the NMRAs, as applicable
iv. Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the NMRAs
v. Suspension or product withdrawal with no advance notice to the NMRAs

b) Reporting obligations (expedited and periodic):

i. Delays or omissions in reporting
ii. Poor quality or incomplete reports
iii. Inconsistencies between reports and other information sources

c) Requests from NMRAs:

i. Failure to provide the requested information or data within the deadline specified by the NMRAs
ii. Poor quality or inadequate provision of data to fulfill requests for information from the NMRAs

d) Fulfillment of commitments:

i. Concerns about the status or fulfillment of RMP commitments
ii. Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization
iii. Poor quality of reports requested as specific obligations, inspections
iv. Delays in the implementation or inappropriate implementation of corrective and preventive actions
v. Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP, GDP)
vi. Inspection information received from other authorities (EAC or non-EAC), which may highlight issues of non-compliance
vii. Concerns following review of the PSMF
viii. Non-inspection-related information received from other authorities, which may highlight issues of non-compliance
ix. Other sources of information or complaints

4. Re-inspections

Re-inspection shall take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the

obligations, including evaluation of changes in the pharmacovigilance system. Re-inspection may be conducted due to the failure to implement appropriate corrective and preventive actions in response to a previous inspection.

5. Remote inspections

These pharmacovigilance inspections shall be performed by inspectors remote from the premises of the MAH or firms employed by the MAH. The mode of remote inspection for sites located outside the EAC shall include internet or telephone and shall involve review of documentation, safety database, source documents, and PSMF. Interviews of relevant staff shall be arranged where necessary. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g., a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the NMRAs.

FREQUENCY

Domestic or foreign MAHs or any firms employed to fulfill the MAH's pharmacovigilance obligations shall be inspected once every 2 and 3 years, respectively, depending on the type of inspection to be performed.

NMRAs shall plan pharmacovigilance inspections based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources while maintaining a high level of public health protection. NMRAs shall establish pharmacovigilance inspection programs depending on the location of the MAHs.

There are several factors that need to be considered when establishing pharmacovigilance inspection programs. These shall include, but are not limited to, the following:

i. Compliance history and re-inspection date recommended during previous pharmacovigilance inspections
ii. Products with additional risk minimization activities, limited alternative in the market, with mass use and requires PASS
iii. New MAHs/change in MAH or that which has never been inspected before and has many products in the EAC market
iv. MAHs whose products have safety concerns and availability of pharmacovigilance resources by MAH
v. Changes in PV system, such as change of QPPV, pharmacovigilance safety database, contractual arrangements, and transfer of PSMF

SITES TO BE INSPECTED

Any party carrying out pharmacovigilance activities in whole or in part and on behalf of or in conjunction with the MAH shall be inspected in order to confirm their capability to support the MAH's compliance with pharmacovigilance requirements.

INSPECTION PLANNING

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up, and documented in accordance with inspection procedures, as outlined in **Annex 12** and **Annex 16**. A systematic and risk-based approach shall be used to prioritize the inspections.

CLASSIFICATION OF PHARMACOVIGILANCE INSPECTIONS OBSERVATIONS

CRITICAL:

A deficiency in pharmacovigilance systems, practices, or processes that adversely affects the rights, safety, or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

MAJOR:

A deficiency in pharmacovigilance systems, practices, or processes that could potentially adversely affect the rights, safety, or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

MINOR:

A deficiency in pharmacovigilance systems, practices, or processes that would not be expected to adversely affect the rights, safety, or well-being of patients.

INSPECTION FOLLOW-UP

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

i. Review of the MAH's corrective and preventive action plan
ii. Review of the periodic progress reports, when deemed necessary
iii. Requests for submission of previously un-submitted data; variations (e.g., to amend product information); and impact analyses (e.g., following review of data that were not previously considered during routine signal detection activities)
iv. Requests for issuing safety communications, including amendments of marketing and/or advertising information; requests for a meeting with the MAH to discuss deficiencies, impact of the deficiencies, and action plans
v. Communication of the inspection findings to other NMRA authorities (including outside the EAC)
vi. Other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (may include recalls or actions relating to the marketing authorizations or clinical trial authorizations)

QUALIFICATION AND TRAINING OF PHARMACOVIGILANCE INSPECTORS

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by their Partner States should be officials of, or appointed by, the Partner State in accordance with national regulation and should follow the provisions of the NMRAs.

It is recommended that pharmacovigilance inspectors are appointed based upon their experience and the minimum requirements defined by the NMRA. In addition, consideration should be given to the recommendations for training and experience described in the EAC procedures.

Inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting, and reporting inspections.

They should also be trained in pharmacovigilance processes and requirements in such a way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes should be in place to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of the concerned NMRA.

JOINT INSPECTIONS WITHIN EAC

The EAC Secretariat shall coordinate joint inspections. There shall be cooperation between NMRAs to minimize duplication and maximize the use of available resources. NMRAs will make use of the shared information on planned and conducted inspections to facilitate this and to adapt the scope and/or timing of their inspections. Each Partner State shall adopt the inspections below, but joint inspections will be carried out within the region.

SELF-AUDITING

MAHs shall be required to perform audits of their pharmacovigilance systems including risk-based audits of their quality systems. Risk-based audits of pharmacovigilance systems shall cover all are as listed in these guidelines and the respective pharmacovigilance legislation in each Partner State. The audit shall focus on the areas of highest risk to the organization's pharmacovigilance and its quality system, with the risk to public health being of prime importance.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in these regulations to determine its effectiveness.

The audit activities shall include verification, examination, and evaluation of the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system and its quality system.

The MAH shall develop audit criteria that reflect their pharmacovigilance and quality systems and maintain records, statements, or other information, which are relevant to the audit criteria and can be verified by the NMRAs during pharmacovigilance inspections.

The risk-based audit shall be assessed in the following three stages.

1. Strategic level audit planning

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 program, usually for a period of 2-5 years. The audit strategy shall include a list of audits that will be performed including areas to be audited, methodology, assumptions, governance, risk management, and internal controls of all parts of the pharmacovigilance system.

2. Tactical level audit planning

This is a set of one or more audits planned for a specific timeframe, normally for a year. The audit program shall be prepared in line with the long-term audit strategy and shall be risk based. The program shall be approved by top management with overall responsibility for operational and governance structure. The risk assessment shall focus on the quality system for pharmacovigilance activities, critical pharmacovigilance processes, key control systems, and identified high-risk areas in place.

3. Operational level audit planning

Written procedures shall be in place regarding the planning and conduct of individual audits including the timeframes. The audits shall be conducted in accordance with the written procedures. The risks relevant to

the area under review shall be identified and assessed during planning and shall include appropriate risk-based sampling and testing methods.

AUDIT REPORTING

i. Audit findings shall be reported in line with their relative risk level and shall be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes, and parts of processes. The grading system shall be defined in the description of the quality system for pharmacovigilance. The classification of the findings shall be as described in section 12.6 of these guidelines. The findings shall be documented in an audit report and shall be communicated to management in a timely manner and issues that need to be addressed urgently shall be reported expedited manner.
ii. The QPPV shall be notified of any audit findings relevant to the pharmacovigilance system in the EAC, irrespective of where the audit was conducted.
iii. The MAH shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the PSMF.

ACTIONS AND FOLLOW-UP

i. Corrective actions, including a follow-up audit of deficiencies, shall be taken where necessary.
ii. The management of the organization shall be responsible for ensuring there is a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions shall include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.
iii. The audit shall involve evaluating the effectiveness of actions taken with the products for the purpose of minimizing risks and supporting their safe and effective use in patients.
iv. The organization shall use performance indicators to continuously monitor the good performance of pharmacovigilance activities.
v. Evaluation of audit work shall be undertaken by means of ongoing and periodic assessment of all audit activities, auditee feedback, and self-assessment of audit activities (e.g., quality assurance of audit activities, compliance to code of conduct, audit program, audit procedures).

AUDITORS' QUALIFICATIONS, SKILLS, EXPERIENCE, AND CONDUCT

1. Audits shall be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited. Pharmacovigilance audit activities should be independent. Auditors shall be free from interference in determining the scope of auditing, performing pharmacovigilance audits, and communicating audit results.
2. Auditors shall demonstrate and maintain proficiency in terms of the knowledge, skills, and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. They shall have knowledge, skills, and abilities in the following:

    i. Audit principles, procedures, and techniques
    ii. Applicable laws, regulations, and other requirements relevant to pharmacovigilance
    iii. Pharmacovigilance activities, processes, and system(s)
    iv. Management system(s)
    v. Organizational system(s)
    vi. Documents and information collected by the internal auditor to be treated with appropriate confidentiality and discretion

OUTSOURCING

The organization may use an outsourced audit service provider, however, the ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization. Documentation of the agreements shall be drawn between the organization and the service provider that shall include the scope, objectives, and procedural requirements.

NATIONAL MEDICINE REGULATORY AUTHORITIES (NMRAS), PUBLIC HEALTH PROGRAMS, AND HEALTH FACILITIES AUDITS

NMRAs, public health programs, and health facilities shall perform regular independent risk-based audits of their pharmacovigilance tasks and the quality system. The audits shall be conducted at regular intervals according to a common methodology agreed upon by the EAC Partner States to ensure that the quality system complies with the requirements.

NMRAs shall conduct audits and supervision of the pharmacovigilance activities of the public health programs and health facilities to ensure that they meet their pharmacovigilance obligations.

CHAPTER 13 SAFETY COMMUNICATION

Risk communication refers to the exchange of real-time information, advice, and opinions between experts and people facing threats to their health, economic, or social well-being. The fundamental goal of risk communication is to provide timely, meaningful, relevant, and accurate information in clear and understandable terms targeted to a specific audience for minimizing the risk burden.

Communicating safety information to patients and healthcare professionals is essential for achieving the objectives of pharmacovigilance. Promoting the rational, safe, and effective use of medical products and minimizing risks contribute to the protection of patients and public health.

AIMS OF SAFETY COMMUNICATION

Safety communication aims to:

a) Provide timely, evidence-based information on the safe and effective use of medical products and health technologies
b) Facilitate changes to healthcare practices (including self-medication practices), where necessary.
c) Change attitudes, decisions, and behaviors in relation to the use of medical products and health technologies.
d) Support risk minimization behavior.
e) Facilitate informed decisions on the rational use of medical products and health technologies.
f) Support public confidence in the NMRA system, when performed in an effective and high-quality manner.

STEPS IN RISK COMMUNICATION

The risk communication process is a step-by-step process that involves the following:

a) Identifying the issue and its context
b) Assessing the risk and benefits
c) Identifying and analyzing options
d) Selecting a strategy
e) Implementing the strategy
f) Monitoring and evaluation of results

The EAC Partner State NMRAs shall communicate the risk related to medical products safety guided by the risk communication procedure for medicine safety.

PRINCIPLES OF SAFETY COMMUNICATION

The following principles of safety communication shall be applied:

a) Safety communication shall deliver relevant, clear, accurate, and consistent messages and reach the right audiences at the right time for them to take appropriate action.
b) Safety communication shall be tailored to the appropriate audiences (e.g., patients, healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs while maintaining the accuracy and consistency of the information conveyed.
c) The need for communicating safety information shall be considered throughout the pharmacovigilance and risk management process and should be part of risk assessment and risk minimization measures.
d) There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g., NMRAs, other public bodies, MAHs).

e) Information on risks shall be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions, and expected time to recovery.
f) Safety communication shall address the uncertainties related to a safety concern. This is of particular relevance for new information, which is often communicated while NMRAs are conducting their 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., use of absolute risks and not just relative risks); when comparing risks, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the risk-benefit balance may also be considered.
i) Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly with regard to 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 AUDIENCE

The primary target audiences for safety communication issued by NMRAs and MAHs should be patients, caregivers, and healthcare professionals who use (i.e., prescribe, handle, dispense, administer, or take) medical products.

CONTENT OF SAFETY COMMUNICATION

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information shall not include any material or statement that might constitute advertising.

Safety communication shall contain:

i. Important new information on any authorized medicinal product that has an impact on the medicine's risk-benefit balance under any conditions of use.
ii. The reason for initiating safety communication clearly explained to the target audience.
iii. Any recommendations to healthcare professionals and patients on how to deal with a safety concern.
iv. When applicable, a statement on the agreement between the MAH and the NMRAs on the safety information provided.
v. Information on any proposed change to the product information (e.g., SmPC or PIL).
vi. Any additional information about the use of the medical product or other data that may be relevant for tailoring the message to the targeted audience.
vii. A list of literature references, when relevant, or a reference to where more detailed information can be found, and any other background information considered relevant.
viii. A reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

COMMUNICATION CHANNELS

Relevant communication tools and channels should be considered when issuing a safety communication in order to

reach the target audiences and meet their growing expectations. Different communication tools and channels shall include but not limited to:

i. Direct healthcare professional communication (DHPC)
ii. Communication materials from NMRAs targeted at healthcare professionals
iii. IEC materials to patients and the general public (e.g., brochures, flyers, public alerts)
iv. Press communication (e.g., press releases, press briefing)
v. Websites
vi. Social media and other online communications
vii. Bulletins and newsletters
viii. Inter-NMRA communication
ix. Responding to enquiries from the public
x. Other means such as publications, scientific, and professional journals
xi. Conferences, seminars, and workshops

EFFECTIVENESS OF SAFETY COMMUNICATIONS

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. Mechanisms shall be introduced in order to measure the effectiveness of the communication. A research-based approach is recommended to establish that safety communications have met the necessary standards. This approach may measure different outcomes, including behavior, attitudes, and knowledge.

SAFETY COMMUNICATION WITHIN EAC

For safety issues concerning any of the Partner States, prior to the publication of a safety announcement the NMRAs shall inform each other not less than 24 hours in advance, unless urgent public announcements are required for the protection of public health. Communications shall follow the procedures described in **Annex 15**.

For medical products registered within the EAC, the EAC Secretariat and the lead country NMRA shall be responsible for the coordination between NMRAs regarding safety announcements.

The following safety announcements that relate to medical products authorized in EAC Partner States shall require coordination by the EAC Secretariat and lead NMRA:

i. The suspension, withdrawal, or revocation of a marketing authorization due to changes to its risk-benefit balance
ii. Restriction of indication or treatment population or the addition of a new contraindication
iii. Dissemination of a DHPC
iv. Other emerging safety concerns judged by EAC and NMRAs as likely to give rise to public or media interest in the Partner States (e.g., a publication of important safety findings in a [scientific] journal, safety-related regulatory action taken in a Partner State or in a country outside the EAC)

EXCHANGE OF SAFETY INFORMATION PRODUCED BY THIRD PARTIES

There are situations where new safety information has been published by a party other than the NMRA of a Partner State (e.g., scientific journals, learned societies, and other NMRA authorities outside the EAC). NMRAs should bring to the attention of the EAC Secretariat any such safety information that they become aware of together with the timing of the publication, if known. Where necessary and after evaluation of the information, the EAC Secretariat and lead NMRA shall prepare and disseminate a safety announcement to address the information from the third party.

SAFETY COMMUNICATION FOR THE MARKETING AUTHORIZATION HOLDER IN THE EAC

When the MAH in the EAC intends to make a public announcement relating to safety concerns regarding use of a medical product, at the same time or before the public announcement is made, the MAH shall be required to seek approval from the relevant NMRAs in the Partner States as per **Annex 14**. NMRAs within the Partner States shall provide such approval as early as possible but not more than 7 calendar days.

The MAH shall ensure that information given to the public is presented objectively and is not misleading.

Whenever an MAH becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of a medicinal product registered in the EAC, the MAH should inform the relevant NMRAs in Partner States and make every effort to share the content of the communications with the relevant NMRAs.

PUBLICATION OF DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

The NMRAs may publish the final DHPC. The MAH shall be informed of the intent to publish the DHPC so that the timing for such publication is aligned with that of the dissemination of the DHPC in the Partner States. The NMRAs in the Partner States may also issue an additional safety announcement and disseminate to the relevant healthcare professionals' organization(s) as appropriate. This communication shall be in accordance with the DHPC plan (**Annex 13**).

CHAPTER 14 REGULATORYACTIONS

GENERAL CONSIDERATIONS

EAC Partner State NMRAs shall enforce relevant legislation and ensure compliance with pharmacovigilance requirements in order to protect public health. When non-compliance with pharmacovigilance NMRA obligations is detected, the necessary actions will be determined on a case-by-case basis. Actions to be taken shall depend on the potential negative public health impact of non-compliance and instances of non-compliance may be referred for enforcement action. In addition, in the event of non-compliance, NMRA options may include the following:

i. Education and facilitation: MAHs may be informed of non-compliance and advised on how this can be remedied
ii. Inspection: Non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved
iii. NMRAs shall issue a formal warning letter reminding MAHs of their pharmacovigilance obligations to the NMRAs
iv. Naming non-compliant MAHs: NMRAs shall consider a policy of making public a list of MAHs found to be seriously or persistently non-compliant
v. Urgent safety restriction
vi. Variation of the marketing authorization
vii. Suspension of the marketing authorization
viii. Revocation of the marketing authorization
ix. Product recalls

The Partner States shall agree on common range of recommendations that may be taken as a result of the assessment and conclusion of the signal assessment. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the totality of the information, the need for action should be considered throughout the signal management process.

For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch. The review of available information at the signal validation or signal prioritization stages may similarly conclude that the evidence is sufficiently strong to inform healthcare professionals and patients. In such situations, it is still necessary to proceed with a formal assessment of the signal in order to confirm (or deny) the safety issue in order to extend or lift the temporary action.

The assessment may require active monitoring of the signal or provision of additional information by the MAH in order to confirm that the conclusion is valid for all indications and patient groups. The assessment may also conclude that the issue needs to be reviewed periodically, for example through the PSURs.

Actions may include additional investigations or risk minimization activities if the mechanisms of occurrence of the suspected adverse reaction highlight the possibility of preventing or mitigating the adverse reaction. If the conclusion was based on limited evidence, it may be necessary to conduct a PASS to investigate the potential safety issue.

Whenever additional activities are requested by the NMRA to the MAH, the request should specify a timeframe by which they should be completed, including progress reports and interim results, proportionate to the severity and public health impact of the issue. MAHs and competent authorities should consider the feasibility of conducting a study within the set timelines considering the characteristics of the safety issue of interest, such as its incidence and the need for a prospective study design. Temporary measures to ensure the safe and effective use of the medicinal product or to eliminate the risk should be considered, including the possibility of temporarily suspending the marketing authorization of the medicinal product.

If there is no evidence of a risk for patients, the NMRA may decide that no further assessment or action is required.

WITHDRAWAL OF A PRODUCT FROM THE MARKET ON RISK-BENEFIT GROUNDS

After a risk-benefit evaluation of a product wherein the risks outweigh the benefits and the proposed risk minimization measures are considered inadequate to redress the balance, the medical product should be withdrawn from the market and healthcare professionals and patients/the public should be informed as appropriate. In case the MAH withdraws the medical product due to safety concerns, they shall be obliged to immediately report to the NMRAs.

FUTURE CONSIDERATIONS

EAC Partner States, the EAC Secretariat, and stakeholders will aim to develop a vigilance framework on products that are currently not regulated by some of the Partner States but need regulation in the future. These products may include, but are not limited to, antiseptics, disinfectants, blood and blood products, cosmetics, food and food supplements, and nutraceuticals.

APPEAL

For products that have been suspended and had marketing authorization cancelled by the NMRA, the MAH may make a written appeal to the NMRA to review its decision.

All notice of appeals must be made within 30 calendar days from the date of the NMRA's notification.

The MAH shall make an appeal by making a case for the review based on the reasons given for the product's initial rejection. The grounds for the request shall be based on the information that was submitted in the product's dossier. Any additional or new information that was not earlier submitted will not be accepted.

The NMRA may review or uphold its earlier decision.

REFERENCES

European Medicines Agency (EMEA). Guideline on good pharmacovigilance practices (GVP): Module XI.

EMEA. Guideline on good pharmacovigilance practices (GVP): Module V – Risk management systems (Rev 2). 24 February 2016.EMEA. Guideline on good pharmacovigilance practices (GVP): Module IV – Pharmacovigilance audits (Rev 1). 3 August 2015.

EMEA. Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management. October 2017.

EMEA. Guideline on good pharmacovigilance practices (GVP): Module II – Pharmacovigilance system master file (Rev 2). 28 March 2017.

Therapeutic Goods Administration, Department of Health, Australian Government. (2017, September 2017). *Pharmacovigilance inspection program: Guidance for medicine sponsors* (version 1.0). Retrieved from https://www.tga.gov.au/node/764026

ANNEX 1: ADR/AEFI REPORTING FORM

Note: Reporters' and patients' identities are held in strict confidence by the EAC and protected to the fullest extent of the law

Type of Report

Initial☐ Follow-up☐ Serious ☐ Not Serious☐ Medical product☐ Vaccine☐

Patient Information

Patient ID/initials:_____ Gender: Male☐ Female☐ Weight(kg)_____Pregnancy status: Yes No Full address_____ Telephone Number_____

*Date of birth :_ _/ _ _/ _ _ (dd/mm/yyyy) OR Age at onset:*_____Medical History (Provide any relevant medical history and laboratory results including dates, if done) ……

Details of suspected medical product

Name of suspected medicine (s) (specify brand name and manufacturer if known)	Generic name	Route	Dose and frequency	Date started	Date stopped	Batch no. & expiry date	Indication (Reason for use)
1.							
Other medicines used at the same time and/or in the last one month (including herbal medicines)							

Details of suspected vaccine

				Diluent (if applicable)			
Name of vaccine	Date of vaccination	Time of vaccination	Dose (1st, 2nd, 3rd, etc.)	Batch/lot No. & expiry date	Name of diluent	Batch/lot No. & expiry date	Date and time of re- constitution

Brief description of the ADR/AEFI

Description of the AEFIs *(for vaccines)*

Severe local reaction >3days Encephalopathy Toxic shock syndrome Thrombocytopenia Anaphylaxis Generalized urticaria (hives) Injection site abscess High fever ≥38°C

Other(specify) _____

Date of ADR/AEFI onset: _ _ / _ _/_ ___ Time of onset:_____Date ADR/AEFI stopped: _ _ / _ _/_ _ __

Severity of the ADR/AEFI

Mild☐ Moderate☐ Severe☐ Fatal☐ Unknown☐

Reason for seriousness

Prolonged hospitalization☐ Congenital anomaly☐ Disability☐ Death☐ Life threatening☐

Action taken

Drug withdrawn☐ Dose increased☐ Dose reduced☐ Dose not changed☐ Not applicable☐ Unknown☐

Outcome

Recovered☐ Recovering☐ Recovered with sequelae☐ Not recovered☐ Death☐ Unknown☐

Causality of the ADR/AEFI

Certain☐ Probable/Likely☐ Possible☐ Unlikely☐ Unclassifiable☐

Therapeutic failure (Provide information on medicine(s) or vaccine(s) that showed lack of efficacy)

Medication errors (Provide details of medication errors)

Additional information (Provide any other relevant additional information below)

Administrative Information

Report title:	Form ID number:	Date of reporting:	
Name of institution:	Email Address:		Country:
	Contact/Tel No:		
Name of reporter:	Contact:	Email:	

GUIDANCE ON REPORTING

What to report

- Report all adverse drug reactions/events suspected both serious and those that are not serious.
- Report any adverse reaction or AEFIs even if you are not certain the product caused the event.

When to Report

- For serious ADRs, report within 24-48 hours of notification
- For AEFIs, report immediately after you are notified
- For non-serious events, report as soon as possible but not later than 15 days

Who is to Report

- All healthcare providers should report as part of their professional responsibility any suspected adverse drug reactions and AEFIs

Where to Report

- Reports should be sent to the NMRAs
- Reports can also be sent to the national AEFI committee

How to report

- Fill in the sections that apply to your report
- Start date of administration for the suspected drug and the date when the suspected reaction occurred

Severity of reaction

Mild: ADR/AEFI that requires no change in treatment with the suspected drug. Requires suspected drug to be withheld, discontinued, or otherwise changed. No prolonged hospitalization.

Moderate: ADR/AEFI requires the suspected drug to be withheld, discontinued, or otherwise changed. Prolongs hospitalization by at least 1 day. ADR is the reason for admission.

Severe: ADR/AEFI requires intensive medical care, causes permanent harm to the patient.

Fatal: ADR/AEFI either directly or indirectly leads to death of the patient.

Detection of ADR/AEFIs in a Patient

Take the following steps:

Take proper history and conduct proper examination of the patient.

Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised.

Verify that the onset of the suspected ADR was after the drug was taken, not before, and discuss carefully the observation made by the patient.

Determine the time interval between the beginning of drug treatment and the onset of the event.

- Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status (De-challenge). If appropriate, restart the drug treatment and monitor recurrence of any adverse events (Re-challenge).
- Analyze the alternative causes (other than the drug) that could on their own have caused the reaction.
- Use relevant up-to date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction.

Please note that submission of a report does not imply that the health worker or the product caused or contributed to the adverse event.

WHO-UMC causality assessment scale

Causality Term	Assessment
Certain	• Event of laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically *(i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)* • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drugs withdrawal lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ unclassified	• Event or laboratory test abnormality • More data for proper, assessment needed or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because of insufficient or contradictory information • Data cannot be supplemented or verified

Confidentiality

All information pertaining to the reported event should at all times be treated in confidence and protected from an authorized access transmission of use.

ANNEX 2: PATIENT ADVERSE DRUG REACTIONS REPORTING FORM

ADVERSE REACTION PATIENTS' REPORTING FORM

(For reporting adverse reactions and product problems by non-healthcare providers)

Note: Identities of patient will remain confidential

I. PERSON REPORTING	
❑ Patient ❑ Community health worker ❑ Mother ❑ Relative ❑Other ❑ Specify: _____	Sex: Male ❑ Female ❑ Age of the patient_____

II. BRIEF DESCRIPTION OF THE REACTION/EVENT (Describe how the medicines affected you?)	
…… ……..…… ……....	Date Reaction Started →___ /___ /____ Date Reaction Stopped (if known)→___ /____ /_____ Date reported……

III. SUSPECTED MEDICINE USED (Which medicines do you think caused the reaction?)					
Name of suspected medicine(s)	**Dosage**	**How many times per day**	**Route (swallow, injection, applied…)**	**Date & time when the medicines were taken**	
1.				**Start date**	**Stop date**
2.					
3.					

IV. DESCRIPTION OF ANY HERBAL MEDICINE THE PATIENT WAS TAKING (Did you use any other medicines including herbal?)

V. SERIOUSNESS/SEVERITY OF THE ADVERSE REACTION (Please tick the appropriate)	
❑Discomfort but able to work	❑Caused persistent disability or incapacity
❑Discomfort could not work	❑Caused a congenital anomaly
❑Required or prolonged hospitalization	❑Patient died: Date of death _____
❑Life threatening	❑Others, please give details……..…..

VI. SOURCE OF THE MEDICINE (Where did you get the medicine from?)	
❑Hospital Pharmacy	❑Traditional Healer
❑Retail Pharmacy	❑ Supermarket/General shop
❑ Wholesale Pharmacy	❑Family/Neighbor
❑ADDO/Drug Shop	❑Others, please specify……..…..…

VII. REPORTER NAME AND CONTACT ADDRESS	
Name: (Optional): Contact Phone No: _____ Email: (if available) _____ Date of this report: _____	Contact Address:
Thank you for your cooperation	***Ref No. (for official use)***

ANNEX 3: MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM

Type of Report*

Initial ☐ Follow-up ☐

Category of event*

Public health threat ☐ Death/Serious injury ☐ Other ☐

Date of reporting: **Date of AE Onset:** **Date AE stopped:**

Patient information

Patient ID/initials: _____ Gender: Male ☐ Female ☐ Weight (kg)_____

Full address_____ Telephone Number _____

Date of birth:_ _/ _ _/ _ _ (dd/mm/yyyy) OR Age at event onset:_____

Patient history (co-morbidities and medication)_____ Pregnancy status Yes ☐ No ☐ N/A ☐

Device Information*

Brand name:		Serial/lot no.:
Common name: *(e.g., catheter, central venous, peripherally inserted)*	Model:	Catalogue:
Name of manufacturer:	Address:	

Operator of device at time of onset

Healthcare Professional ☐ Patient ☐ Caregiver ☐ N/A ☐

Usage of device *(choose whichever applies)*

Single use ☐ Reuse of reusable ☐ Reuse of single use ☐ Reserviced/refurbished ☐

Problem noted prior to use ☐ other (specify) ☐ _____

Date of Implant:	Date of Explant:
Device disposition/current location:	Expiry date *(if applicable)*:

Diagnostics section *(for diagnostics only)*

Type of specimen used (e.g., blood, saliva, etc.):		
No. of patients involved:	No. of tests done:	No. of false positives:
No. of false negatives:	No. of true positives:	No. of true negatives

List of other devices involved in the event*

Description of event

Remedial Action/Corrective Action/Preventive Action

Patient outcome*

Continued ☐ Recovered ☐ Recovering ☐ Disability ☐ Death ☐

Details of reporter*

Name of reporter: **Email/contact:** **Designation/Occupation:**

Name of institution:

Location address:

Guidance on reporting	
Report Type ***Initial:*** The first report that the reporter (sponsor, manufacturer) is submitting about an event. The reporter expects to have to submit further information about the event at a later date. ***Follow-up:*** Additional information to a previous (initial, follow-up) report. **Report Category** ***Public Health Threat:*** *(Serious public health threat or concern)* These reports must be submitted within **24 hours** of the manufacturer, user becoming aware of the event. ***Death/Serious Injury****:* Choose this category when the event subject of the report resulted in the death or serious injury of a patient, user, or other person. ***Other****:* Choose this category when the event subject of the report was a "near miss" or is the result of testing or other analysis and an event or further occurrence could lead to the death or serious injury of a patient, user, or other person. **Clinical Event Information** Provide as much detail about the event as possible, including what happened and what led up to the event (e.g., the type of surgery or treatment). If the device is implantable, provide date of implant and explant.	**Device Information** ***Device Disposition/Current Location:*** Where and in what state the device is at the time of the report (e.g., destroyed/lost or with manufacturer undergoing testing, with original reporter). **Patient Information** This will include the patient's age, gender, and/or weight and other relevant patient history. **List of other devices involved in the event:** Some events are caused by the combined action of two or more devices. List any other device(s) that were being used at the time of the event, if known. A final report is considered to be a complete report and therefore **all fields marked with an ✱ must be completed.** **Where to Report** Reports should be sent to the NMRAs. **Confidentiality** All information pertaining to the reported event should always be treated in confidence and protected from an authorized access transmission of use.

ANNEX 4: PRODUCT QUALITY REPORTING FORM

Type of complaint *(Check whichever is applicable)*

Colour change ☐ Suspected falsified ☐ Molding ☐ Turbidity ☐ Mislabeling ☐ Packaging ☐

Particulate matter ☐ Caking ☐ Separating ☐ Therapeutic ineffectiveness ☐

Others ☐ *Please Specify*:_____

Product Category (Check whichever is applicable)

Medicinal product ☐ Vaccine ☐ Herbal product ☐

Other ☐ *Please Specify*:_____

Product Details *(Please fill whichever applies)*

Brand name:	Generic name:	
Manufacturing date:	Expiry date:	Batch/lot no.:
Name of manufacturer: Address:	Name of distributor/supplier: Address:	

Product dosage form

Tablets/Capsules ☐ Suspension/Syrup ☐ Injectable ☐ Creams/Ointment/Liniment/Paste ☐

Ear/Eye drops ☐ Powder for oral ☐ Pessaries ☐ Suppository ☐

Other ☐ *Please Specify*:_____

Storage conditions

Does product require refrigeration? Yes ☐ No ☐

Was product available at facility? Yes ☐ No ☐

Was product stored following manufacturer recommendation? Yes ☐ No ☐

Was product dispensed and returned by patient? Yes ☐ No ☐

Name and address of the health facility where product was obtained or bought

Description of the complaint

Details of reporter

Name:	**Designation/Occupation:**
Name of institution:	
Location address:	
Tel. No.:	**Email address:**

ANNEX 5: PATIENT ADR ALERT CARD

Front side

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME: .....

AGE: ..... GENDER: .....

DATE ISSUED: .....ADDRESS: .....

SUSPECTED DRUG(S): .....

DESCRIPTION OF REACTION: .....

Other comments (if any): .....

.....

Please carry this card with you at all times and remember to show it to your healthcare provider at each time of consultation	***Tafadhali hakikisha umebeba kadi hii kila wakati na kumbuka kumwonyesha mhudumu wa afya unapo pata matibabu***

NMRA Contact details

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD *Rear side*

The alert card is to be given to:

- Patients who are hypersensitive/allergic/intolerant to a particular drug.
- Patients who developed a "near-fatal" reaction to any particular drug.
- Patients who had a drug-induced morbidity to any drug.
- Patients who had hospital admission due to an adverse reaction to any drug.

ANNEX 6: FORMAT OF A RISK MANAGEMENT PLAN

OVERVIEW OF THE RMP PARTS AND SECTIONS

Part I Product(s) overview
Part II Safety specification
Section I Epidemiology of the indication(s) and target population(s)
Section II Non-clinical part of the safety specification
Section III Clinical trial exposure
Section IV Populations not studied in clinical trials
Section V Post-authorization experience
Section VI Additional EAC requirements for the safety specification
Section VII Identified and potential risks
Section VIII Summary of the safety concerns
Part III Pharmacovigilance plan (including post-authorization safety studies)
Part IV Plans for post-authorization efficacy studies
Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
Part VI Summary of the risk management plan
Part VII Annexes

PRODUCT OVERVIEW

This section should provide information on the RMP and the overview of the product. This should include active substance, pharmacotherapeutic group, name of the marketing authorization applicant for initial marketing authorization applications, marketing authorization holder for RMPs submitted with post-authorization procedures, and medicinal product(s) to which this RMP refers. Authorization procedure(s) (centralized, mutual recognition, decentralized, national); brief description of the product including:

i. Chemical class
ii. Summary of mode of action
iii. Composition (e.g., origin of active substance of biologicals, relevant adjuvants, or residues for vaccines)
iv. Indications
v. Pharmaceutical form and strengths

SAFETY SPECIFICATIONS

This section should provide adequate information on the safety profile of the medicinal product with a focus on aspects that need further risk management activities. This section should contain a description of each of the eight modules as listed below:

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

Refer to chapter 7 (pharmacovigilance plan) and chapter 11 (PASS) of these guidelines and the current version of ICH E2E pharmacovigilance planning guideline.

SUMMARY OF THE RISK MANAGEMENT PLAN

This section should provide a risk minimization plan for each of the safety concerns raised in the safety specification sections. It should include routine and any other risk minimizations including justification and indicators to measure the effectiveness of the plan.

RMP ANNEXES

i. Tabulated summary of planned, ongoing, and completed pharmacovigilance study program
ii. Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan
iii. Specific adverse event follow-up forms
iv. Protocols for proposed and ongoing studies in RMP part IV
v. Details of proposed additional risk minimization activities
vi. Other supporting data (including referenced material)
vii. Summary of changes to the RMP over time

ANNEX 7: FORMAT AND CONTENT OF THE PROTOCOL OF NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDIES

INTRODUCTION

The study protocol should be concise, while providing the information needed to understand how the study will answer the research question and assess the validity of the study design.

All headings and sub-headings of the format presented in this guidance should always be included and the same numbering should be used. Additional sub-headings can be added as necessary. Where a heading or sub-heading does not apply to the study (e.g., protection of human subjects), "Not applicable" should be stated with a short justification. All dates should be indicated in the format "DD Month YYYY" (e.g., 15 August 2018). Annex 1 should be used to list stand-alone documents not included in the protocol, such as contact details of responsible parties and all investigators, or sections 9.6 data management, 9.8 quality control, and 10 protection of human subjects, which can be maintained apart from the study protocol where they represent standard procedures applied to all studies. In this case, a summary should be provided in the corresponding section of the protocol and reference should be made to Annex 1. Annexes can be added to provide documents referred to in the protocol.

The text in green italics is intended to guide the reader on the principal points to be considered for writing that section of the protocol. It should be deleted if this guidance is used as a template.

As a reminder, the MAH(s) involved should keep a copy of the protocol signed by the QPPV or his/her delegate (with the date of the signature), to be available for any future request or inspection.

This guidance may be later revised based on experience.

1. **PASS information**: PASS information should be provided in a table on the title page of the study protocol.

Title	Informative title including a commonly used term indicating the study design and the medicinal product, substance, or drug class concerned
Protocol version identifier	Number
Date of last version of protocol	Date
Clinical trials registry reference number	Registration number in the clinical trials registry; indicate "Study not registered" if the study has not been registered
Active substance	List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study
Medicinal product	List of centrally authorized medicinal product(s) and/ or, if possible, of nationally authorized products subject to the study
Product reference	Reference number(s) of centrally authorized products and/or, if possible, of nationally authorized products subject to the study
Marketing authorization holder(s)	Marketing authorization holder(s) that initiate(s), manage(s), or finance(s) the study
Joint PASS	"Yes" or "No"
Research question and objectives	Summary of the research question and main objectives
Country(-ies) of study	List of countries where the study is to be conducted; if countries have not been identified yet, or if the list is not complete, this should be stated
Author	Name and contact details of the main author of the study protocol

2. Marketing authorization holder(s)

MAH(s)	Name, address, and contact details of the MAH(s)

MAH contact person	Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)

3. **Table of contents (PASS)**: The study protocol should include a table of contents.
4. **Responsible parties:** List of all main responsible parties, including the principal investigator, a coordinating investigator for each country in which the study is to be performed, and other relevant study sites. Contact details and the list of all investigators can be kept in a standalone document to be listed in Annex 1 and to be available upon request.

In case of a joint PASS, any sharing of responsibilities (e.g., for management of adverse events) or distribution of tasks between MAHs and other responsible parties should be mentioned in this section. Contact persons for each MAH should be mentioned.

5. **Abstract:** Standalone summary of the study protocol including all the subsections below.

    i. Title: The title should include 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: "Population" includes the setting and study population
    vi. Variables
    vii. Data sources
    viii. Study size
    ix. Data analysis
    x. Milestones

6. **Amendments and updates:** Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
2	Date	Text	Text	Text
…	Date	Text	Text	Text

7. **Milestones:** Planned dates for study milestones should be indicated in a table as indicated below. Milestones between (< >) are optional and should be included only if applicable. Start of data collection and end of data collection are defined in Module VIII of the GVP (where the study uses data from existing electronic data bases such as claims, prescriptions, or healthcare records, "secondary use of data" applies to these definitions). Other important timelines can be added.

Milestone	Planned date
Start of data collection	Date
End of data collection	Date
<Study progress report 1>	Date
<Study progress report 1>	Date
<Study progress report 1>	Date
<Interim report 1>	Date
<Registration in the EU PAS register>	Date
Final report of study results	Date

8. **Rationale and background:** Short description of the safety hazard(s), safety profile, or 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.
9. **Research question and objectives**: Research question that explains how the study will address the issue that led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures. Objectives should be organized as primary or secondary objectives where applicable.
10. **Research methods:** Description of the research methods, including:

    i. *Study design*: Overall research design and rationale for this choice, specifying the study design proposed (cohort, case-control, etc.) and any comparison groups. The primary and secondary endpoints and the main measure(s) of effect should be mentioned. The strength of the study design to answer the research question may be explained in this section.
    ii. *Setting*: Setting and study population defined in terms of persons, place, study time period, and selection criteria, including the rationale for any exclusion criteria and their impact on the number of subjects available for analysis. Plans for baseline visits and follow-up visits should be described. Representativeness of the study population as regards the source population should be addressed. 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.
    iii. *Variables*: Definition of exposures, outcomes, and other variables including measured risk factors, co-morbidities, co-medications, etc., with operational definitions and measurement; potential confounding variables and effect modifiers should be specified.
    iv. *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 is based on secondary analysis an existing data source, such as electronic health records or claims databases, any information on the validity of the recording and coding of the data should be reported. For exposures or outcomes not previously validated, validation performed in the study should be described or otherwise addressed. Linkage methods between data sources should be described as appropriate. 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.
    v. *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. All assumptions used to calculate the study size or precision of the study should be presented and justified.
    vi. *Data management*: Data management and statistical software(s) to be used in the study, including procedures for data collection, retrieval, collection, and preparation. Data collection methods and tools (e.g., paper-based or electronic case reporting forms; monitoring, if any; and supervision) can be summarized in this section and fully described or presented in an annex.
    vii. *Data analysis*: Rationale for the choice of statistical techniques and major steps that led from raw data to a final result, including methods used to correct inconsistencies or errors, impute values,

modify raw data, categorize, analyze, 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.

viii. *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 the statistical programming performed to generate the results. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

ix. *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.

x. *Other aspects*: Any other aspect of the research method not covered by the previous sections.

11. **Protection of human subjects:** Safeguards in order to comply with national and EU requirements for ensuring the wellbeing and rights of participants in a non-interventional PASS.
12. **Management and reporting of adverse events/adverse reactions:** Procedures for the collection, management, and reporting of individual cases of adverse events/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. For studies where reporting is not required, this should be stated. Any arrangements made between MAHs for the management and reporting of adverse events/reactions in joint PASS should be specified.
13. **Plans for disseminating and communicating study results**: Any plans for submission of progress reports and final reports; any arrangements made between MAHs for the dissemination and communication of study results of joint PASS.
14. **References**: Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow for retrieval of the document. Feasibility or pilot studies that were carried out to support the development of the protocol (e.g., 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 NMRA upon request. Feasibility or pilot studies that are part of the research process should be described in the protocol (e.g., a pilot evaluation of the study questionnaire[s] used for the first set of patients recruited into the study).
15. **Annexes:** 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.

ANNEX 8: FORMAT OF THE PASS FINAL STUDY REPORT

1. **Title**: Title including a commonly used term indicating the study design and sub-titles with date of final report and name and affiliation of main author. If the study has been registered in the clinical trials registry. With regard to the Register, the final study report should mention on the title page "Register No:" with the registration number and the web link to the study record.
2. **Abstract**: The abstract of the final study report should include a summary of the study methods and findings.
3. **Marketing authorization holder**: Name and address of the marketing authorization holder.
4. **Investigators**: Names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators, and list of all collaborating primary institutions and other relevant study sites. Such information should be provided for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the NMRA and national competent authorities upon request.
5. **Milestones**: Dates for the following milestones:
    i. Start of data collection (planned and actual dates)
    ii. End of data collection (planned and actual dates) 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 (planned and actual date)
    vi. Any other important milestone applicable to the study, including date of study registration in the Register and date of protocol approval by an Institutional Review NMRA/Independent Ethics Committee if applicable
6. **Rationale and background**: Description of the safety concerns that led to the study being initiated or imposed, and critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. **Research question and objectives**: Research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.
8. **Amendments and updates to the protocol**: List of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.
9. **Research methods**:
    a) *Study design*: Key elements of the study design and the rationale for this choice.
    b) *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.
    c) *Subjects*: Any source population and eligibility criteria of study subjects. 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.
    d) *Variables*: All outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.
    e) *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.

f) *Bias*: Any efforts to assess and address potential sources of bias at the design stage.
g) *Study size*: Study size, rationale for any study size calculation, and any method for attaining projected study size.
h) *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.
i) *Statistical methods:* Description of the following items:
    i. Main summary measures
    ii. All statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
    iii. Any methods used to examine subgroups and interactions
    iv. How missing data were addressed
    v. Any sensitivity analyses
    vi. Any amendment to the plan of data analysis included in the study protocol, with rationale for the change
j) *Quality control*: mechanisms to ensure data quality and integrity.

10. **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 sub-sections:
    a) *Participants*: Numbers of study subjects at each stage of study, such as numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, 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.
    b) *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, such as analyses of subgroups and interactions, and sensitivity analyses.
    f) *Adverse events and adverse reactions*: Summary of all adverse events/adverse reactions collected in the study, in line with requirements described set in these guidelines.
11. 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 PASS, and, where relevant, impact of the results on the risk-benefit 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.

e) *Other information*: Any additional or complementary information on specific aspects not previously addressed.

12. **Conclusions**: main conclusions of the study deriving from the analysis of the data.
13. **References**

ANNEX 9: METHODOLOGICAL ASPECTS OF SIGNAL DETECTION FROM SPONTANEOUS REPORTS OF SUSPECTED ADVERSE REACTIONS

Monitoring of databases of spontaneously reported suspected adverse reactions (in the format of individual case safety reports [ICSRs]) is an established method of signal detection. The monitoring process is facilitated by statistical summaries of the information received for each "drug-event" combination (DEC) over defined time periods. To limit the chances of failing to detect a signal and to ensure that the processes in place are controlled and predictable in terms of resources required, it is recommended that these summaries are produced in a routine periodic fashion. For the same reasons, when possible, the criteria for selecting DECs for further investigation should be objectively defined. The aim of this Annex is to describe components of an effective system for routine scanning of accumulating data focusing on components that have been proved to be effective.

This Annex lists some of the methodological aspects that should be considered in detecting potential signals. The proposed approach complements the classical disproportionality analysis with additional data summaries, based on both statistical and clinical considerations. Although disproportionality methods have been demonstrated to detect many adverse reactions before other currently used methods of signal detection, this is not true for all types of adverse reactions. Hence a comprehensive and efficient routine signal detection system will seek to integrate a number of different methods to prioritize DECs for further evaluation.

The specific details of implementation of the methods proposed may vary depending on, for example, the nature of the medicinal products in the dataset or the rate at which new ICSRs are received. A general principle is that any system of signal detection should be monitored not only for overall effectiveness but for the effectiveness of its components (e.g., statistical methods and specific group analyses).

The decision based on the assessment of the data summaries described herein is whether more detailed review of ICSRs should be undertaken. Such review may then prompt a search for additional data from other pharmacovigilance data sources. The decision process may rely on factors beyond the data summaries, for instance if the suspected adverse reaction is a specific incidence of a class of events already listed in the summary of product characteristics (SmPC). So far as possible, the decision process should be formally pre-specified and validated. In each case it should be fully documented.

I. Abbreviations

ADR	*Adverse drug reaction*
DEC	*Drug-event combination*
HLT	*High-level term (in MedDRA)*
ICSR	*Individual case safety report*
PT	*Preferred term (in MedDRA)*
SDA	*Signal detection algorithm*
SDR	*Signal of disproportionate reporting*
SMQ	*Standardized MedDRA query*
SOC	*System organ class (in MedDRA)*

II. Statistical methods

When the accrual to the database is too large to allow individual scrutiny of all incoming ICSRs, it is useful to calculate summary statistics on (subsets of) the data that can help to focus attention on groups of ICSRs containing an adverse reaction. Generally, such statistics are used to look for high proportions of a specific adverse event with a given medicinal product, compared to the reporting of this event for all other medicinal products (disproportionate reporting). Sudden temporal changes in frequency of reporting for a given

medicinal product may also indicate a change in quality or use of the product with adverse consequences (which could include a reduction in efficacy).

III. Disproportionate reporting

Disproportionality statistics take the form of a ratio of the proportion of spontaneous ICSRs of a specific adverse event with a specific medicinal product to the proportion that would be expected if no association existed between the product and the event. The calculation of the expected value is based on ICSRs that do not contain the specific product and it is assumed that these ICSRs contain a diverse selection of products most of which will not be associated with the event. Hence the reporting proportions for events in these ICSRs will reflect the background incidence of the event in patients receiving any medicine. There are a number of different ways to calculate such statistics and this choice is the first step involved in designing a statistical signal detection system.

When an adverse event is caused by a medicine, it is reasonable to assume that it will be re- ported more often (above the reporting rate associated with the background incidence), and hence the reporting ratio will tend to be greater than one. Thus, high values of the ratio for a given DEC suggest further investigation may be appropriate. In practice, a formal set of rules, or signal detection algorithm (SDA), is adopted. This usually takes the form of specified thresholds that the ratio or other statistics must exceed, but more complex conditions may also be used. When these rules are satisfied for a given DEC, it is called a signal of disproportionate reporting (SDR). Then a decision needs to be made regarding whether further investigation is required.

A further decision needs to be taken as to whether the statistics are to be calculated across the whole database or if modifications based on subgrouping variables would be of value. While the decision is motivated by theoretical consideration, the specific choice of whether to use subgroups and, if so, which to use, should be based on empirical assessment of signal detection performance. In particular, the impact on the false positive rate should be considered. Whether the database is sufficiently large to avoid very low case counts with in subgroups may also be a factor in this decision.

1. Considerations related to performance of signal detection systems

The performance of signal detection systems, including the SDA, can be quantified using three parameters that reflect the intended objective of the system. Desirable properties are:

1. High sensitivity (the proportion of adverse reactions for which the system produces SDRs)
2. High positive predictive value or precision (the proportion of SDRs that relate to ad-verse reactions)
3. Short time to generate SDRs (that can be assessed from a chosen time origin, possibly the granting of a marketing authorization to the first occurrence of an SDR for an adverse reaction)

Estimates of these performance parameters depend on the particular reference set of known adverse reactions selected for their evaluation and are also not fixed because spontaneous reports accumulate over time. They are thus best used as relative measures for comparing competing methods of signal detection within the same spontaneous reporting system at the same point in time.

The following factors may affect the performance of signal detection systems:

i. MedDRA hierarchy

A precondition for automated screening of DECs for adverse reactions is the availability of schemes for classifying adverse events and medicinal products. The nature and granularity of these schemes affects the performance of the screening. MedDRA, used for reporting suspected adverse reactions for NMRA purposes, provides terms for adverse events and classifies the mina multi-axial hierarchical structure and a choice must be made whether

to screen at one level of granularity (e.g., system organ class [SOC], high-level term [HLT], preferred term [PT]) or several and whether to include all terms or only a subset. Screening at the second finest level of granularity (i.e., PT), has been shown to be a good choice in terms of sensitivity and positive predictive value.

Finally, focus of statistical signal detection on adverse events considered clinically most important avoids time spent in assessments that are less likely to benefit patient and public health. A subset of MedDRA terms judged to be important medical events (IMEs) is thus considered a useful tool in statistical signal detection when filtering results for medical review.

The remarks above relate to routine signal detection and not to targeted monitoring of potential risks associated with specific products where ad hoc use of other levels of MedDRA terms may be appropriate. In addition, although not formally defined, MedDRA term subgroups such as HLT and standardized MedDRA query (SMQ) have proven better for signal detection than the PTs, and some of them are effectively synonymous. The definition of a synonym in this context is the pragmatic one—that two PTs are considered synonyms if it is reasonable to suppose that a primary reporter of a suspected adverse reaction, presented with a single patient and without a specialist evaluation, would not necessarily be able to decide which term to use. It may also be appropriate to combine such terms when they relate to identified areas of interest.

ii. Thresholds

The SDA applied to the summary statistics for each DEC usually takes the form of a set of threshold values such that SDRs occur only if each statistic exceeds its corresponding thresh- old. Very low thresholds will result in large, and potentially unmanageable, numbers of SDRs to investigate with a higher probability of being false. This will also reduce the resources avail- able for assessment of true SDRs. Too high thresholds will result in identification of adverse reactions being delayed or even entirely prevented. Thus, the appropriate choice of thresholds is fundamental to the success of the statistical signal detection system.

This has also been confirmed by studies comparing different disproportionality methods and different sets of thresholds showing that the former can achieve similar overall performance by choice of appropriate SDA. Therefore, in contrast to the choice of disproportionality statistic, it is the choice of SDA to define an SDR that will strongly influence signal detection performance.

Thresholds for disproportionality methods are usually based on two separate indicators, one reflecting the disproportionality statistic itself and another based on the number of ICSRs received. For a reason discussed later, limiting false positives is better handled by raising the threshold for the number of ICSRs than that for the disproportionality statistic. For the disproportionality statistic, in practice, rather than the point estimate, a formal lower confidence bound is often used. The rationale for its use is that when the statistic is based on few ICSRs, it falls further below the point estimate and makes an SDR less likely. Hence, this is an intuitive way of incorporating into the signal detection process the degree of confidence about the reliability of the data. It has also been shown that a threshold based on the lower confidence bound performed better alone than with an additional threshold for the absolute value of the disproportionality statistic itself.

In addition, it has been shown that a correlation exists between the value of a disproportionality statistic and the relative risk of an adverse reaction when exposed to the medicinal product estimated in epidemiological studies, therefore setting any threshold on the lower confidence bound of the disproportionate statistic above 1 might lead to missing an adverse reaction for which the risk ratio is not high.

Finally, there appears to be a reduction in positive predictive value with a medicinal product's time on the market, hence it might be more efficient to vary the amount of effort to invest in signal detection over the life

cycle of the product. This might involve the use of differing thresholds to define an SDR depending on the time of the product on the market.

iii. Periodicity of monitoring

A one-month interval between consecutive data summaries has been investigated in validation studies for signal detection methods. More frequent monitoring has also been used, for instance for medicinal products under additional monitoring or during intensive vaccination programs. The appropriate frequency of monitoring may vary with the accumulation of knowledge of the risk profile of a specific active substance/medicinal product.

iv. Spontaneous ICSR databases

The performance has also been shown to depend on the nature of the spontaneous ICSR data- base and this appears to be related to the range of medicinal products included in the database.

An important inference from these considerations is that organizations doing signal detection should assess the performance of a signal detection system directly on the database to which it will be applied. This will allow for detection of new adverse reactions and the workload involved to be predicted and controlled by appropriate changes to the SDA. As databases evolve in terms of numbers of ICSRs included and their mix of medicinal products, periodic reassessment of performance should be undertaken.

v. Subgroup analysis and stratification

Spontaneous ICSR databases cover a range of medicinal products that have different indications and that are used across a broad range of patient populations. Also, ICSR reporting patterns vary over time and between different geographical regions. Many quantitative SDAs disregard this diversity, which may result in an SDR either being masked or in an association being incorrectly flagged as a signal.

Stratification and subgroup analysis are generally used in epidemiology to reduce bias due to confounding and may also have advantages in statistical signal detection. Subgroup signal detection here is meant as analyses carried out to detect ADRs within specific ICSR subgroups (e.g., by indication, age group, region, or time period). Stratification involves combining results from within different subgroups to obtain an adjusted result for the whole dataset. The comparison of stratified versus subgroup analysis has shown that the subgroup analysis consistently performed better. Moreover, subgroup analysis has also shown to provide clear benefits in both sensitivity and precision over crude analyses for large international databases. However, such benefits may not be obtained in small databases.

Subgrouping variables that showed the most promising results included age and reporting region/country, but it is likely that choice of variables for subgroup analyses varies according to the database.

2. Increased ICSR reporting frequency

Most routine signal detection is aimed at identifying unknown, potentially causal associations between medicinal products and adverse events that are assumed to be constant over time. However, some causal associations of medicinal products with events of interest in the context of pharmacovigilance may show a marked temporal variation. Examples are manufacturing quality issues, a developing culture of abuse, evolving antimicrobial resistance or changes in the use of the product and, in particular, new off-label use. One way of detecting signals associated with such events, that may add value to simple disproportionality methods, is to monitor changes in the frequency of overall reporting for the products.

However, changes of reporting frequency are also expected that do not reflect new safety issues of the medicinal products. These may result from rapid increases in use when the product is first marketed or new indications are authorized, sudden changes in exposure (e.g., seasonal use of vaccines), publicity associated with unfounded safety concerns, reporting promoted by patient support schemes not clearly labelled as studies, clusters of ICSRs reported in the scientific literature, or duplicated ICSR reports.

There are several options for detecting temporal changes in reporting frequency. The simplest method examines the changes in the number of ICSRs received per product over a fixed time period as an absolute count. Statistical tests compare recent counts with the latest count, testing for significant increases. Similar methods can be used at the DEC level and, for these, relative values compared to the total ICSR count for the product may be considered as an alternative to absolute counts. However, the method disregards quantitative changes in exposure, which would impact the frequency of adverse reactions.

Another option is to consider changes in the disproportionality statistics over time. This approach is less susceptible to increase in number of ICSRs triggered by effects related to the product rather than a specific adverse event (e.g., general publicity about the product, stimulated reporting or changes in exposure), however, results will still be influenced by the background distribution in the rest of the database and not only by changes in reporting frequency for the specific medicinal product. In addition, results might be less reactive to transient temporal variations since the focus is on changes in statistics based on the cumulative count, not in comparing recent counts with the latest count. This problem will be more pronounced when large numbers of cases have accumulated, as proportional changes will then be smaller.

Limited work has been performed to assess the effectiveness of these methods even if theoretically they seem appealing. Thus, these methods might be implemented with ongoing quality control measures to ensure acceptable performance.

3. Methods aimed at specific groups of adverse events

    1. *Designated medical events*

Some medical events are known to result, in most occasions, from exposure to medicines. Thus, when such events are reported, the prior probability of a causal relationship to one of the medicinal products listed in the ICSR is high. Hence, the ICSRs will evoke concerns even before an SDR is observed. A list of these terms, complemented by important and serious events that should not be missed, should then be created and can serve as a safety net in signal detection. It is recommended that these designated medical events (DMEs) are drawn to the attention of signal detection assessors irrespective of any other statistical methods used and that they are prioritized for clinical review. Elements of the DME list are generally a relatively small subset of the IME list. The list of DME should also be periodically reviewed based on experience gained and performance.

    2. *Serious events*

The seriousness of events described in spontaneous ICSRs does not obviously relate to the probability that they are causally related with the medicine. However, it may impact the patient and public health importance should they later prove to be related. This reason is a rationale for prioritizing assessment of serious events. Complementary to the creation of a list of DMEs and in addition to the use of lists of IMEs, a simple approach to such prioritization is to highlight new ICSRs in which a death is reported and to give separate counts of those ICSRs for each DEC. It should be appreciated that this may be a rather imprecise criterion and prioritizing all ICSRs with reported death may result in many false positive signals. Hence, it is considered that further methodological research may be required in this area.

4. Methods aimed at specific patient populations

When ICSR databases are sufficiently large, some groups of patients may be identified that merit separate attention in signal detection due to known or suspected systematic differences in their responses to medicines. Two such groups that can be differentiated in most databases are the youngest and oldest patients.

A caveat relevant to analyses restricted to any subset of spontaneous ICSRs is that homogeneity of adverse events may be increased resulting in greater potential for masking of signals. For example, analyses within a group of patients who are the main recipients of a class of medicines may not highlight effects related to the entire class. A possible solution is to monitor specific patient groups in parallel to analyses of the total population.

i. *Pediatric population*

Often a single pediatric group is chosen below a selected age threshold. Although childhood is a period of rapid change and no threshold is likely to define a homogenous group, this succeeds in defining a population with marked developmental, physiological, and psychological differences from adults.

Separate presentation of suspected adverse reactions that are detected in the pediatric population and use of both clinical and statistical methods seem to be justified to improve the detection of signals for the pediatric population. Statistical disproportionality tools should be applied to ICSRs reported for children to increase the ability to detect signals in the pediatric population from spontaneous ICSR databases. Within-group disproportionality statistics that are significantly higher than those in the non-pediatric group should be highlighted for additional consideration. Additionally, given the lower number of ICSRs usually received for the pediatric population compared to the adult population, it is recommended to use a lower threshold based on the number of ICSRs received.

An additional aid to focusing on pediatric safety issues can be provided by a list of adverse events (a targeted medical events list) that tend to have more serious outcomes in children than adults. This list should be used to reduce missed signals that are more clinically relevant in the pediatric population, otherwise not flagged by other methods. The age threshold for pediatric signal detection should be chosen to align with the upper age limit from this guideline.

ii. *Geriatric population*

Specific signal detection measures aimed at older recipients of medicines area reasonable pre- caution given the high frequency of concomitant use of multiple medicines and the possibility of impaired physiological elimination mechanisms.

The age threshold at which such measures should be implemented has not been clearly established. Although the proportion of patients for whom suspected adverse reactions are reported increases with age, some research has suggested that this can be explained by more common use of medicines. Thus, it may be better to choose a threshold based on increased exposure rather than possible increased susceptibility. Alternatively, a consistent approach is to use the same age group in routine signal detection as selected for other pharmacovigilance activities.

For routine signal detection processes, it is recommended that ICSRs from patients above the chosen age threshold should be clearly identified and that, as for the pediatric population, within-group disproportionality statistics that are significantly higher than those within the non-geriatric group should be highlighted for additional consideration.

5. Methods aimed at specific circumstances of medicines use

In addition to the description of the clinical manifestation of the suspected adverse reaction, ICSRs may include information on the circumstances of medicine use which could have contributed to the occurrence of the adverse reaction, such as abuse, misuse, overdose, medication error, or occupational exposure.

Although the coding of these circumstances is enabled as PTs in MedDRA, they are qualitatively different from the clinical circumstances that are the focus of disproportionality-based signal detection. Firstly, they are manifestly related to at least one medicinal product identified in the ICSR. With suspected adverse reactions in normal circumstances of use, this relationship is a matter of clinical judgment. Secondly, the circumstances described by each of these terms differ depending on the product concerned. Hence, between-medicine comparisons of reporting frequency of ICSRs with MedDRA codes describing these circumstances are both unnecessary and potentially misleading.

However, knowledge of these circumstances can appreciably alter the assessment of causality when reviewing a potential signal. Thus, it is recommended that the numbers of ICSRs with the respective MedDRA codes should be displayed for each DEC

The EAC regional procedures on pharmacovigilance inspections cover, at least, the following processes:

i. Sharing of information
ii. Pre-authorization inspections
iii. Coordination of pharmacovigilance inspections in the EAC
iv. Preparation and planning of pharmacovigilance inspections
v. Prioritization of pharmacovigilance inspections
vi. Conduct of pharmacovigilance inspections
vii. Sign memorandum
viii. Reporting and classification of the pharmacovigilance inspections findings
ix. Communication of the findings
x. Interaction with PSAC in relation to inspections and their follow-up
xi. Record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections
xii. Sanctions and enforcement in case of serious non-compliance; recommendations on the training and experience of inspectors performing pharmacovigilance inspections
xiii. Procedures to be revised and updated as deemed necessary; new procedures may be developed when need is identified in relation to the inspection process

ANNEX 10: FORMAT AND LAYOUT OF PSMF

The PSMF may be in electronic form on condition that a clearly arranged, printed copy can be made available to national NMRA authorities if requested. In any format, the PSMF 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 PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

The PSMF should be written in English, indexed in a manner consistent with the headings described, and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic bookmarking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

The documents and particulars of the PSMF shall be presented with the following headings and, if in hardcopy, in the order outlined below.

COVER PAGE

i. The unique number assigned by the electronic system or manually to the PSMF
ii. The name of the MAH, the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable)
iii. The name of other concerned MAH(s) (sharing the pharmacovigilance system)
iv. The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system)
v. The date of preparation/last update
vi. The QPPV, Annex A
vii. The list of tasks that have been delegated by the QPPV, or the applicable procedural document, Annex B
viii. The curriculum vitae of the QPPV and associated documents
ix. Contact details
x. The lists of contracts and agreements
xi. Sources of safety data, Annex C
xii. Lists associated with the description of sources of safety data (e.g., affiliates and third-party contacts, computerized systems and databases [Annex D], pharmacovigilance process, and written procedures [Annex E])
xiii. Lists of procedural documents Pharmacovigilance System Performance, Annex F
xiv. Lists of performance indicators
xv. Current results of performance assessment in relation to the indicators quality system, Annex G
xvi. Audit schedules
xvii. List of audits conducted and completed products,
xviii. List(s) of products covered by the pharmacovigilance system Annex H
xix. Any notes concerning the MAH per product document and record control,
xx. Logbook
xxi. Documentation of history of changes for Annex contents, indexed according to Annexes A-I and their content if not provided within the relevant Annex itself

The PSMF shall contain the following sections:

1. Qualified person responsible for pharmacovigilance (QPPV)

The information relating to the QPPV provided in the PSMF shall include:

i. Description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain, and improve compliance.
ii. A summary curriculum vitae with the key information on the role of the QPPV, including proof of registration within the EAC.
iii. Contact details.
iv. Details of back-up arrangements to apply in the QPPV's absence.
v. A list of tasks that have been delegated by the QPPV shall also be included in the Annexes.

The details provided in relation to the QPPV should also include the description of the QPPV's qualifications, experience, and registrations relevant to pharmacovigilance (including registration with relevant NMRA). The contact details supplied should include name, postal address, telephone, fax, and email and should represent the usual working address of the QPPV, which may therefore be different from an MAH address. If the QPPV is employed by a third party, even if the usual working address is an office of the MAH, this should be indicated and the name of the company the QPPV works for provided.

2. Organizational structure of the marketing authorization holder

A description of the organizational structure of the MAH 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 organizations and operational units relevant to the fulfillment of pharmacovigilance obligations. This should include third parties. The PSMF shall describe:

i. The organizational structure of the MAH(s), showing the position of the QPPV in the organization.
ii. The site(s) where pharmacovigilance functions are undertaken covering ICSR collection, evaluation, safety database case entry, PSUR production, signal detection and analysis, RMP management, pre- and post-authorization study management, and management of safety variations to product.
iii. Diagrams may be particularly useful; the name of the department or third party should be indicated.

3. Outsourced activities

The PSMF, where applicable, shall contain a description of the activities and/or services subcontracted by the MAH 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 authorized in the EAC region.

Links with other organization, 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 fulfillment of pharmacovigilance obligations should be provided. Individual contractual agreements shall be made available at the request of national NMRA authorities and the Agency or during inspection and audit and the list provided in the Annexes.

4. Sources of safety data

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 the EAC. This shall 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 a contact point (address, telephone, email) for the site. The list may be located in the Annexes of the PSMF. Information about third

parties (license partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements.

Flow diagrams indicating the main stages, timeframes, and parties involved shall be used. However, represented, the description of the process for ICSRs from collection to reporting to NMRA authorities should indicate the departments and/or third parties involved.

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance, or support programs sponsored by the MAH through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit, and QPPV oversight. In the interests of harmonization, it is recommended that the list should be comprehensive for products authorized in the EAC, irrespective of indication, product presentation, or route of administration. The list should describe, on a worldwide basis, the status of each study/program, applicable country(ies), product(s), and 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 ongoing studies/programs as well as studies/programs completed in the last 2 years, and may be located in an Annex or provided separately.

5. Computerized systems and databases

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 shall be described in the PSMF.

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 computer system functionality shall also be described; the change control, nature of testing, back-up procedures, and electronic data repositories vital to pharmacovigilance compliance shall be included in summary, and the nature of the documentation available described. For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, mechanisms used to assure the integrity and accessibility of the safety data, and, in particular, the collation of information about adverse drug events shall be described.

6. Pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. A description of the procedural documentation available (SOPs, manuals, at a regional and/or national level, 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 PSMF. A description of the process, data handling, and records for the performance of pharmacovigilance covering the following aspects shall be included in the PSMF:

i. Continuous monitoring of product risk-benefit 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.
ii. Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements.

iii. ICSR collection, collation, follow-up, assessment, and reporting; the procedures applied to this area should clarify what are local and what are regional activities.
iv. PSUR scheduling, production, and submission.
v. Communication of safety concerns to consumers, healthcare professionals, and the NMRA authorities.
vi. Implementation of safety variations to the SmPC and PILs; procedures should cover both internal and external communications.

In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision-making and action.

The description must be accompanied by the list of processes under the topic 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 NMRA regulatory requests for information, 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, shall comprise the procedural document reference number, title, effective date, and document type (for all SOPs, work instructions, manuals, etc.).

Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this should be indicated (and the names of the applicable countries provided).

7. Pharmacovigilance system performance

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the monitoring methods applied and contain, at a minimum:

i. Assessment of correctness reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of reporting over the past year.
ii. Metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by NMRA authorities regarding the quality of ICSR reporting, PSURs, or other submissions.
iii. An overview of the timeliness of PSUR reporting to NMRA authorities in the EAC; the annex should reflect the latest figures used by the MAH to assess compliance.
iv. An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and NMRA regulatory deadlines, including the tracking of required safety variations that have been identified but not yet been submitted.
v. Where applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.
vi. Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in the annex to the PSMF alongside the results of (actual) performance measurement.

ANNEX 11: PHARMACOVIGILANCE METHODS

PASSIVE SURVEILLANCE

a) Spontaneous Reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, NMRA, or other organization (e.g., WHO, regional centers, poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious ADRs. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related NMRA activity, media attention, and the indication for use of the drug.

b) Systematic Methods for the Evaluation of Spontaneous Reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated.

These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection. Data mining techniques have also been used to examine drug-drug interactions. Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining.

Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

c) Case Series

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

d) Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. Such methods include online reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early post-marketing phase, companies might actively provide health professionals with safety information and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes). Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., early post-marketing phase vigilance in Japan).This should be regarded as a form of spontaneous event reporting; thus, data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

ACTIVE SURVEILLANCE

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through an RMP.

Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

a) Sentinel Sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

b) Drug Event Monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

c) Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations, can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patient with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

COMPARATIVE OBSERVATIONAL STUDIES

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case control studies, and cohort studies (both retrospective and prospective).

a) Cross-Sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

b) Case-Control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (e.g., the elderly, children, pregnant women).

For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

c) Cohort Study

In a cohort study, a population at risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes.

Like case-control studies, the identification of patients for cohort studies can come from large, automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (e.g., the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

There are several automated databases available for pharmaco-epidemiologic studies. They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

TARGETED CLINICAL INVESTIGATIONS

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large, simplified trial might be conducted. Patients enrolled in a large, simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified, and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource intensive.

DESCRIPTIVE STUDIES

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

a) Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

b) Drug Utilization Study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies, denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of in appropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

ANNEX 12: PROCEDURE FOR PLANNING, COORDINATING, AND CONDUCTING PHARMACOVIGILANCE INSPECTIONS

Purpose:

To provide guidance for planning, coordinating, and conducting pharmacovigilance inspections.

Scope:

This SOP is applicable for use at EAC Partner States, NMRAs.

Responsibility:

The EAC Secretariat is responsible for the maintenance of this SOP.

Responsibilities

1.1. EAC Secretariat

1.2. Heads of NMRAs

1.3. Director responsible for pharmacovigilance

1.4. Manager/head, pharmacovigilance department

1.5. Manager/head, Quality Management System

1.6. Pharmacovigilance inspectors

1.7. Secretary/data clerk, pharmacovigilance department

Definition of terms

Inspection report (IR): Details about the definition, availability, signatures, language, and con- tent of the IR can be found in the Union procedure on the preparation, conduct, and reporting of EU pharmacovigilance inspections.

Inspected entity: In this context, refers to the marketing authorization holder.

Lead inspector: The inspector whose responsibility includes organization of the practicalities of the inspection with the inspected entity and leading the conduct of the inspection on site.

Reporting inspector: The inspector designated by the reporting inspectorate to coordinate the preparation of the inspection, conduct of the inspection, and activities of the inspectors.

Abbreviation and acronyms

CAPA	Corrective and preventive actions
EAC	East Africa Community
IR	Inspection report
MAH	Marketing authorization holder
NMRA	National Medicines Regulatory Authority
PSMF	Pharmacovigilance system master file
QPPV	Qualified person for pharmacovigilance
SOP	Standard operating procedure

1. PROCEDURE

1 Generals

All the NMRAs within the EAC identify a joint inspection coordination within its ranks specifically for joint inspection coordination purposes; preferably head of the Pharmacovigilance Department.

For the purpose of collaboration and communication, a joint inspection coordination committee should be created with the joint pharmacovigilance inspection coordinators as primary members.

1.1. Planning of a pharmacovigilance inspection

Planning shall be undertaken by the EAC Secretariat in collaboration with the lead NMRA.

Identify MAH for a pharmacovigilance inspection.

1.1.1. Allocate resources to conduct the inspection including making the necessary logistical arrangements. The resources include:

i. Selection of inspectors (reporting inspector, lead inspector) with the necessary training and experience in performing pharmacovigilance inspections
ii. Sufficient inspection days
iii. Financial resources

1.1.2. Announce the inspection to the inspected entity unless it is "for cause" inspection to investigate an immediate public health or compliance concern:

i. An advance notice of a period of 6-8 weeks for a routine inspection.
ii. The announcement communication shall include the name of the inspector(s), MAH, objectives and nature of the inspection (i.e., routine, product specific, pre-authorization) and, if known, the proposed address of the inspection site(s). Additional information, including the PSMF number, any specific product authorizations to be reviewed, the intention to perform the inspection remotely, if applicable, can be added, as appropriate.
iii. The announcement shall be issued to the relevant QPPV, requesting confirmation of the inspected entity's availability, and that access to all required documents/databases will be provided.

1.1.3. The lead inspector shall prepare the inspection plan, which may include:

i. The objectives and scope of the inspection.
ii. Identification of the inspection team members and their respective roles.
iii. The date and place where the inspection is to be conducted.
iv. Identification of the functional units to be inspected.
v. Identification of documents/electronic tools which will be reviewed, and to which access is required, in so far as is possible.
vi. The expected time and duration for each major inspection activity (premises, processes, etc.).
vii. The schedule for the opening and closing meetings.
viii. Relevant aspects of the inspection plan, for example the agenda and document access requirements, may be shared with the inspected entity in advance, to ensure the availability of relevant personnel and documentation.

1.1.4. A request for the inspected entity to submit information for the purposes of inspection preparation shall be made. The inspection type (e.g., systems or product specific) and objectives will determine the pre-inspection documentation required, however, requests may routinely include submission of the PSMF. Additional supportive data demonstrating how the pharmacovigilance system operates or, describing specific issues of interest may also be requested, as appropriate. The timeline and method of

submission of documentation shall be clearly defined for the inspected entity.

1.1.5. Inspector(s) shall familiarize themselves with the pharmacovigilance system and any relevant product-specific issues, prior to the inspection. The information submitted by the inspected entity may be considered, as follows:

i. Previous pharmacovigilance inspection history.
ii. Information concerning the functioning of the pharmacovigilance system.
iii. Feedback from other NMRAs functions, in particular pharmacovigilance assessors and any issues arising from regulatory activities that may be relevant to the inspection.

1.2. Coordinating the PV inspection

1.2.1. The inspectors shall verify that the site(s) identified for inspection, and included in the inspection announcement, are appropriate with respect to ensuring the objectives of the inspection can be achieved .Where there is any change, an amended announcement shall be issued.

1.2.2. If teleconference(s) are planned during the inspection with experts, assessors, MAH personnel located off site, etc., this should be identified in advance.

1.2.3. If, upon agreement from the body commissioning the inspection, it is decided to conduct a remote inspection, the inspected entity should be contacted to make the necessary arrangements. The inspected entity should be requested to provide a description of the electronic tools available to facilitate inspection conduct. Consideration should be given to any compatibility issues that may arise and, where feasible, testing should be performed in advance. Back-up arrangements should also be considered.

1.2.4. Any communication between NMRAs and/or EAC shall be documented.

1.3. Conducting the pharmacovigilance inspection

The inspection activities shall be carried out in accordance with the inspection plan. The inspection plan can be amended during the inspection to ensure that the objectives are achieved. Any amendment to the plan shall be documented.

Information to fulfill the inspection can be collected by:

i. Review of relevant documents
ii. Examination of computer systems
iii. Conduct of interviews
iv. Review of internal and external communication (e.g., logbooks, registries, communication with authorities)

Any refusal of access to records and retrieval of documentation that the inspector(s) has a legal right to access shall be documented in the inspection report. This should then be communicated with the EAC Secretariat for further action and decision on consequences.

1.3.1. Prior to start of the inspection, an opening meeting must take place between the inspection team and the company being inspected. The chair of the meeting should be the lead inspector. The purpose of the opening meeting is to:

i. Introduce the inspection team.
ii. Explain the regulatory framework for the conduct of the inspection.
iii. Provide information about the scope and the objectives of the inspection.
iv. Clarify logistics, timeframes, and other references included in the inspection plan.
v. Introduce the MAH representatives attending the inspection.

vi. Allow the company to present an overview of the pharmacovigilance system.
vii. Clarify with the MAH representatives whether there are any anticipated difficulties foreseen in relation to the conduct of the inspection.

1.3.2. The inspectors shall review the documents, processes, and systems depending on the type, scope, and focus of the inspection.

1.3.3. All inspection observations shall be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating non-compliance.

1.3.4. At the end of the inspection, the inspector(s) should conduct a closing meeting with the company being inspected. The QPPV should ensure his/her team attends the meeting. The purpose of the closing meeting is to:
i. Explain the grading definitions for findings.
ii. Explain the procedures and timelines for distribution of the report, response, and any follow-up measures.
iii. Present a summary of the inspection findings to ensure that the results of the inspection are clearly understood.
iv. Provide the inspected party with an opportunity to correct misconceptions and misunderstandings in response to the findings.

1.3.5. An inspection may consist of visits to more than one location. If appropriate, a closing meeting may be held at each location inspected.
Exceptional circumstances may occur that require premature termination of inspection. In such event, the deviations from the inspection plan and the reason for early termination should be documented in the inspection report.

1.4 CLASSIFICATION OF PHARMACOVIGILANCE INSPECTIONS OBSERVATIONS

Critical:
A deficiency in pharmacovigilance systems, practices, or processes that adversely affects the rights, safety, or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major:
A deficiency in pharmacovigilance systems, practices, or processes that could potentially adversely affect the rights, safety, or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor:
A deficiency in pharmacovigilance systems, practices, or processes that would not be expected to adversely affect the rights, safety, or well-being of patients

1.4. **Reporting of the inspection**

The IR template has been provided in Annex 10. It shall be prepared in English and in the format provided within the timelines stipulated in this SOP.

An IR shall be prepared by the members of the inspection team, coordinated by the lead inspector or reporting inspector as provided for in the pharmacovigilance inspection report format, and presented within 45 working days from the end of the inspection.

1.4.1. Where multiple inspections were done and a combined inspection report is prepared, the time is

calculated from the last day of the last inspection.

1.4.2. The CAPA should be provided by the MAH within a defined time period of 45 working days after receiving the report and in accordance with the dates outlined on the inspection report request. If a response is not received within the stipulated timeframe, the absence of a reply should be recorded in the IR.

1.4.3. The MAH response shall be assessed by the inspectors, including the impact of comments on the inspection findings, if any, and the adequacy of the proposed CAPA.

1.4.4. This assessment shall be included in the final version of the IR and issued within 30 working days of receipt of the MAH response.

1.4.5. The final adopted IR shall be signed by the lead inspector and other inspectors as required by this SOP.

1.4.6. In the event that proposed CAPA or the timelines of requested actions are not accepted, additional follow-up procedures shall be defined in writing.

1.4.7. The MAH shall clarify in writing that all CAPAs will be completed as scheduled.

1.4.8. A confirmation on inspection completion shall then be issued.

1.5. **Record management and archiving**

2. The procedure for record keeping and archiving of documents obtained and/or resulting from the pharmacovigilance inspections shall be in accordance with the EAC pharmacovigilance compendium.

1.6. **Appendices**

1.6.1. Inspection checklist
1.6.2. Pharmacovigilance inspection report format
1.6.3. Pharmacovigilance inspection outcome sharing form

1.7. **Revision history**

SOP Version	Date Authorized	Reason for Change	Authorized By

ANNEX 13: DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION PLAN (DHPC)

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)PLAN	
Medicinal product(s)/active ingredient(s)	
Marketing authorization holders	In cases where the DHPC concerns several MAHs of the same active substance or is part of a class review, the holders are strongly encouraged that a single consistent message is sent to healthcare professionals in each of the EAC Partner States. All concerned MAHs in each Partner State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each of the Partner States. The letter circulated in each of the Partner States should cover all active substance-containing products authorized in that Partner State. It is encouraged that the MAH in each of the Partner States acts as the contact point for the NMRA. If no originator product is marketed in the Partner State, it is encouraged that one of the concerned generic companies acts as contact point for the NMRA.
Safety concern and purpose of the communication	Consider using the title of the DHPC to describe the safety concern.
DHPC recipients	List all (groups of) recipients of the DHPC in this section (e.g., general practitioners, specialists, community pharmacists, hospital pharmacists, nurses, professional societies, national associations).
Partner states where the DHPC will be distributed	
Timetable Delete steps which are *Date not applicable*	
DHPC and communication plan agreed by NMRAs *DHPC and communication plan agreed by EAC* *Dissemination of DHPC*	

ANNEX 14: TEMPLATE FOR DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

<Date>

<Active substance, name of medicinal product and main message

<*(e.g., introduction of a warning or a contraindication)*>

Dear healthcare professional,

<Name of marketing authorization holder> in agreement with <the EAC> and the <National Medicine Authority (NMRA) >OR <NMRAs>: would like to inform you of the following

Summary

Guidance: This section should be in bold/larger font size than the other sections of the DHCP and preferably in bullet points.

- <Brief description of the safety concern in the context of the therapeutic indication, recommendations for risk minimization (e.g., *contraindications, warnings, precautions of use)*, and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

Background on the safety concern

Guidance: This section may include the following information:

<Brief description of the therapeutic indication of the medicinal product>

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamics mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors)>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimization>

<A statement if the product information is to be or has been revised, including a description of the changes made or proposed> Guidance: No need, however, to include or attach the precise (translated) text of the product information which, at the time of dissemination of the DHCP, may not be available as final approved translations)

<Place of the risk in the context of the benefit>

<The reason for disseminating the DHCP at this point in time>

<Any evidence supporting the recommendation (e.g., include citation[s] of key study/ies)>

<A statement on any previous DHCPs related to the current safety concern that have recently been disseminated>

<Any schedule for follow-up action(s) by the MAH/NMRA, if applicable>

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g., name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

<For biological medicinal products, also include a reminder to report the product name and batch details>

<Mention if product is subject to additional monitoring and the reason why>

Contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes *(if applicable)*

<Link/reference to other available relevant information, such as information on the website of an NMRA>

<Additional scientific information, if applicable><List of literature references, if applicable>

ANNEX 15: MODEL PROCEDURE FOR PREPARATION, DISSEMINATION, AND PUBLICATION OF SAFETY COMMUNICATIONS

Purpose

To ensure that Partner State NMRAs prepare and publish safety communications in a timely and consistent manner, as well as disseminate this information within the EAC region.

Scope

This SOP applies to safety communications related to medical products and health technologies within the EAC region.

Responsibilities

Heads of NMRAs

Heads of pharmacovigilance departments

Pharmacovigilance officers

EAC Secretariat

Information communication and technology department

Public relations office

Definitions

DHPC: Direct Healthcare Professional Communication

EAC: East African Community

MAH: Market Authorization Holder

NMRA: National Medicine Regulatory Authority

PSAC: Pharmacovigilance Scientific Advisory Committee

SOP: Standard Operating Procedure

Procedure

Preparation of safety notification

1. Head of pharmacovigilance department identifies a safety concern/issue to be communicated from signal detection, international alert, etc.
2. The responsible NMRA makes the decision on the type and channel of communication.
3. S/He determines key messages to be addressed in the communication.
4. Prepare first draft of the communication tailored to appropriate audience.
5. Send the draft to national pharmacovigilance advisory committee for review.
6. Amend communication in line with national pharmacovigilance advisory committee discussions and recommendations.

7. Consult with public relations office in translation of the communication to all relevant languages of the target audience.
8. The communication shall be signed off by responsible officer at the respective NMRAs.

Dissemination and publication of safety information

1. Depending on the nature of safety alert communication, the safety issue will be disseminated by pharmacovigilance department or the public relations office.
2. The public relations office shall publish the communication in all the relevant channels of communication depending on the target audience.

Handling of communication at EAC level

1. The responsible NMRA informs the EAC Secretariat.
2. The EAC Secretariat coordinates the notification of the issue to other Partner State NMRAs.

Records

File of the safety alerts issued

Reference

Change history

SOP Version	Date Authorized	Reason for Change	Authorized By

ANNEX 16: PHARMACOVIGILANCE INSPECTION REPORT

Company Name:

PSMF:

Inspection number: [Enter inspection reference number as applicable]

Date of issuance:

SECTION A: ADMNISTRATIVE INFORMATION

Inspection type:	
Name and address(es) of site(s) inspected:	
Contact person:	
Date(s) of inspection:	
Lead inspector:	
Reporting inspector:	
Accompanying inspector(s) and experts:	
Previous pharmacovigilance inspections: (Date and inspecting authority)	
Purpose of inspection:	
Products selected to provide system examples:	As part of the general systems review, there are products chosen for close evaluation of ADR reports, PSURs, etc.
Name and location of the QPPV:	Name: Contact details:
Date of first issue of report to MAH:	Date of submission
Deadline for submission of responses by MAH:	
Date(s) of receipt of responses from MAH:	
Date of final version of report:	
Report author:	Name Job title

SECTION B: GENERAL INFORMATION

1. Scope and reason for the inspection
2. Reference texts and documents for the inspection
3. Conduct of the inspection with summary of the organization and any significant changes and action taken since the last inspection

SECTION C: INSPECTED ITEMS

SECTION D: FINDINGS

Definitions of inspection finding grading

1. Critical (CR) Findings

Finding CR1 Use the categories (and subcategories) listed in Appendix I followed by a short title for the finding
<<Inspector to add text>> References: Directive 2001/82/EC as amended, Article xxx Volume 9B, section xxx (as appropriate) Add any local requirement (if appropriate)
Root cause analysis
<<MAH to add text>>
Further assessment
<<MAH to add text>>
Corrective action(s)
<<MAH to add text>>

Deliverable(s) <<MAH to add text>>	**Due date(s)** <<MAH to add text>>
Preventative action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	**Due date(s)** <<MAH to add text>>
Recommendation / Observation (amend as necessary)	

2. Major (MA) Findings

Present the major findings as corresponding to the definition

Finding MA1 Use the categories (and subcategories) listed in Appendix I followed by a short title for the finding	
<<Inspector to add text>> References: Directive 2001/82/EC as amended, Article xxx Volume 9B, section xxx (as appropriate) Add any local requirement (if appropriate)	
Root cause analysis	
<<MAH to add text>>	
Further assessment	
<<MAH to add text>>	
Corrective action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>
Preventative action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>
Recommendation / Observation (amend as necessary)	

3. Minor (MI) Findings

Present the minor findings as corresponding to the definition

Finding MI1 Use the categories (and subcategories) listed in Appendix I followed by a short title for the finding	
<<Inspector to add text>> References: Directive 2001/82/EC as amended, Article xxx Volume 9B, section xxx (as appropriate) Add any local requirement (if appropriate)	
Root cause analysis	
<<MAH to add text>>	
Further assessment	
<<MAH to add text>>	
Corrective action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>
Preventative action(s)	
<<MAH to add text>>	
Deliverable(s) <<MAH to add text>>	Due date(s) <<MAH to add text>>

Recommendation / Observation (amend as necessary)

Comment:

SECTION E:

1. Conclusions recommendations
2. Evaluation by the inspectors of the response from the inspectee
3. Final conclusions and recommendations

SECTION F: DATE AND SIGNATURES OF LEAD AND OTHER INSPECTORS, EXPERTS IF APPLICABLE

ANNEX 17: STANDALONE SIGNAL NOTIFICATION FOR ACTIVE SUBSTANCE/ INN

BRAND NAME

1.0 ADMINISTRATIVE INFORMATION

Date of this notification	
Active substance(s) (invented name[s])	
Pharmaceutical form(s)/Route(s) of administration/Strength(s)	
Marketing authorization holder(s)	
QPPV	
MAH contact person for the signal	

Authorization procedure and number *[Tick the appropriate box (es) below and complete as appropriate.]*	
	Centralized:
	National:

EAC – Partner State(s) NMRA in which the MAH holds a marketing authorization for the medicinal product(s) *[Choose the appropriate.]* ☐ Burundi ☐Kenya ☐Rwanda ☐Uganda ☐South Sudan ☐Tanzania ☐Zanzibar

Only applicable for non-centrally authorized products

Marketing authorization legal basis *[Tick the appropriate below.]*	
	Full application
	Generic application
	Hybrid application
	Similar biological application
	Well-established use application
	Fixed combination application
	Informed consent application
	Other – Please specify:
Next PSUR submission date *[if PSURs are required for the medicinal product]*	DD Month YYYY PSUR not required.

SIGNAL DESCRIPTION

HIGHLIGHTS

Clinical relevance: (Text)

(Please briefly summarize how seriousness criteria were met in the cases, e.g., fatal, life-threatening, hospitalization, etc.)

Relevant statistical measures: (Text)

(Please provide the relevant risk and odds ratio (ROR) values (in particular the lower bound of the 95% confidence interval) from EAC-Vigilance,

as well as any other relevant statistical measures, if applicable.)

Patient exposure: (Text)

(Please provide the most recent estimate of the population cumulatively exposed to the medicinal product in the post-authorization setting and in clinical trials, if applicable. Methods used to calculate the exposure do not need to be included.)

Previous awareness: (Text)

(Please provide information on any regulatory actions or previous assessments, performed at national, EAC level in relation to the signal. Please ensure, wherever possible, that the signal is not already addressed in other EAC SmPCs for the active substance or considered by EAC/PRAC.)

Additional sources other than EAC–Vigilance database:

☐ Literature ☒ Clinical trials ☐ MAH database ☒ Other [please specify below]

BACKGROUND (Text)

(This section should include a concise summary of the relevant information on the product(s)/active substance (including therapeutic indication[s]), and on the adverse reaction(s) (e.g., morbidity, epidemiology, case definition)

SIGNAL VALIDATION AND FURTHER ASSESSMENT

Evidence from EAC–Vigilance

Date of the query: / /
(DD/MM/YYYY)

Monitoring periodicity (Text).

(This section should include a summary of evidence from EAC-Vigilance, highlighting the strength of evidence, clinical relevance, and a summary of the supportive cases. MedDRA terms used, number of cases, positive de-challenge or re-challenge, seriousness, dose-reaction relationship, biological and temporal plausibility, causality assessment, clinical context [e.g., drug interactions, specific population, risk factors], and quality of documentation should be provided.)

5.2.7 Evidence from other sources (Text)

(This section should include a summary of all additional evidence [e.g., from the MAH database, scientific literature, clinical trials]

CONCLUSION (Text)

(This section should include a brief statement highlighting why further analysis by the NMRAs is warranted and proposed actions.)

ANNEXES (Text)

List of literature references, if applicable

List of attachments, if applicable

ANNEX 18: PROCEDURE FOR RECEIVING AND PROCESSING OF ADVERSE DRUG REACTION (ADR) REPORTS

Purpose

To provide guidance for receiving and processing of adverse drug reaction (ADR) and adverse events (AEs) reports.

2. Scope

The SOP is applicable for use at EAC Partner State NMRAs.

3. Responsibility

The manager/head of the department dealing with pharmacovigilance is responsible for the maintenance of this SOP.

4. Accountability

Director of the directorate under which pharmacovigilance falls is accountable for this SOP.

5. Distribution List

The hard copy shall be distributed to:

5.1 Head of NMRA

5.2 Director responsible for pharmacovigilance

5.3 Manager/head, pharmacovigilance department

5.4 Manager/head, Quality Management System

5.5 Regulatory officers in the pharmacovigilance department

5.6 Secretary/data clerk, pharmacovigilance department

The controlled electronic copy shall be distributed to all other NMRA staff.

6. Abbreviation and acronyms

ADR: Adverse Drug Reaction

AE: Adverse Event

7. Procedure

7.1.1 Receiving ADR and AE Reports

7.1.2 Reports of suspected adverse reactions and events to medicines, vaccines, medical devices, herbal/alternative medicines, nutraceuticals, and cosmetics shall be received at NMRAs via electronic reporting system, courier, post, hand delivery, email, telephone, or fax.

7.1.3 The regulatory officer shall acknowledge receipt of the report by way of a telephone call or email within 5 working days from date of receipt.

7.1.4 The receiving officer shall check if the following minimum data elements have been included on the report as per Addendum 1 (FOM001/MIP/PMS/SOP/001) or Addendum 2 (FOM002/MIP/PMS/SOP/001) within 5 working days:

- An identifiable reporter
- An identifiable patient

- An adverse reaction
- At least one suspected drug, vaccine, medical device, or cosmetic product

7.1.5 If the reports are incomplete, the regulatory officer shall follow up with the reporter via telephone, email, or any other appropriate means of communication to gather all the necessary required information within 5 working days.

7.1.6 The regulatory officer shall reject ADR or AE reports missing any of the elements in 7.1.4 and efforts to get the information from the reporter is not received within 10 working days after asking for it.

7.2 Sorting out ADR or AE Reports

7.2.1 The regulatory officer shall sort out reports as those related to medicines, vaccines, medical devices, cosmetics, and clinical trials.

7.2.2 After sorting, send clinical trial reports to a person responsible for clinical trials.

7.2.3 Send all reports of issues with drug manufacturing, drug batches, and quality of medicines to the department responsible for post-marketing surveillance and counterfeiting. This should be done after discussion with the manager/head of pharmacovigilance.

7.2.4 Direct reports of problems with devices to the department responsible for medical devices. This should also be done after discussion with the manager/head of pharmacovigilance.

7.2.5 Forward reports related to cosmetics to the department responsible for the same. This should as well be done after discussion with the manager/head of pharmacovigilance.

7.2.6 Sort medicine and vaccine related reports as "serious" or "non serious." Serious reports are those which:

- Resulted in death
- Are life threatening (i.e., where the patient was at risk of death at the time of the reaction, not a reaction which hypothetically might have been fatal if it were more severe)
- Required inpatient hospitalization or prolongation of existing one
- Resulted into persistent or significant disability/incapacity
- Resulted into congenital anomaly/birth defect
- Others – drug interaction reports (except well known) and medically important reactions (e.g., hepatic, renal, hematological)

7.2.7 The regulatory officer shall annotate reports as those related to medicines, vaccines, medical devices, cosmetics, and clinical trials.

7.2.8 Send sorted reports to reviewers for annotation and assessment.

7.3 General considerations

None.

7.4 Appendices

7.4.1 Acknowledgment form

7.5 Revision history

ANNEX 19: PROCEDURE FOR REVIEWING AND ANNOTATING ADVERSE DRUG REACTION (ADR) REPORTS

1. Purpose

To provide guidance for review and annotation of adverse drug reaction (ADR) and adverse events (AEs) reports.

2. Scope

The SOP is applicable for use at EAC Partner State NMRAs for reviewing and annotating reports of suspected ADRs and AEs to medicines, vaccines, medical devices, herbal/alternative medicines, nutraceuticals, and cosmetics.

3. Responsibility

The manager/head of the department dealing with pharmacovigilance is responsible for the maintenance of this SOP.

4. Accountability

Director of the directorate under which pharmacovigilance falls is accountable for this SOP.

5. Distribution List

The hard copy shall be distributed to:

5.1 Head of NMRA

5.2 Director responsible for pharmacovigilance

5.3 Manager/head, pharmacovigilance department

5.4 Manager/head, Quality Management System

5.5 Regulatory officers in the pharmacovigilance department

5.6 Secretary/data clerk, pharmacovigilance department

The controlled electronic copy shall be distributed to all other NMRA staff.

6. Abbreviation and acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
NMRA	National Medicines Regulatory Authority
SOP	Standard Operating Procedure
MedDRA	Medical Dictionary for Regulatory Activities

7. Procedure

7.2 Identifying adverse reaction(s)

7.2.1 Exact terms

7.2.1.1 Identify the reaction term(s) and assume that the exact terms used by the reporters are in MedDRA.

7.2.1.2 However, unusual terms (e.g., specific syndromes) should be checked that they are in the MedDRA dictionary.

7.2.1.3 If the most appropriate MedDRA term is different from the reporter's term, add and underline the MedDRA term in the report (see Appendix 2 for criteria of using specific ADR terms).

7.2.2 Separate adverse reactions in a single patient

7.2.2.1 If there is a time sequence of separate adverse reactions in a single patient or separate reactions with clearly different causalities (e.g., an application or injection site reaction and a systemic reaction), the report may be separated into a sequences ('SEQUENCE 1,' 'SEQUENCE 2,' etc.).

7.3 Identifying the suspected drug(s)

7.3.1 Check the dates of administration and confirm that medicine exposure precedes the onset of the reaction.

7.4 Identifying other information for data entry

7.4.1 Identify any additional information including the treatment of side effects and any relevant past history that may provide an alternative explanation.

7.5 Annotations for specific report types

7.5.1 Deaths

(a) Unrelated Deaths

Reports where death was unrelated to the drug should be reviewed separately from the 'Fatal' reports. For these other deaths, do not annotate 'Fatal,' but instead ensure that 'Death Unrelated' are annotated.

(b) Fatal

For deaths related to a drug, annotate as below:

Top of report	Annotate FATAL, 'DEATH UNRELATED' at top of report.
Annotation	If no reaction term is provided: write FATAL and underline the word 'death.'
Action	Write a summary of fatal reports and save them in your computer. Forward it to Technical Committee for further review.

7.5.2 Congenital abnormality reports

Fetal/Neonatal reports (congenital severity) include abortions, miscarriages, fetuses exposed in utero, fetal reactions, neonatal (first month after birth) reactions, neonates exposed during lactation, malformations, deformities, anomalies, etc.

For deaths related to a drug, annotate as below:

Top of report	Annotate at top of report FATAL FETAL/NEONATAL.
Action	Forward report with narrative to the Technical Committee for further review.

7.6 Vaccines

7.6.1 The AEFI reports should be coordinated together with the Expanded Programme on Immunization (EPI). Send photocopies of all coded vaccine reports to EPI. This should be done soon after receiving AEFI reports.

7.6.2 When considering a vaccine report, check if the reactions can be coded as an AEFI term. Otherwise MedDRA term(s) should be used. These reports should then be sent to EPI.

7.7 Drug interaction reports

7.7.1 Indicate INTERACTION at the top of the report.

7.7.2 Indicate whether such interaction has been previously described (e.g., NMRA ADR bulletin, case studies or literature report). If the reaction is not well known, attach reviewer's summary on the same for further review by the Technical Committee.

8. Review of ADR and AE reports

8.1 Causality assessment and entering of data into Vigiflow

8.1.1 Regulatory officer (first reviewer) shall do causality assessment of valid reports using either the WHO causality assessment scale or Naranjo algorithm.

8.1.2 The report shall then be entered into Vigiflow.

8.1.3 The second reviewer shall review and commit reports into the WHO database.

8.1.4 The regulatory officer shall make an entry in logbook for every Vigiflow entry and note the autogenerated Worldwide Unique Number (Appendix 1: Logbook for Vigiflow data entry).

9. General considerations

9.1 This SOP should be read together with the SOP for receiving and processing of ADR reports.

9.2 Generally the annotation should be in capitals.

Appendix 1: Logbook for Vigiflow data entry

Serial #	Date Received at Pharmacovigilance Center	Date Entered in Vigiflow	Date Committed in Vigiflow	Vigiflow Number	Entered by
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Appendix 2: WHO causality assessment scales

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable / Likely	Event or laboratory test abnormality, with reasonable time relationship to drug in take Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable

	Re-challenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
Conditional / Unclassified	Event or laboratory test abnormality More data for proper assessment needed, or additional data under examination
Un-assessable / Unclassified	Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified

Appendix 3: Naranjo algorithm

	Question	Yes	No	Do Not Know	Score
1.	Are there previous conclusive reports on this reaction?	+1	0	0	
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4.	Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	
7.	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	

TOTAL SCORE:

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

END