GUIDELINES ON GOOD PHARMACOVIGILANCE PRACTICES FOR REGISTRATION HOLDERS

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1. HISTORY

This is the first edition of this document.

2. APPLICATION - Guidance for Registration Holders

This document is for the guidance and support of registration holders for the establishment of their pharmacovigilance system and subsequent reporting of pharmacovigilance data to the National Pharmacovigilance Centre, Drug Regulatory Authority of Pakistan.

3. PURPOSE

Registration holders are stakeholders of pharmacovigilance who have valid registration of therapeutic goods. There are also legal obligations on registration holders to monitor the safety of therapeutic goods. Therefore, there is a need that they should have basic knowledge and understanding of pharmacovigilance activities to fulfil their legal obligations. The purpose of this guidance document is to provide a basic framework for the implementation of the pharmacovigilance programme of Pakistan and to ensure that registration holders are better equipped to monitor the safety of therapeutic goods and to detect, assess, understand, prevent and investigate ADRs/ AE and AEFI reports. The purpose for registration holders is to,-

a. To develop a pharmacovigilance system and monitor the safety of therapeutic goods registered in their name;

b. Collect pharmacovigilance data, perform its assessment and accordingly submit to NPC, DRAP;

c. Cooperate with NPC in the performance of pharmacovigilance inspection;

d. Preparation and submission of periodic safety reports and risk management plan;

e. Design and conduct post-authorization safety studies; and

f. Detect, validate and assess signals and accordingly communicate to NPC and other stakeholders and considers options for risk minimization.

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4. INTRODUCTION

4.1. PV as defined by WHO is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other therapeutic good related problems. Drugs, vaccines and biological are extensively tested in humans during the clinical trials still everything related to their safety i.e. ADRs could not be determined. The limitations of clinical trials are: numbers of trials subjects are less than patients of real practice; trials subjects are highly selective and vulnerable groups such as pregnant women, elderly, children and patients with other diseases and concomitant drugs are excluded in clinical trials; and duration of clinical trials is of few years as compared to real practice. That is why after registration of therapeutic goods when these are released into the market and a large population is exposed to them, some new and unexpected serious ADRs can occur.

4.2. Registration holders are among the most important stakeholders of pharmacovigilance in a country as they have therapeutic goods registered in their name. Furthermore, there are legal obligations on registration holders to monitor the safety of therapeutic goods such to collect pharmacovigilance data, perform assessments, submit data to NPC, submit periodic reports and risk management plans and consider options for risks minimization and communication.

4.3. These modules developed under these guidelines is for the support of registration holders that are drafted as per international practices and pharmacovigilance rules. These guidelines have to be followed by all the registration holders having valid registration of therapeutic goods in Pakistan.

5. DEFINITIONS AND ACRONYMS

Abuse of therapeutic good means persistent or sporadic, intentional excessive use of therapeutic good which is accompanied by harmful physical or psychological effects;

ADR: **"***Adverse Drug Reaction*" or "ADR" means response to drug or therapeutic goods which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal

relationship between a therapeutic good and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a therapeutic good and an occurrence is suspected.

AE: **"***Adverse Event" or "AE"* means any untoward medical occurrence in a patient or clinical investigation subject administered a drug or therapeutic good and which does not necessarily have a causal relationship with this treatment

AEFI: *"Adverse Event Following Immunizations" or "AEFI"* means any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine

DRAP: The Drug Regulatory Authority of Pakistan

Causality Assessment: means the evaluation of the likelihood that medicine or therapeutic good was the causative agent of an observed adverse reaction;

CSC: The Clinical Study Committee of the DRAP.

DLP "Data Lock Point" means the cut-off date appointed for data to be included in periodic benefits-risk evaluation reports based on their international birth date;

HCP: Means any member of the medical, dental, pharmacy, nursing professions, any allied health professional or any other person who in the course of his professional activities may prescribe, recommend, purchase, supply, sell or administer a therapeutic good including medical technologies as registered or enlisted by the Authority

IBD "International birth date" means the date of the first marketing approval or registration for any product containing the active substance granted to any company in any country in the world.

ICH: International Council on Harmonization

ICSR "Individual Case Safety Report" means a report describing a suspected adverse drug reaction related to the administration of one or more drugs or therapeutic goods to an individual patient.

LSO: Local Safety Officer

Medication Error: means 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.

NPC: National Pharmacovigilance Centre of the DRAP.

NPVSF: National Pharmacovigilance System File

Occupational Exposure*:* means exposure to a therapeutic good as a result of one's professional or non-professional occupation. Furthermore, it does not include the exposure to one of the ingredients during the manufacturing process before the release as a finished product.

Off Label Use: Refers to the use of an approved medicine under the direction or supervision of a healthcare professional for an unapproved indication, age group, dosage, route or form of administration.

Overdose of Therapeutic good: means administration of a quantity of a therapeutic good given per administration or cumulatively which is above the maximum recommended dose according to the registered therapeutic good information

PASS Post-Authorization Safety Study.

PBRER: Periodic Benefit-Risk Evaluation Report.

Pharmacovigilance System: means a system used by the registration holder to fulfil the tasks and responsibilities listed in pharmacovigilance

rules and is designed to monitor the safety of therapeutic goods and detect any change to their risk-benefit balance;

PSMF Pharmacovigilance System Master File.

PRAEC Pharmacovigilance Risk Assessment Expert Committee of DRAP

PV: **"**Pharmacovigilance" means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other therapeutic good related problems.

QPPV Qualified Person for Pharmacovigilance

Registration Holder Means manufacturer or importer possessing registration or enlistment of therapeutic goods, as the case may be.

RMP Risk Management Plan

Serious ADRs or AEs: means an untoward medical occurrence that at any dose result in patient death, is life-threatening, require inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or is judged to be a medically important event or reaction;

Therapeutic Goods: Includes drugs or alternative medicine or medical devices or biologicals or other related product as may be notified by DRAP.

WHO-DD: World Health Organization Drug Dictionary.

WHO-UMC: World Health Organization Uppsala Monitoring Centre.

6. MODULES

Module 1

1. PHARMACOVIGILANCE SYSTEM

A pharmacovigilance system is defined as the system used by the registration holder to fulfil the tasks and responsibilities listed in pharmacovigilance rules and these guidelines and is designed to monitor the safety of therapeutic goods and detect any change to their benefit-risk balance. A pharmacovigilance system, like any system, is characterized by its structures, processes and outcomes. For each specific pharmacovigilance process, including its necessary structures, a dedicated module is included in these guidelines.

Registration holder shall establish a pharmacovigilance system for the fulfilment of pharmacovigilance activities and shall evaluate all information scientifically, consider options for risk minimization or prevention and take appropriate measures. The registration holder shall collect, record, store, maintain and analyse the AEs, AEFI and ADRs of all therapeutic goods registered in its name, to monitor their safety. Registration holder shall report to NPC pharmacovigilance data including zero events as per format approved by DRAP and timelines provided in these rules.

The registration holder shall operate a pharmacovigilance system and shall establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities. A description of the pharmacovigilance system shall be developed by the registration holder in the format of a pharmacovigilance system master file (PSMF) and be maintained by the registration holder for all authorised therapeutic goods (see Module 2). The applicant or registration holder is also responsible for developing and maintaining product specific risk management systems (see Module 4)

A dedicated department may be established by a registration holder having infrastructure and equipment with full-time staff without assigning additional duties to any department. When applying for registration of new a therapeutic good, the registration holder needs to submit a description of the pharmacovigilance system, and a proof document stating that the services of the QPPV are in place. These

documents are to be submitted to Registration Board and a copy is also sent to NPC.

1.1. Training of Personnel for Pharmacovigilance

It is a fact that the availability of a sufficient number of competent, qualified and trained personnel is intrinsically linked with the achievement of the required quality in respect of the pharmacovigilance process and its outcomes. Therefore, personnel involved in the performance of pharmacovigilance activities shall receive initial and post-appointment training. The registration holder shall develop and keep training plans, their records and also maintain and develop the competencies of personnel involved. Training plans should be based on training needs assessment and should be subject to continuous monitoring. The training should support continuous improvement of relevant skills, application of scientific progress and professional development and ensure that staff members understand relevant pharmacovigilance requirements as elaborated in rules and guidelines.

1.2. Facilities and Equipment for Pharmacovigilance

Likewise, achievement of the required quality in respect of the pharmacovigilance process and its outcomes is also intrinsically linked with appropriate facilities and equipment. Facilities and equipment should include office space, information technology (IT) systems and electronic storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance and also be available for business continuity. Facilities and equipment which are critical should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.

1.3. Qualified Person for Pharmacovigilance (QPPV)

1.3.1. *Requirement of QPPV or LSO*

Rule 11 (2) define the requirement of QPPV in Pakistan which is reproduced as under:

*"The registration holder shall appoint a qualified person for pharmacovigilance (QPPV), having such experience and qualification as defined by DRAP, who shall be responsible for pharmacovigilance system and shall reside and operate in the country**,** and shall also be responsible for establishment and maintenance of the pharmacovigilance system. In the case of a multinational registration holder, the nomination of a local safety officer (LSO) will also be accepted, who shall reside and operate in the country. The registration holder shall submit the name and contact details of the qualified person to NPC.*"

As evident from the above, in the case of a multinational registration holder, the nomination of a local safety officer (LSO) will be accepted, who shall reside and operate in the country. However, in the case of a local registration holder, there should be a dedicated QPPV who should reside and operate in Pakistan.

Each pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one registration holder, for shared or separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same registration holder, provided that the QPPV is able to fulfil all obligations. The registration holder should submit the name and contact details of QPPV/LSO along with his/her alternate (backup person) to NPC, DRAP.

The registration holder shall provide the following requirements/documents of QPPV or LSO (Qualified Person in Pakistan residing in Pakistan) to the NPC:

i. Letter of appointment from the registration holder of therapeutic goods;
ii. Copies of degree(s);
iii. Training certificate in PV;
iv. Experience certificate in PV;

v. List of products covered by the registration holder;
vi. Job description; and
vii. SOP of appointment and training of the officer.

1.3.2. *Responsibilities of QPPV or LSO*

The QPPV shall be responsible for the establishment and maintenance of the registration holder's pharmacovigilance system and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements and guidelines. Hence, the QPPV should have access to the PSMF and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility. These responsibilities for the pharmacovigilance system means that the QPPV has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of PBRER reports, audit reports and training of personnel in relation to pharmacovigilance. The responsibilities of LSO will be in relation to the pharmacovigilance system of multinational registration holders in Pakistan.

In relation to the therapeutic goods covered by the pharmacovigilance system, specific additional responsibilities of the QPPV or LSO in Pakistan should include:

i. Having an overview of therapeutic goods' safety profiles and any significant safety issues;

ii. Having awareness of any conditions or obligations adopted as part of the registration and other commitments relating to safety or the safe use of the therapeutic goods;

iii. Having awareness of risk minimisation measures;

iv. Being aware of and having sufficient authority over the content of risk management plans;

v. Being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in Pakistan or pursuant to a risk management plan agreed in Pakistan;

vi. Having awareness of post-authorisation safety studies requested by a competent authority including the results of such studies;

vii. Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the pharmacovigilance rules and guidelines;

viii. Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the NPC;

ix. Ensuring a full and prompt response to any request from NPC and DRAP for the provision of additional information necessary for the benefit-risk evaluation of therapeutic goods;

x. Providing any other information relevant to the benefit-risk evaluation to the NPC or any other board or committee of the DRAP; and

xi. Providing input into the preparation of regulatory actions in response to significant safety issues (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).

1.3.3. *Qualification of QPPV or LSO*

The registration holder shall ensure that the QPPV/ LSO has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPV should have a minimum of a bachelor's degree in pharmacy or medicines and basic training in pharmacovigilance. Likewise, training in epidemiology and biostatistics will be an additional benefit. The registration holder should provide the QPPV with training in relation to its pharmacovigilance

system, which is appropriate for his/her role before the QPPV/LSO takes up the position and it must be appropriately documented. Consideration should be given to additional training, as needed, to the QPPV/LSO in relation to the therapeutic goods covered by the pharmacovigilance system.

Module 2

2. PHARMACOVIGILANCE SYSTEM MASTER FILE (PMSF)

The legal requirement for registration holder for maintenance and submission of pharmacovigilance system master file (PSMF) is laid down in Rule.11 (4) of the Pharmacovigilance Rules, which states as under:

"*Registration holder shall maintain the pharmacovigilance system master file (PSMF) on a format approved by DRAP and submit it to NPC within forty-five calendar days when directed. The PSMF shall also be actively submitted to NPC when there is an update."*

2.1. Objectives of Pharmacovigilance System Master File.

The PSMF shall describe the pharmacovigilance system and support/document its compliance with the requirements. It should fulfil the requirements for a PSMF laid down in pharmacovigilance rules and guidelines, and shall also contribute to the appropriate planning and conduct of audits by the registration holder, the fulfilment of supervisory responsibilities of the QPPV, and inspections or other verification of compliance by NPC and DRAP. The PSMF provides an overview of the pharmacovigilance system, which may be requested and assessed by NPC and DRAP during registration application(s) or post-authorisation or pharmacovigilance inspection.

2.2. Submission of Pharmacovigilance System Master File.

Registration holders shall maintain the pharmacovigilance system master file (PSMF) and submit it to NPC within forty-five calendar days when directed. In addition, a notification letter showing amendment or update shall also be submitted to the NPC when there is a change in QPPV/ LSO (Qualified person residing in Pakistan), change in global QPPV or change in location of the PSMF.

Registration holder is also required to submit to the registration board the

summary of the PSMF at the time of registration of therapeutic goods.

2.3. Location of Pharmacovigilance System Master File.

The PSMF/ NPVSF shall be located (physically) either at the site where the main pharmacovigilance activities of the registration holders are performed or at the site where the QPPV/ LSO operates.

2.4. Contents of Pharmacovigilance System Master File.

The content of the PMSF should reflect the global availability of safety information of therapeutic goods authorized for the registration holder, with information on the pharmacovigilance system to the local or regional activities. Multinational registration holders should provide a clear illustration of the key elements of both the global pharmacovigilance system and the National pharmacovigilance sub-system, highlighting the role of QPPV/LSO which pharmacovigilance activities are carried out in Pakistan, which are carried out in the headquarter/globally and how they are integrated. For the multinational registration holder the following two documents are required:

i. **The PSMF** (according to European Good Pharmacovigilance Practice) contain a description of global PV including details of global QPPV; and/ or,

ii. **The National Pharmacovigilance System file (National NPVSF)** describes the key elements of pharmacovigilance activities of multinational registration holders in Pakistan including detail of an LSO.

2.4.1. *Following shall be the contents/ headings of PSMF and/or NPVSF:*

i. Details of the qualified person responsible for pharmacovigilance ;

ii. Details of the organisational structure of the registration holder;

iii. Details of all the sources of the relevant safety data;

iv. Details of all electronic (computerized) systems and databases;

v. Details of all pharmacovigilance processes;

vi. Details of the performance of all drug safety systems; and

vii. Details of all quality systems.

viii. Annexes to PSMF

a. A list of therapeutic goods covered by the PSMF;
b. A list of written policies and procedures
c. A list of tasks that have been delegated by the qualified person for pharmacovigilance;
d. A list of all completed audits, for a period of five years, and a list of audit schedules;
e. A list of performance indicators; and
f. A logbook or 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.

For further guidelines on the above headings & annexures, GVP guidelines Module II of the European Medicine Agency may be consulted.

2.5. Format and Layout

The PSMF may be in PDF or hard format as the case may be. 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.

The PSMF/ NPVSF cover page shall include the name of the registration holder along with the name of the QPPV/LSO and the date of preparation or last update date.

Module 3

3. PHARMACOVIGILANCE INSPECTION AND AUDITS.

3.1. Pharmacovigilance Inspection.

To determine that registration holders comply with pharmacovigilance obligations established within Pakistan, and to facilitate compliance, DRAP will conduct, pharmacovigilance inspections of registration holders' pharmacovigilance system. Such inspections shall be carried out by Federal Drugs Inspectors and NPC officers appointed by the DRAP and empowered to inspect the premise and records; facilities and equipment; documentation and procedures; pharmacovigilance system master file (PSMF) and a sufficient number of trained and qualified staff; and other pertinent process/ documents of registration holders in respect of pharmacovigilance system.

A pharmacovigilance inspection may either be "routine inspections" scheduled according to a risk-based approach or "cause-specific inspections", which have been triggered to examine suspected non-compliance by registration holder or potential risks, usually with impact on a specific product(s). The NPC with the approval of PRAEC will develop a programme of inspection based on the human resources available. The results of an inspection will be provided to the registration holder who will be allowed to comment on any non-compliance identified. If the outcome of the inspection is that the registration holder does not comply with the pharmacovigilance obligations, the NPC may take necessary measures to ensure that a registration holder is subject to effective, proportionate and dissuasive penalties as determined by the PRAEC.

3.1.1. *The objectives of pharmacovigilance inspections*

The objectives of pharmacovigilance inspections are:

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

3.1.2. *Role of Registration Holders*

Registration holders with authorised therapeutic goods and applicants who have submitted new applications may be subject to pharmacovigilance inspections if desired by NPC. Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

- ✓ always to be inspection-ready as inspections may be unannounced or on short notice;
- ✓ to maintain and make available to the inspectors or officers on request, no later than 14 calendar days after the receipt of a request, the pharmacovigilance system master file (PMSF);
- ✓ to ensure that the sites selected for inspection such as manufacturing sites, the scientific office responsible for PV activities, QPPV/ LSO, which may include firms employed by the registration holder to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;
- ✓ to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;
- ✓ to ensure that relevant staff/designated persons involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;

- ✓ to ensure that relevant pharmacovigilance data is accessible from at least one point; and

- ✓to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

3.2. Pharmacovigilance Audit.

An audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable, and in the context of pharmacovigilance, the audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the rules and guidelines.

3.2.1. *A risk-based approach to pharmacovigilance audits*

The risk-based approach to audits focuses on the areas of highest risk to the organisation's pharmacovigilance system, including its quality system for pharmacovigilance activities. The risk-based approach is applied to pharmacovigilance audits wherein the risks (the risk to public health is of prime importance) can be assessed at the following stages:

- ✓ *Strategic Level Audit Planning* resulting in an audit strategy (long term approach period of 2-5 years), which should be endorsed by upper management. The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system along with pharmacovigilance processes, quality system, interactions and interfaces with other departments etc.;

- ✓ *Tactical Level Audit Planning* results in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme. An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long term audit strategy and be approved by upper management with overall responsibility for operational and governance structure. The risk-based audit programme should be based on an appropriate risk assessment and should focus on the quality system, critical pharmacovigilance processes, key control systems relied on PV, and areas identified as high risk along with mitigation plan; and

- ✓ *Operational Level Audit Planning* resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system. Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit programme.

3.2.2. *Reporting and Management of Audits' findings*

The findings of the audit should be documented in an audit report and should be communicated to management in a timely manner. Audit findings should be reported in line with their relative risk level and should be graded such critical, major and minor based on the weakness of the system that also indicates their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes.

The management of the registration holder is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate. Evidence of completion of actions should be recorded in order to document that issues raised during the

audit have been addressed.

3.2.3. *Requirement of Registration Holders for Pharmacovigilance Audit.*

The registration holders in Pakistan may perform a regular risk-based audit(s) of their pharmacovigilance system including audits of its quality system to ensure that the quality system complies with the quality system requirements along with proper documentation of dates and results of audits and follow-up audits. The QPPV should receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of the status of corrective and preventive actions and he/she should be notified about the audit findings.

The registration holders need to place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF). Based on the audit findings, the registration holder needs to ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed. The registration holders need also to ensure that a list of all scheduled and completed audits is kept in the annexed to the PSMF.

Module 4

4. RISK MANAGEMENT SYSTEM (RMS)

At the time of registration, the safety of drugs, vaccines and biological is established only in a few thousand people. When the benefit of a drug, vaccine or biological outweighs its risks in phase-III clinical trials, it gets market authorization (registration). However, at the time of registration, all the risks are not known. When the drug is launched in the market, a large population is exposed to it which leads to risks of a new type. Therefore, there should be a system to manage these risks.

Risk management is the identification, assessment, and prioritization of risks associated with the use of a drug, followed by the coordinated and economical application of resources to minimize, monitor, and control the probability and impact of new ADRs or a new aspect of known ADR.

The risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to drugs including the assessment of the effectiveness of those activities and interventions.

The overall aim of risk management is to ensure that the benefits of a particular drug, vaccine and biological exceed the risks by the greatest achievable margin for the individual patient and the target population as a whole.

4.1. Risk Management Plan

Risk Management Plan (RMP) is a detailed description of the risk management system with the aim to document the risk management system considered necessary to identify, characterise and minimise a medicinal product's important risks. To this end, RMP contains.-

a. **The Safety Specification:** the identification or characterisation of the safety profile of the medicinal product, 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'**);

b. **The Pharmacovigilance Plan**: the planning of pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions (**the 'pharmacovigilance plan'**);

c. **The Risk Minimization Plan:** the planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (**the 'risk minimisation plan'**).

4.2. Responsibilities of the Registration Holders with Regards To Risk Management Plan.

Registration holder is responsible for:

i. Having an appropriate risk management system in place;

ii. Ensuring that the knowledge and understanding of the drug's safety profile, following its use in clinical practice, are critically reviewed;

iii. The Registration holder should monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of the drug and update the risk management system and the RMP accordingly.

iv. Ensuring that they constantly monitor the risk of their drugs in compliance with pharmacovigilance rules and GVP guidelines and report the results as required by NPC; and

v. Taking all appropriate actions to minimize the risks of their therapeutic goods and maximize the benefits including ensuring the accuracy of all information produced by the company in relation to its drugs, and actively updating and communicating it when new information becomes available.

4.3. Overview of the Parts and Modules of the RMP.

The RMP is divided into several parts, with the safety specification of the RMP organized into modules to increase flexibility.

Part-I: Product (s) overview.

Part-II: Safety Specification.

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

Module SII: Non-Clinical part of the safety specification.

Module SIII: Clinical Trails Exposure.

Module SIV: Population not studies in clinical trials.

Module SV: Post-authorization Experience.

Module SVI: Additional requirement for safety specification in Pakistan.

Module SVII: Identified risks and potential risks.

Module SVIII: Summary of the safety concerns.

Part-III: Pharmacovigilance Plan

Part-IV: Plan for post-authorization efficacy studies.

Part V: Risk Minimization measure (including evaluation of the effectiveness of risk minimization measures).

Part VI: Summary of the Risk Management Plan.

Part VII: Annexes.

4.4. Submission of Risk Management Plan.

In Pakistan, Rule 11 (11) of Pharmacovigilance rules regulate the submission of Risk Management Plans (RMPs), which shall be submitted by registration holders for all new drugs in their application dossier to the Registration Board at the time of submission of an application for registration of drugs. A copy of said RMP may also be submitted to the NPC. Moreover, NPC with the concurrence of PRAEC, at a later stage of the drug's life may direct the registration holder to submit an ad-hoc RMP, if so desired. The ad-hoc RMP may also be voluntarily submitted by the registration holder if new safety information has come to knowledge due to its own assessment. The RMP is a dynamic document that should be updated throughout the life cycle of the drug. 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.

4.5. Format & Content of Risk Management Plan

Part-I:	**PRODUCT (S) OVERVIEW.**
Part-II:	**SAFETY SPECIFICATION**. **Module SI:** Epidemiology of the indication (s) and target population (s). **Module SII**: Non-Clinical part of the safety specification. **Module SIII:** Clinical Trails Exposure. **Module SIV:** Population not studies in clinical trials. **Module SV:** Post-authorization Experience. **Module SVI**: Additional requirement for safety specification in Pakistan. **Module SVII:** Identified and potential risks. ▪ Identification of safety concerns in the initial RMP submission ▪ New safety concerns and reclassification with a submission of an updated RMP ▪ Details of important identified risks, important potential risks and missing information. **Module SVIII**: Summary of the safety concerns.
Part-III:	**PHARMACOVIGILANCE PLAN (including post-authorization safety studies)** ▪ Routine Pharmacovigilance activities ▪ Additional Pharmacovigilance activities
Part-IV:	**PLAN FOR POST-AUTHORIZATION EFFICACY STUDIES**
Part V:	**RISK MINIMIZATION MEASURE (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION MEASURES).** ▪ Risk Minimizatio Plan

	▪ Summary of Risk minimization measures.
Part VI:	**SUMMARY OF THE RISK MANAGEMENT PLAN**
Part VII:	**ANNEXES.** **RMP Annex 1** **RMP Annex 2:** Tabulated summary of planned, on-going, and completed pharmacovigilance study programme **RMP Annex 3:** Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan RMP Annex 3 – part A: Requested protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP RMP Annex 3 – part B: Requested amendments of previously approved protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP RMP Annex 3 – part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority **RMP Annex 4:** Specific adverse event follow-up forms **RMP Annex 5:** Protocols for proposed and on-going studies in RMP part IV **RMP Annex 6:** Details of proposed additional risk minimisation activities **RMP Annex 7:** Other supporting data (including referenced material) **RMP Annex 8:** "Summary of changes to the risk management plan over time"

Module 5

5. COLLECTION, MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE DRUG REACTIONS

5.1. Collection of Adverse Events or Adverse Drug Reactions:

Registration holder shall record all AEs, ADRs and AEFIs with therapeutic goods registered on its name in the country which is brought to its attention, whether reported spontaneously by a patient or healthcare professional or occurring in the context of a post-authorization study and shall not refuse to consider reports of suspected serious and non-serious ADRs received through email or by telephone from patients and healthcare professionals.

The registration holder shall collect ADRs, AEFIs and AEs and report to NPC in the following conditions, namely:-

(i) Passive surveillance;

(ii) Active surveillance; and

(iii) Post-authorization studies.

In accordance with the ICH-E2D guidelines, two types of safety reports are distinguished in the post-authorisation phase: reports originating from unsolicited sources and those reported as solicited.

5.2. Unsolicited Reports

5.2.1. *Spontaneous report*

Spontaneous reporting is an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization (e.g. World Health Organization, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more therapeutic good and that does not derive from a study or any organized data collection

scheme.

5.2.2. *Literature report*

The medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of therapeutic good, particularly in relation to the detection of new safety signals or safety issues. Report of suspected adverse reactions from the medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by a registration holder to identify and record ICSRs. In addition, the registration holder shall monitor all medical literature and report any domestic ADRs within fifteen or ninety calendar days based on their seriousness.

5.2.3. *Report from non-medical sources*

If a registration holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example, the lay press or other media, it should be managed as a spontaneous report. Every attempt should be made to follow up the case to obtain the minimum information that constitutes a valid ICSR. With regard to the submission of those ICSRs, the same modalities and time frames should be applied as for other spontaneous reports.

5.3. Solicited Reports

Solicited reports are those reports which are derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. With regard to the submission as ICSRs, solicited reports should be classified as study reports. They should have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria.

5.4. Validation of Report

Only valid ICSRs qualify for submission. In accordance with ICH-E2D guidelines, all reports of suspected adverse reactions should be validated before submitting them to the competent authorities to make sure that the minimum criteria (mandatory information) are included in the reports. Four minimum criteria are required for ICSRs validation:

a. one or more identifiable reporter;
b. one single identifiable patient;
c. one or more suspected therapeutic goods; and
d. One or more suspected adverse reactions.

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR. Therefore, registration holders should validate the reports, accordingly before submission to NPC, DRAP.

5.4.1. *Mandatory & Essentially Required Information.*

Registration holder collects all the information required to be filled in the ADR reporting form. In case complete information is not available, fill all the essentially required fields/ information. In case essentially required information is not available, it should be made sure that the reporting form must contain all the mandatory information. Mandatory Information is the minimum criteria for reporting therefore a form without mandatory information will not be accepted.

Mandatory Information	Essentially Required Information.
1. Patient Information. 2. One or more suspected reaction (s). The reaction	1. Patient initials, and age at the time of reaction. 2. Sex of the patient. 3. Reaction term (s). 4. Time-to-onset of reaction (start date/time of suspected drug +start date/time of reaction)

terms must be given. 3. One or more suspected drug (s). 4. Reporter Information.	5. Suspected drug (s) (dose, strength, dosage) 6. Indication for use. 7. Seriousness of reaction 8. Outcome of reaction 9. De-challenge 10. Re-challenge (not always ethical to perform) 11. Reporter information (designation, contact details) 12. Case Narrative in free text (chronology of happening of ADRs) 13. Date of report.

5.5. Follow-up of Reports

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases as enumerated in essentially required information. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, or cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum criteria for reports validation. Any attempt to obtain follow-up information should be documented.

The provision in ICSRs of information on the patient's age is important in order to be able to identify safety issues occurring specifically in the paediatric or elderly population. Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern.

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, and if the information is incomplete, attempts should be made to follow up with the consumer to obtain consent to contact a nominated healthcare professional to obtain further information. When the case is subsequently confirmed totally or partially by a healthcare professional, the medical confirmation should be captured in the ICSR in line with ICH-E2B guidelines for healthcare professionals' definition.

5.6. Data Management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence, protected from unauthorised access. With regard to patient's and reporter's identifiability, case report information should be transmitted between registration holder and NPC in accordance with pharmacovigilance rules,

To ensure pharmacovigilance data security and confidentiality, strict control measures should be in place to provide access to documents and to databases only to authorised personnel. This security measure should be extended to the complete data path. With regard to this, procedures should be implemented to ensure security and the non-corruption of data during data transfer.

Registration holders should develop a proper database for case report storage, retrieval and E2B format conversion. In addition, a procedure should be in place to account for the identification and management of duplicate cases at data entry and during the generation of aggregated reports.

5.7. Quality Management

Registration holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data

coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving. Correct data entry, including the appropriate use of terminologies: MedDRA dictionary should be used for coding ADRs, and WHO-DD should be used for coding therapeutic goods. The pharmacovigilance data should be quality controlled, either systematically or by regular random evaluation. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures.

5.8. Duplicate Reports.

A duplicate refers to the same individual case reported by a primary source to describe suspected adverse reaction (s) related to the administration of one or more medicinal products to an individual patient at a particular point in time. This individual case may be reported by different senders, through different routes, whereby the case information may be handled differently by the processor of the case, which makes it difficult to identify the reported cases as duplicates.

The presence of duplicates in any pharmacovigilance database can create misleading signals and can pose significant problems for analysing signals and therefore impact on the safety monitoring and potential regulatory actions. Regardless of the system used for collecting and organizing ICSRs, there should always be an appropriate mechanism in place for identifying duplicates. Examples of common causes of duplicate reports are:

- ✓ A consumer and a healthcare professional reporting the same reaction occurrence;
- ✓ Multiple healthcare professionals treating the same patient reporting the same reaction occurrence;
- ✓ A reaction occurrence being reported by the original reporter to both the registration holder and NPC;
- ✓ Literature reporting of the same reaction occurrence for generics.

5.9. Management of Duplicate Reports.

Handling duplicate reports typically involve three steps: searching/detection

of duplicates; confirmation of duplicates; and management of duplicates.

5.9.1. *Identification of duplicates*

Databases should be reviewed regularly to identify duplicates. As a general rule, every newly received ICSR referring to an individual case should be considered a potential duplicate and should be checked thoroughly against the cases that are already present in the database. Therefore, screening for duplicates should be done at the time when a new report arrives in the database i.e. during data entry or during the process of loading ICSRs that have been received electronically. Duplicate searches are generally based on similarities in a patient, adverse reaction and medicinal product data. Different search criteria may be suitable for different datasets. For pharmacovigilance systems that do not have to deal with large datasets, a simple table that sorts the reports by age, sex, suspected/interacting medicinal products and adverse reactions can be suitable to detect similarities.

5.9.2. *Confirmation of duplicates cases*

Upon identification of potential duplicates, a manual confirmation will always be necessary. A well-documented case, including a case narrative, is a prerequisite to confirm if two cases are duplicates and it is of utmost importance, and this can be achieved if the registration holder submits each ICSR with essentially required information as discussed earlier. Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content. Registration holders could also collaborate with NPC in the detection of duplicate reports. If there is conflicting or limited information, which on the first review does not allow the determination that the cases are duplicates, additional information from the reporter or sender needs to be sought.

5.9.3. *Management of duplicates cases.*

A challenge to be faced in duplicate management relates to situations where conflicting or divergent information is provided by different senders. Attempts should be made to obtain clarification. If this is not

possible, the case narrative should reflect information from both sources. Confirmed duplicates that have been detected after data entry are usually managed through a merging process. By merging cases, usually, a master case is created in a database, which refers to the case chosen or created to represent the duplicated information. Duplicate cases are generally managed through a process of merging two or more cases into one master case. This process can consist of one of the following approaches:

(i) *Allocation of the master case:* The allocation of a master case refers to the procedure where one of the confirmed duplicate cases is allocated as the master case and retains its classification as a valid case. The master case should support all pharmacovigilance activities such as signal detection and medical review of ICSRs. The allocation of a master case procedure necessitates the "invalidation/inactivation" of the subordinate duplicates. This means that subordinate duplicate cases remain in the database for the purpose of audit trails, but will not be used for any other pharmacovigilance purpose. Follow-up information received for any of the subordinate duplicate cases will need to be evaluated and, incorporated into the master case unless the same, or more precise, information is already present in the master case.

(ii) *Creation of a master case:* The creation of a master case refers to the procedure where a master case is created with a new Worldwide Unique Case Identifier based on all the information contained in the subordinate duplicate cases. All of these subordinates are flagged as duplicates and linked to the master case and remain valid for the purposes of receiving follow-up information; only the master case, will be used for pharmacovigilance activities such as signal detection and medical evaluation.

5.10. Special Situations

5.10.1. *Use of therapeutic goods during pregnancy*

Reports, where the embryo or foetus may have been exposed to therapeutic good (either through maternal exposure and/or if the suspected therapeutic good was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth. Reports of exposure to therapeutic goods during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse reactions and the exposure to the suspected medicinal product.

Individual cases with an abnormal outcome associated with a therapeutic good following exposure during pregnancy are classified as serious reports and should be submitted on expedite basis. This especially refers to: reports of congenital anomalies or developmental delay, in the foetus or the child; reports of foetal death and spontaneous abortion; and reports of suspected adverse reactions in the neonate that are classified as serious. A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to NPC.

5.10.2. *Use of therapeutic goods in paediatrics or elderly population*

The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population. In addition, the concomitant medication and other relevant histories of the elderly patients shall be properly included in the report.

5.10.3. *Report of overdose, abuse, misuse, and medication error or occupation exposure.*

Reports of the above categories with no associated suspected adverse reaction/ adverse outcome should not be submitted as ICSRs. They should be recorded when becoming aware of them and considered in the periodic safety update reports as applicable. Reports of overdose, abuse, misuse, medication error and occupation exposure associated with suspected adverse reactions /adverse outcomes should be subject to submission in accordance with Rule.11 (13) of the Pharmacovigilance Rules. They should be routinely followed up to ensure that the information is as complete as possible with regard to the symptoms, suspected medicinal products name, outcomes, the context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

5.10.4. *Report of lack of therapeutic efficacy.*

Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed up if incomplete. Therapeutic goods used in critical conditions or for the treatment of life-threatening diseases, vaccines, antibiotics, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the therapeutic goods. The requirement to submit these specific reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional post-authorisation efficacy study. This is because they refer to the main end point of the study.

Clinical judgment should be used when considering if cases of lack of therapeutic efficacy qualify for submission. For example, a report of lack of therapeutic efficacy with an antibiotic used in a life-threatening situation where the use of the medicinal product was not in fact appropriate for the infective agent should not be submitted. However, a report of lack of therapeutic efficacy for a life-threatening infection,

which appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be submitted.

For vaccines, cases of lack of prophylactic efficacy should be submitted, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of prophylactic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate.

5.11. Significant Safety Issues

These are the issues related to the safety of therapeutic goods and require prompt communication from the registration holder to NPC. Significant safety issues" include but are not limited to-

(a) modification or removal of an approved indication for safety reasons based on sound scientific evidence which was not scientifically established through clinical trials;

(b) addition of a contraindication;

(c) major changes to warnings, precautions or adverse reactions statements in the product information for safety reasons in any country where the therapeutic good is marketed;

(d) withdrawal or suspension of availability of the therapeutic good in another country based on signals indicating seriousness and quality of information;

(e) issues identified by the registration holder as a result of their own signal management process once the assessment has been completed and actions are proposed;

(f) significant safety results from post-marketing clinical studies;

(g) safety issues due to misinformation in the therapeutic good information;

(h) safety issues related to the use outside the terms of the therapeutic good information or directions for use;

(i) safety issues concerning the quality of any raw materials used in the therapeutic good;

(j) a quality defect, adulteration, contamination or spurious therapeutic good associated with a serious adverse reaction report; and

(k) issues for which the registration holder is considering sending a direct healthcare professional communication (DHPC) in any country where the therapeutic good is being marketed;

5.12. How and where to Report

The clock for the submission of a valid ICSR starts as soon as the information containing the minimum criteria has been brought to the attention of the registration holder. This date should be considered as day zero. The timelines for submission are based on calendar days. Similarly, when additional significant information is received for a previously submitted case, the clock for the submission of a follow-up report starts again from the date of receipt of the relevant follow-up information. For the purpose of submission of ICSRs, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case, or could change its seriousness criteria; non-significant information includes updated comments on the case assessment or corrections of typographical errors in the previous case version.

The registration holder shall submit the ICSRs in E2B xml (either R2 or R3) format on the following official email address of the NPC: npc@dra.gov.pk .

However, the NPC may waive off the online email submission for some local registration holders if they have not yet developed the pharmacovigilance system in line with these guidelines. These local registration holders shall submit the reports on CIOMS form-I **(Annex-A)** manually in hard format on the following mailing address of the DRAP:

In-charge National Pharmacovigilance Centre,
Division of Pharmacy Services
Drug Regulatory Authority of Pakistan
3rd Floor, TF Complex,
7-Mauve Area, Islamabad.

Phone No: +92-51-9107413, +92-51-9107299

5.13. Timelines of Reporting- When to Report:

In accordance with Rule.11 (5), of Pharmacovigilance Rules, the registration holder shall submit AEs, ADRs and AEFIs originating from spontaneous reporting or from post-authorization studies as per the following timeline to the NPC:

(i) Submit to NPC database domestic serious AEs, ADRs and AEFIs within fifteen calendar days following the day on which registration holder concerned gained knowledge of the event;

(ii) Submit to NPC database non-serious AEs, ADRs and AEFIs that occur in the country, within ninety calendar days following the day on which the registration holder concerned gained knowledge of the event;

(iii) Submit to NPC database zero event report within ninety calendar days; and

(iv) Registration holder shall monitor all medical literature and report any domestic ADRs within fifteen or ninety calendar days based on its seriousness.

Furthermore, for other cases following shall be the timelines for submission shall apply as specified with the respective rules:

(i) In accordance with Rule.11 (12) of Pharmacovigilance rules, the registration holder shall report to NPC and the concerned board or committee any identified significant safety issue as soon as possible within fifteen calendar days of the awareness of the issue. Registration holder shall also inform the NPC in the event of new risks or risks that have changed or changes to the risk-benefit balance have been detected.

(ii) In accordance with Rule.11 (13) of Pharmacovigilance Rules, the registration holder shall submit to NPC within fifteen calendar days of its awareness, those reports which are associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

(iii) In accordance with Rule.11 (14) of Pharmacovigilance Rules, lack of therapeutic efficacy in case of vaccines, contraceptives, antimicrobial and drugs used in critical conditions or life-threatening situations shall be reported to NPC within fifteen calendar days.

Module 6

6. PERIODIC BENEFIT RISK EVALUATION REPORT (PBRER).

6.1. Objectives

The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the drugs or therapeutic goods, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The PBRER should contain an evaluation of new information relevant to the drug or therapeutic good that became available to registration holders during the reporting interval, in the context of cumulative information by:

i. Summarizing relevant new safety information that could have an impact on the benefit-risk profile of the drug or therapeutic good;

ii. Summarizing any important new efficacy/effectiveness information that has become available during the reporting interval;

iii. Examining whether the information obtained by the registration holders during the reporting interval is in accord with previous knowledge of the product's benefit and risk profile; and

iv. Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

6.2. Scope of the PBRER

The main focus of each PBRER is 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 in any country. All pertinent new safety and

efficacy /effectiveness information discovered during the reporting interval should be discussed in the appropriate sections of the PBRER.

6.3. Format of PEBRER

The required format and contents of PBRERs are those described in the ICH-E2C (R2) guidelines that can be assessed from ICH site. However, PSUR developed in accordance with European Good Pharmacovigilance practices will also be accepted, if a specific benefit-risk evaluation is performed. The presentation of the PRBRER shall be as under:

Part I: Title page including signature

Part II: Executive Summary

Part III: Table of Contents

1. Introduction
2. Worldwide marketing authorisation status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
   - 5.1. Cumulative subject exposure in clinical trials
   - 5.2. Cumulative and interval patient exposure from marketing experience
6. Data in summary tabulations
   - 6.1. Reference information
   - 6.2. Cumulative summary tabulations of serious adverse events from clinical trials
   - 6.3. Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
   - 7.1. Completed clinical trials
   - 7.2. Ongoing clinical trials
   - 7.3. Long-term follow-up
   - 7.4. Other therapeutic use of a medicinal product
   - 7.5. New safety data related to fixed combination

therapies

8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, ongoing or closed
16. Signal and risk evaluation
    - 16.1. Summaries of safety concerns
    - 16.2. Signal evaluation
    - 16.3. Evaluation of risks and new information
    - 16.4. Characterization of risks
    - 16.5. Effectiveness of risk minimization (if applicable)
17. Benefit evaluation
    - 17.1. Important baseline efficacy and effectiveness information
    - 17.2. Newly identified information on efficacy and effectiveness
    - 17.3. Characterization of benefits
18. Integrated benefit-risk analysis for authorized indications
    - 18.1. Benefit-risk context – Medical need and important alternatives
    - 18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices.

6.4. Obligations of Registration Holders in Pakistan.

1. As general practice PBRER is submitted across the globe for all new drugs after their registration by registration holders as per the following

frequency: every six months for the first two years; annually for the subsequent two years; and at three years intervals thereafter. In Pakistan Rule. 11 (8) of the Pharmacovigilance Rules govern the PBRER submission which state that: "*registration holder shall submit PBRER for all new drugs as per International Council on Harmonization (ICH) format E2C (R2), after its registration in Pakistan in line with the International frequency that is based on its IBD".* This means that if the international frequency is six-month submission the same will be followed in Pakistan, if it is twelve months then it will also be twelve months in Pakistan.

2. The PBRER submission shall be made within the stipulated time period as specified in Rule.11 (9) of the Pharmacovigilance Rules which state that: *"registration holder shall submit PBRER as per the following timelines, namely;-*

   a. *PBRER covering intervals of six or twelve months is to be submitted within seventy calendar days of DLP. The DLP of PBRER is based on the IBD of the said drug;*

   b. *PBRER covering intervals in excess of twelve months within ninety calendar days of DLP; and*

   c. *Ad-hoc PBRER within ninety calendar days of DLP, unless otherwise specified in the ad-hoc request. Ad-hoc PBRER are reports outside the routine reporting requirements and may be requested by Registration Board or NPC due to safety risk or any other reason. Where an ad-hoc report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the registration holders."*

3. As per Rule.11 (10) of the Pharmacovigilance rules, registration holders are not required to submit PBRER for generic drugs, drugs that have well-established use, alternative medicines and medical devices in normal condition. However, they will be bound to submit the PBRER

for these therapeutic goods only if such obligation is laid down as a condition of registration or when required by the concerned board or committee or NPC on the basis of concerns relating to pharmacovigilance or due to lack of periodic safety reports relating to an active substance after the registration has been granted.

Module 7

7. POST-AUTHORIZATION SAFETY STUDIES

7.1. Post Authorization Safety Study (PASS)

A Post-Authorisation Safety Study (PASS) is defined as *"any study relating to a registered drug conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the drug, or of measuring the effectiveness of risk management measures". A PASS may be interventional or non-interventional."*

1. In Pakistan, Rule. 11 (7) of the Pharmacovigilance Rules govern the PASS studies which is reproduced as under:

   "Registration holder shall conduct voluntarily non-interventional specific studies on the efficacy and safety if it is found that there is risk associated with the drug or if it is imposed by the Registration Board on the recommendation of PRAEC. Post-authorization safety and efficacy study can also be initiated in the case if it is laid down as a condition of registration for the specific drug."

2. In addition, Pharmacovigilance Risk Assessment Expert Committee (PRAEC) under Rule. 10 (1) (f) of the Pharmacovigilance Rules may *also recommend to the Registration Board to impose obligations on registration holder to conduct post-authorization safety and efficacy studies if it is found that during the evaluation of data, there is a safety concern with the use of the drug.*

   A PASS is non-interventional if the following requirements are cumulatively fulfilled.

   - the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation/registration;
   - the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current

practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and

- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires, blood samples and patient follow-up may be performed as part of normal clinical practice.

In Pakistan, the Bio-Study Rules, 2017 regulate the licensing of contract research organizations, laboratories for clinical research, bio-availability and bio-equivalence study centres and clinical trial sites. Likewise, Bio-Study Rules, 2017 also regulate the registration of clinical trials/ clinical studies and bio-availability/ bio-equivalence studies of therapeutic goods and on human subjects. As per the rules, clinical trials/ studies from Phase I to Phase IV are entertained under the Bio-Study Rules, 2017.

PASS could be interventional or non-interventional. If PASS is an interventional study of Phase-IV origin, then the registration holder or investigator would apply to the clinical trial section/ CSC of the Division of Pharmacy Services as per relevant provisions of Bio Study Rules, 2017 for the approval of trial sites and the study.

7.2. Methods for Post Authorization Safety Studies:

1. Active Surveillance (Intensive Monitoring Schemes, Prescription/Drug Event Monitoring and Registries);

2. Observational Studies (Cross-Sectional, Case-Control and Cohort Studies);
3. Clinical Trials; and
4. Drug Utilization Studies.

7.3. Active Surveillance

Active surveillance is a process that involves enhanced or targeted monitoring for certain events or therapeutic goods and seeks to ascertain completely the number of adverse events or adverse drug reactions through a continuous pre-planned process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. It can be achieved through Intensive Monitoring Scheme (Sentinel sites) Prescription/ Drug Event Monitoring and Registries

7.3.1. *Intensive Monitoring Schemes (Sentinel Sites)*

Intensive monitoring is a system of record collection in designated areas, e.g. hospital units or by specific healthcare professionals in community practice. The data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be (potentially) causally related to the medication. Monitoring may also be focused on certain major events that tend to be medicine-related such as hepatic disorders, renal failure, haematological disorders or bleeding. Intensive monitoring may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system.

7.3.2. *Prescription/Drug Event Monitoring*

In prescription event monitoring (PEM), patients may 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 date), dosage, clinical events and reasons for discontinuation can be included in the questionnaire. PEM tends to be used as a method to study safety just after product launch. In PEM, there is the opportunity to collect more detailed information on adverse events from a large number of physicians and/or patients.

7.3.3. *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 standardised 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. 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.

7.4. 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, active surveillance programmes or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

7.4.1. *Cross-Sectional Studies (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. These studies are best used to examine the prevalence of disease at a 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 utilised when exposures do not change over time.

7.4.2. *Case-Control Study*

In a case-control study, cases of disease (or events) are identified and patients from the source a population that gave rise to the cases but who do not have the disease or event of interest at the time of selection are then selected as controls. The odds of exposure are then compared between the two groups. Patients may be identified from an existing database or using a field study approach, in which data are collected specifically for the purpose of the case-control study. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (e.g. the older persons, children, pregnant women). Existing large population-based databases are a useful and efficient means of providing needed 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 medicinal product (or several products) and one specific rare adverse event, as well as to identify multiple risk factors for adverse events. Factors of interest may include conditions such as renal and hepatic dysfunction that might modify the relationship between the exposure to the medicinal product and the adverse 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, a case-control study may also provide the absolute incidence rate of the event.

7.4.3. *Cohort Study*

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each study participant. A study participant might be exposed to a medicinal product at one time during follow-up, but unexposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication 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. They are also useful for the evaluation of multiple adverse events within the same study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan medicinal product) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (older persons, children, patients with comorbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist

7.5. Clinical Trials

When important risks are identified from pre-approval clinical trials, further clinical trials might be called for to evaluate the mechanism of action for the adverse reaction. If PASS is the interventional study of Phase IV origin then provisions of Bio-Study Rules, 2017 shall apply. In some instances,

pharmacodynamics and pharmacokinetic studies might be conducted to determine whether a particular dosing regimen can put patients at an increased risk of adverse events. Genetic testing may 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 medicinal product in clinical practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and therapeutic drug monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from preapproval 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 older persons, pregnant women, children or patients with renal or hepatic disorders. Children, older persons and persons with co-morbid conditions may metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials may be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

7.6. Drug Utilization Studies

Drug utilisation studies (DUS) describe how a medicinal product is prescribed and used in routine clinical practice in large populations, including older persons, children, pregnant women or patients with hepatic or renal dysfunction. These populations are often not eligible for inclusion in randomised clinical trials. Stratification by age, sex, concomitant medication and other characteristics allows a comprehensive characterisation of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. Denominator data may be derived from these studies to determine rates of adverse events. DUS has been used to describe the effect of regulatory actions and media attention on the use of medicinal products in everyday medical practice, to examine the relationship between recommended and actual clinical practice, to monitor medication errors and

to determine whether a medicinal product has the potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. DUS are particularly useful as a first step in the design of post-authorisation safety studies, to obtain a sufficient understanding of the characteristics of the user population of the medicinal product under study and the determination of the most appropriate comparator as well as important potential confounders to consider. They are also useful to provide a first indication of the level of public health impact anticipated if there is a true causal association between the exposure of interest and an adverse event, for the example given the size of the population exposed, the extent of off-label use, and so on. For regulatory purposes, DUS for which the main aim is to add knowledge to the safety of medicinal products or the effectiveness of risk minimisation measures may be classified as PASS**.**

7.7. Structures and Processes

The structures and processes of PASS studies are presented in the preceding sections.

7.8. Study Registration

The interventional PASS of phase IV origin that fall under the ambit of Bio-Study Rules, 2017 whether to be conducted voluntarily or pursuant to obligations imposed by PRAEC must be initiated in Pakistan once the Clinical Study Committee (CSC) of the DRAP has approved/ registered the study as per Form-VI of Bio-Study Rules, 2017. The PRAEC must be informed about the approval of the CSC and about the subsequent initiation of an interventional PASS of Phase IV origin through a communication letter.

7.9. Study Protocol

Non-interventional PASS conducted pursuant to an obligation imposed by PRAEC or voluntarily need to have a written study protocol. The study protocol should be developed by individuals with appropriate scientific background and experience such as principal/co-priniciple investigators etc. For non-interventional PASS that is imposed as an obligation, the registration

holder or the investigator on his behalf need to submit a draft protocol to PRAEC for consideration and approval. The qualified person in Pakistan (QPPV or LSO) or his/her delegate should be involved in the review and sign-off of study protocols required in the risk management plan in Pakistan that is agreed by the PRAEC, or in protocol of non-interventional PASS conducted voluntarily in Pakistan. Both non-interventional PASS and interventional PASS of Phase IV origin should be conducted in Pakistan after getting proper ethical clearance from the institutional review board and National bioethics committee.

7.10. Format and content of the study protocol

For non-interventional PASS conducted pursuant to an obligation imposed by PRAEC, the study protocol shall follow the format described as follows:

1.	**Title**	Informative title including a commonly used term indicating the study design and the medicinal product, substance or medicinal product class concerned, and a sub-title with a version identifier and the date of the last version
2.	**Registration holder**	Name and address of registration holder along with contact info of QPPV/ LSO.
3.	**Responsible parties**	Names, titles, qualifications, addresses and affiliation of the main author(s) of the protocol, principal/co-principle investigator, sponsor etc. List of collaborating institutions.
4.	**Abstract**	Stand-alone summary of the study protocol with sub-sections such as title with subtitles including version and date of the protocol and name and affiliation of main author; rationale and background; research question and objectives; study design; population; variables; data sources; study size; data analysis; and milestones.
5.	**Amendments and updates**	Any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol

		where the change has been made.
6.	**Milestones**	Table with planned dates for the activities such as start and end of data collection, study progress reports, interim report(s) where applicable, and final report of study results.
7.	**Rationale and background**	Short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and a short critical review of relevant 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.
8.	**Research question and objectives**	The research question that explains how the study will address the issue and research objectives, including any pre-specified hypotheses and main summary measures.
9.	**Research methods**	The research method must include the following: Study design, setting, variables, data sources, study size, data management, data analysis, quality control and. limitations of the research methods.
10.	**Protection of human subjects**	Approval from instituional review board and from the National bio-ethics committee.
11.	**Management and reporting of adverse events/adverse reactions**	Procedures for the collection, management and reporting of individual cases of suspected adverse reactions/events and of other medically important events that might influence the evaluation of the risk-benefit balance of the product while the study is being conducted.
12.	**Plans for disseminating and communicating study results**	Plans for submission of progress reports and final reports.
13.	**References.**	

The above format may also be followed for the non-interventional PASS required in the risk management plan agreed in Pakistan.

7.11. Amendments to the Study Protocol:

Amendment to the protocol of interventional PASS of phase IV origin should be made with the approval of the institution review board, National bioethics committee and the CSC as per Bio-Study Rules, 2017. Likewise, an amendment to the protocol of non-interventional PASS that is conducted pursuant to an obligation imposed should be made with the approval of the institutional review board, the National bioethics committee and the PRAEC.

7.12. Reporting of Safety Data and Study Reports

7.12.1. *Data relevant to the risk-benefit balance of the product.*

The registration holder shall monitor the data generated while the non-interventional PASS is being conducted and consider their implications for the risk-benefit balance of the drug. Any new information that may affect the risk-benefit balance of the drug should be communicated immediately in writing or as a significant safety issue to NPC.

The registration holder or the sponsor of interventional PASS of phase IV origin should report all information that may affect the benefit-risk balance and safety of investigational product to the CSC of DRAP as per Rule 8 (17) and Rule 12 of the Bio-Study Rules, 2017.

7.12.2. *Reporting of adverse reactions/adverse events.*

Individual cases of ADRs and AEs of non-interventional PASS should be reported to NPC as per the timelines provided in Module 5 and Section 5.13. Likewise, SAEs and other events of interventional PASS of phase IV origin need to be reported to CSC as Rules 8 and 12 of the Bio-Study Rules, 2017. Adverse events/adverse reactions collected in studies with primary data/ secondary data collection should be recorded and summarised in the interim safety analysis and in the final study report.

7.12.3. *Progress report and the interim report of study results.*

The progress report and interim results of non-interventional PASS conducted voluntarily or pursuant to obligations imposed should only be submitted upon a request from the PRAEC.

The progress report and interim results of interventional PASS of phase IV origin should be submitted to CSC as per Rule 8 (3) of the Bio-Study Rules.

7.12.4. *Final study report*

For non-interventional PASS conducted pursuant to an obligation imposed by the PRAEC, the final study report shall be submitted to PRAEC within 12 months of the end of data collection. If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

Likewise, the final report of interventional PASS of phase IV origin should be submitted to CSC as per rule 8 (6) of the Bio-Study Rules, 2017. A copy of the final report/results of interventional PASS of phase IV origin conducted pursuant to an obligation imposed should also be submitted to PRAEC.

If PRAEC is not satisfied with the results/final report of non-interventional PASS conducted pursuant to an obligation/ conducted voluntarily or with the final report/results of interventional PASS of Phase IV origin conducted pursuant to an obligation, then it would recommend any other regulatory action/risk minimization measures for implementation in Pakistan as appropriate.

Module 8

8. SIGNAL MANAGEMENT

8.1. Definition of Signal

World Health Organization define a signal as "reported information on a possible causal relationship between an adverse event and a drug or a therapeutic good, 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. The publication of a signal usually implies the need for some kind of review or action"

The more recent definition of a signal is given by CIOMS Medical Sciences working group in its report of 2010 which is defined as under:

"*Information that arises 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".*

8.2. Responsibilities of Registration holders

Registration holders should continuously monitor the safety of therapeutic goods for any new information that might have an impact on the registration of therapeutic goods and inform the authorities accordingly. The registration holders should collaborate with the PRAEC for the assessment of the signals by providing additional information when requested. Registration holders shall keep their product information up-to-date in the light of scientific knowledge, including the assessments and recommendations made by the PRAEC. The registration holder should submit the details of detected signals through communication letter along with scientific data and other communication to the PRAEC on the following address:

Secretary, *Pharmacovigilance Risk Assessment Expert Committee (PRAEC)*

Additional Director, National Pharmacovigilance Centre,
Division of Pharmacy Services, Drug Regulatory Authority of Pakistan
3rd Floor, TF Complex, G-9/4. Mauve Area, Islamabad.
Email. npc@dra.gov.pk, 051-9107413

8.3. Signal Management Process

A set of activities performed to determine whether, based on an examination of individual case safety reports (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 therapeutic good or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The signal management process concerns all stakeholders involved, but, more specifically registration holders and NPC, DRAP. Whereas the ADRs database will be a major source of pharmacovigilance information, the signal management process covers signals arising from any source, only signals related to an adverse reaction shall be considered

8.4. Steps in Signal Management Process

Signals detected through any sources should be handled according to the registration holder's own signal management process, taking into account the general principles outlined below. The signal management process covers all steps from detecting signals to recommending action(s) as follows:

8.4.1. *Signal Detection*

The process of looking for and/or identifying signals using data from any source. 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 case (e.g. signals detected from published studies, healthcare record data), assessment of aggregated data should be considered.

8.4.2. *Signal Validation*

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 take into account the strength of the evidence, the clinical relevance/context and the previous awareness of the association. A signal for which the signal validation process has verified 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 is called a validated signal. Sometimes, the signal validation process led to the conclusion that the available documentation at the point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted, that is called non-validated signal.

8.4.3. *Signal Prioritization*

The process, continuously performed throughout signal management, 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 therapeutic good and thus require urgent attention and management without delay. In some circumstances, signals that could cause media attention and/or public concerns (e.g. adverse events following mass immunisation) may deserve special attention. The timeframe for further management of the signal will depend on the prioritisation.

8.4.4. *Signal Assessment*

The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally

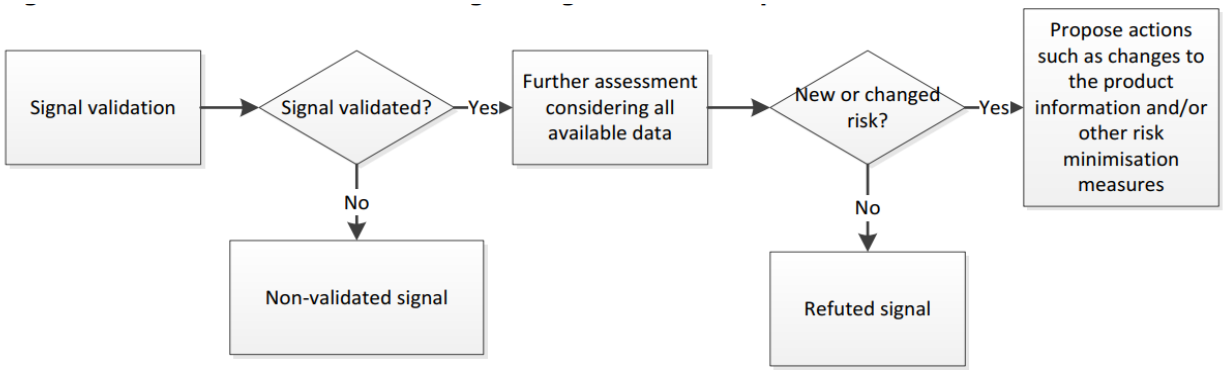
associated with the active substance or drugs or therapeutic good or whether known risks have changed. This review may include nonclinical and clinical data and should be as comprehensive as possible regarding the sources of information.

8.4.5. *Recommendation for Action*

The effect of the newly identified risks shall be evaluated on the benefit-risk ratio of the therapeutic goods and subsequent risk minimization actions shall be initiated by registration holders. The information should be promptly communicated to NPC, DRAP and to PRAEC through communication letters or email along with all justification on the official mailing and email address.

8.4.6. *Exchange of Information*

NPC-DRAP and registration holders shall accordingly communicate with healthcare professionals, media and patients etc. about the new signal.



Module 9

9. SAFETY COMMUNICATIONS

9.1. Safety Communication

The safety communication module guides NPC, DRAP and registration holders on how to communicate and coordinate safety information. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimising risks and contributing to the protection of patients and public health.

Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the prescribing information (i.e. the summary of product characteristics (SmPC) or safety specification, package leaflet (PL) and the labelling of the packaging.

9.2. Content of Safety Communication

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information should not include any material or statement which might constitute advertising under the DRAP Act, 2012. Contents include important new information; reason for initiating safety communication; any recommendations to healthcare professionals and patients; information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL); additional information about the use of the therapeutic good; a list of literature references; and a reminder about reporting ADRs as per guidelines.

Good communication is the one that is issued timely; target the right audience; use appropriate channels; provide essential and useful information; use appropriate language, and is truthful. Therefore, it contributes to risk minimization; help HCPs to make wise decisions in their choice of

therapeutics; foster trust in Regulatory Authorities, Provincial Centres and Registration holders.

9.3. Requirements for Registration holders

As soon as a registration holder intends to make a public announcement relating to information on pharmacovigilance concerns concerning the use of a therapeutic good, and in any event at the same time or before the public announcement is made, the registration holder is required to inform the DRAP. Registration holders shall ensure that information to the public is presented objectively and is not misleading. Registration holder may also inform DRAP if it becomes aware that a third party intends to issue communications that could potentially impact the risk-benefit balance of therapeutic goods in Pakistan. Likewise, NPC in some cases may also communicate with registration holders through different means such as letters or web announcements when a signal is detected or if a response of the registration holder is required on the detected signal.

9.4. Target Audiences

The primary target audiences for safety communication issued by NPC and registration holders should be patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) therapeutic goods.

As primary target audiences, **healthcare professionals** play an essential role in ensuring that therapeutic goods are used as effectively and safely as possible. Effective safety communication enables them to take adequate actions to minimise risks and to give clear and useful information to their patients. This ultimately promotes patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concerns at the same time.

Patients, consumers and healthcare professional organisations can play a role as multipliers as they can disseminate important safety information to target audiences.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on therapeutic goods. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the DRAP in addition to the information they receive from other sources.

9.5. Means of Safety Communication or Risk communication Plan

Following are some of the means adopted for safety communication:

9.5.1. *Direct healthcare professional's communication (DHPC):*

A direct healthcare professional communication (DHPC) is a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a registration holder or NPC, to inform them of the need to take certain actions or adapt their practices in relation to a drug. Dear healthcare professional letter is a form of direct healthcare professional communication. DRAP may issue safety communications targeting healthcare professionals directly. These may be published on the website of the DRAP. These communications often complement other means for communicating a safety concern (e.g. a DHPC) and are issued around the same time. They contain the DRAP recommendations and advice for risk minimisation for healthcare professionals and provide relevant background information.

9.5.2. *Documents in lay language:*

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. It can also be an additional tool that healthcare professionals can use in their communication with patients. Lay language documents of the registration holders should contain the NPC's recommendations and

advice for risk minimisation for patients and should be accompanied by relevant background information.

9.5.3. *Press communication:*

Press communication includes press releases and press briefings which are primarily intended for journalists. The public relations officer nominated by DRAP is the only person authorized to engage with the media. DRAP may send press releases directly to journalists in addition to publishing them on DRAP's website. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the DRAP's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system. Press releases may also be prepared and published by registration holders. Their press releases should refer to the regulatory action taken by the DRAP. Relevant ongoing reviews should be mentioned in any communication by the registration holders.

9.5.4. *Website:*

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

9.5.5. *Social media and other online communications*

Online safety information may also be disseminated via social media platforms such as Facebook, Twitter and LinkedIn and other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised

9.5.6. *Therapeutic good safety alert*

When a new safety concern is detected, it is promptly issued in the form of therapeutic goods safety alert by NPC, DRAP. The therapeutic good safety alerts are communicated uploaded on the DRAP website or sometimes through social media as the public safety information for healthcare professionals, patients and registration holders. NPC may also communicate through email or other web-based announcment with the registration holders when a signal is detected.

9.5.7. *Newsletter:*

Bulletins and newsletters provide at regular intervals information about therapeutic good and their safety and effectiveness. These tools may serve as reminders of previous communications. NPC can reach a large audience with these tools by using web-based and other available means. Through newsletter findings and regulatory status of medicines is communicated within Pakistan as well as globally. The newsletter is for everyone concerned with the issues of PV and provides practical information and advice on drug and therapeutic goods' safety and information about emerging safety issues.

9.5.8. *Inter and Intra country communication:*

NPC-DRAP shall inform the provincial pharmacovigilance centres in a timely manner about the regulatory actions taken at the level of national level with regards to the new safety concern. DRAP may also inform regional bodies and regulatory authorities of other states about the newly detected safety concerns. Likewise, other regulatory authorities and regional and international bodies such as WHO and UMC also share new safety concerns with DRAP.

9.5.9. *Advisories:*

NPC, DRAP and other Divisions of the Drug Regulatory Authority of Pakistan also prepare advisories for different stakeholders about the safety and quality of therapeutic goods, which after approval are

disseminated through different means with pharmacovigilance stakeholders.

9.5.10. *Responding to enquires from the Public:*

DRAP and registration holders should have systems in place for responding to enquiries about therapeutic goods from individual members of the public. In Pakistan, there is the Pakistan Citizen Portal mobile application where the public can complain about public offices on any matter of their daily life including the matters related to therapeutic goods. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by DRAP. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

Module 10

10. RISK MINIMIZATION MEASURES

10.1. Risk Minimization Measures

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a drug or therapeutic good, or to reduce their severity or impact on the patient. Planning and implementing risk minimisation measures and assessing their effectiveness are key elements of risk management.

Risk minimisation measures aim to optimise the safe and effective use of a therapeutic good throughout its life cycle. The risk-benefit balance of a therapeutic good can be improved by reducing the burden of adverse reactions or by optimising benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, and patient follow-up). Risk minimisation measures should therefore guide optimal use of therapeutic good in clinical practice with the goal of supporting the provision of the right therapeutic good, at the right dose, at the right time, to the right patient and with the right information and monitoring.

10.2. Routine Risk Minimization Measures.

Risk minimisation measures may consist of routine risk minimisation or additional risk minimisation measures. Routine risk minimisation applies to all drugs and involves the use of the following tools

- ✓ the summary of product characteristics/ prescribing information;
- ✓ the labelling (e.g. on inner and outer carton);
- ✓ the package leaflet;
- ✓ the pack size(s);
- ✓ the legal status of the product.

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

The summary of product characteristics /prescribing information and

the package leaflet are important tools for risk minimisation as these are standardised formats for informing healthcare professionals and patients about therapeutic goods. Routine risk communication messages about ADRs could be found under the relevant section of SmPC/ prescribing information/package leaflet of the therapeutic good so that an informed decision on the treatment can be made. Likewise, risk minimisation activities recommending specific clinical measures to address the risk could be found in specific sections of SmPC/prescribing information where warning and precaution messages, recommendations and information on addressing the risks of the product could be found.

10.2.2. *Pack size*

We know that every pack size is specifically authorised for a medicinal product, planning the number of "dosage units" within each pack and the range of pack sizes available can be considered a form of routine risk management activity. Therefore, controlling the number of "dosage units" should mean that patients will need to see a healthcare professional at defined intervals, thus increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered. Likewise, small pack size can also be useful, especially if overdose or diversion are thought to be major risks.

10.2.3. *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 authorisation 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. Typically it includes information on whether or not the medicinal product is subject to medical prescription. It may also

restrict where the medicinal product can be administered (e.g. in a hospital) or by whom it may be prescribed (e.g. specialist).

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicinal product and the setting (hospital or institutions having defined facilities etc) in which the medicinal product can be given or used. When considering the classification of a medicinal product as subject to restricted medical prescription, the following factors shall be taken into account

- 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;
- 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; and
- 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.

Special medical prescription

These medicinal products contain a substance/ API classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force and are likely, if incorrectly used, will present a substantial risk of medicinal abuse, and lead to addiction or be misused for illegal purposes. Drugs such as narcotic drugs, psychotropic substances and precursor chemicals are considered controlled drugs in Pakistan as per DRAP Act, 2012. A specific quota of molecules /APIs falling under the categories of these drugs is

allocated for the manufacturing of such medicinal products. The records of purchase, import, dispensing, production, distribution and sale are to be kept at all levels and may be asked by the regulator at any time to avoid their misuse. These types of drugs require a special prescription from the healthcare professionals or even in some cases the drug could only be dispensed in hospitals, and their sale and dispensing record is maintained at retail sale level and in hospitals.

10.3. Additional Risk Minimisation Measures

Safety concerns of a medicinal product are in normal conditions adequately addressed by routine risk minimisation measures. In some exceptional cases, however, routine risk minimisation measures will not be sufficient for some risks and therefore additional risk minimisation measures will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product. When additional risk minimisation activities are needed, safety concerns are to be prioritised in terms of frequency, seriousness, severity, impact on public health and preventability. Likewise, careful consideration is then to be given to whether the goal/aim can be reached with routine minimisation activities, and, if not considered sufficient, which additional minimisation measure(s) is (are) will be the most appropriate. Additional risk minimisation activities/measures 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.

Additional risk minimisation measures that may be considered in addition to the routine measures include the following:

- ✓ Educational programmes;
- ✓ Controlled access programmes; and
- ✓ Other risk minimisation measures

10.4. Educational programmes

Educational programmes are based on targeted communication to supplement

the information in the summary of product characteristics (SmPC)/prescribing information and patient leaflet (PL). 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 minimise selected risks.

10.4.1. *Aim of Educational Programme*

The aim of an educational programme is to improve the use of medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk. Ideally, educational materials should be available in a range of formats to ensure that access is not limited by disability or access to the internet. When feasible the appropriateness of the tool and media for the target audience (e.g. suitable language, pictures, diagrams, or other graphical support) should be user tested in advance, in order to optimise the success of the implementation phase. In the context of an educational programme, 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).

10.4.2. *Contents of Educational Programmes*

Any educational programme should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes should not be used for promotional activities. The content of any educational material should be fully aligned with product information for a therapeutic good, such as the SmPC and PL, and should add rather than duplicate SmPC and PL information. Promotional elements, either direct or veiled (e.g. logos, product brand colours, 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 minimisation.

10.4.3. *Educational tools*

Should focus on clearly defined actions related to specific safety concerns described in the RMP and should not be unnecessarily diluted by including ambiguous statements (s) or such information that is not immediately relevant to the safety concern and that is already adequately presented in the SmPC or package leaflet. Educational tools should refer the reader to the information of SmPC and the package leaflet. There is an introductory statement that the educational material is essential to ensure the safe and effective use and appropriately manage important selected risks. Other elements for inclusion in an educational tool could be:

- ✓ Guidance on prescribing, including patient selection, testing and monitoring;
- ✓ Guidance on the management of such risks (to healthcare professionals and patients or carers); and
- ✓ Guidance on how and where to report adverse reactions of special interest.

10.4.4. *Educational tools targeting Healthcare Professionals*

The aim of any educational tool targeting a healthcare professional is 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 reaction) associated with the drug or therapeutic good and the specific important risks needing additional risk minimisation measures, including:

- ✓ selection of patients;
- ✓ treatment management such as dosage, testing and monitoring;
- ✓ special administration procedures, or the dispensing of a medicinal product; and
- ✓ details of the information that needs to be given to patients.

The format of a particular tool depends upon the fact that which message would be delivered. For example, where a number of actions

are needed before writing a prescription for a patient, a checklist may be the most suitable format in such a case. A brochure may be more appropriate to enhance awareness of specific important risks with a focus on the early recognition and management of adverse reactions. Likewise, posters for display in certain clinical environments can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the objective of the tool.

10.4.5. *Educational tools targeting patients and/or carers*

The aim of tools targeting patients and/or carers is to enhance their awareness of the early signs and symptoms of specific adverse reactions that cause the need for additional risk minimisation measures and on the best course of action to be taken should any of those sign or symptoms occur. The patient educational tool could be used to provide information on the correct administration of the product and to remind the patient about important activity, for example, a diary of dosing or a diagnostic procedure that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the safe and effective use of the therapeutic good are adhered to.

10.4.6. *Patient alert card*

Its aim is to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) and it is to be kept by a patient at all times and reaches/share with the relevant healthcare professional when required. The information should be kept to the minimum necessary in order to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including an emergency. The ability to carry the patient alert card with ease (e.g. it can be fitted in a wallet) should be a key design feature of this tool.

10.5. Controlled access programmes

A controlled access programme consists of interventions that seek to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status. The use of such a programme is limited and guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is life-threatening), and the likelihood that this risk can be managed by such a programme. Therefore, controlled access should only be considered as a tool for minimising 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 programme 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.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled-access programme are listed below (they may be included individually or in combination) such as:

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

For example, monitoring of the patient's health status, laboratory values or other characteristics prior to and/or during treatment, e.g. electrocardiogram, liver function tests, regular blood tests, pregnancy tests (which can be part of a pregnancy prevention programme). Measures should be put in place to

ensure that monitoring takes place according to the SmPC where this is critical to the risk-benefit balance of the product.

10.6. Other risk minimisation measures

10.6.1. *Controlled Distribution System*

A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of products from single or multiple identified distribution points facilitate traceability of the product. For instance, these sorts of measures could be considered for controlled drugs as notified by DRAP to prevent misuse and abuse that also require a special prescription as described in the routine minimization action.

10.6.2. *Pregnancy Prevention Programme*

A pregnancy prevention programme (PPP) is a set of interventions aimed at minimising pregnancy exposure during treatment with a therapeutic good that has known or potential teratogenic effects. The scope of such a programme is to ensure that the female patients are not pregnant when starting therapy and do not become pregnant during the course of treatment or soon after stopping the therapy. It could also target male patients when the use of a medicinal product by the biological father might have a negative effect on pregnancy outcomes. This tool combines the use of educational tools with interventions to control appropriately access to the medicine, therefore, the following elements individually and/or in combination could be used for the development of a PPP such as:

- ✓ educational tools targeting healthcare professionals and patients to inform about the teratogenic risk and required actions to minimise this risk (e.g. guidance on the need for more than one method of contraception, different types of contraception, how long to avoid

pregnancy when the treatment is stopped.);

- ✓ controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product;
- ✓ prescription limited to a maximum of 30 days' supply;
- ✓ counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy

10.6.3. *Direct Healthcare Professional Communication (DHPC)*

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by NPC, DRAP, to inform them of the need to take certain actions or adapt their practices in relation to a therapeutic good. For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product.

7. REFERENCES

1. Pharmacovigilance Rules, of Drug Regulatory Authority of Pakistan.
2. The Importance of Pharmacovigilance Safety Monitoring of Medicinal Product
3. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool
4. The Safety Monitoring of Medicinal Products Guidelines for Setting Up and Running a Pharmacovigilance Centre.
5. Good Pharmacovigilance Practices Guidelines of European Medicines Agency.
6. E2B, E2C, E2D and E2E guidelines of ICH>
7. Pakistan National Pharmacovigilance Guidelines.

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ANNEXURE I

CIOMS FORM I

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

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