



PAKISTAN NATIONAL PHARMACOVIGILANCE GUIDELINES

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GOVERNMENT OF PAKISTAN
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HISTORY

This is the first edition of these guidelines.

APPLICATION

This is a guide and support document for the following stakeholders:

- ✓ Healthcare professionals;
- ✓ Patients;
- ✓ Technical Staff at Pakistan National Pharmacovigilance Centres;
- ✓ Technical Staff at Provincial Pharmacovigilance Centres;
- ✓ Pharmacovigilance Officers across the country;
- ✓ Technical Staff at Public Health Programmes;
- ✓ Hospitals;
- ✓ Registration Holders of Therapeutic Goods; and
- ✓ National Regulatory Authorities of other countries.

PURPOSE

The purpose of this guidance document is to provide a basic framework for the implementation of pharmacovigilance programme of Pakistan and to ensure that stakeholders are better equipped to monitor the safety of therapeutic goods and to detect, assess, understand, prevent and investigate ADRs/ AE report. The overall aims are:

- To operationalize the pharmacovigilance programme of Pakistan;
- To detect, validate, assess new signals in Pakistan pharmacovigilance database;
- To continuously monitor the risk-benefit balance of therapeutic goods in Pakistan's market;
- To encourage patient, healthcare professionals and therapeutic goods' sale points to report suspected ADR/ AEs;
- To provide training to provincial pharmacovigilance centres and public health programmes and to provide face to face training to healthcare professionals;
- Recommend regulatory actions based on the safety of therapeutic goods;
- To disseminate the safety communication to relevant stakeholders;
- To coordinate with regional and international bodies for the development of vibrant PV system in Pakistan.

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Acronyms

AE	:	Adverse Event
ADR	:	Adverse Drug Reaction
AEFI	:	Adverse Event Following Immunization
CIOMS	:	Council for International Organizations of Medical Sciences
DHPC	:	Direct Healthcare Professional Communication
DIBD	:	Development International Birth Date
DLP	:	Data Lock Point
DRAP	:	Drug Regulatory Authority of Pakistan
DSUR	:	Development Safety Update Report
HCP	:	Healthcare Professional
IBD	:	International Birth Date
ICH	:	International Council on Harmonization
ICSR	:	Individual Case Safety Report
MedDRA	:	Medical Dictionary for Regulatory Activities
PASS	:	Post-Authorization Safety Studies
PAES	:	Post-Authorization Efficacy Studies.
PBRER	:	Periodic Benefit Risk Evaluation Report
PHP	:	Public Health Programme
PNPC	:	Pakistan National Pharmacovigilance Centre
PO	:	Pharmacovigilance Officer
PV	:	Pharmacovigilance
PPC	:	Provincial Pharmacovigilance Centre
PRAEC	:	Pharmacovigilance Risk Assessment Expert Committee
PV	:	Pharmacovigilance
SUSAR	:	Suspected Unexpected Serious Adverse Reactions
TGSP	:	Therapeutic Goods' Sale Points (Distributors, wholesaler, Retailer)
RMP	:	Risk Management Plan
WHO-DD	:	World Health Organization Drug Dictionary
WHO-UMC	:	World Health Organization, Uppsala Monitoring Centre.

Chapter No.1: Structure of Pharmacovigilance Programme of Pakistan.

1.1 Introduction

There is limited safety information about the investigational drug during the clinical trials, but once the drug is released into the market after registration, large population is exposed to the drug and hence new and unexpected serious adverse drug reactions can occur. The limitations of clinical trial are: numbers of trial subject 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 disease and concomitant drugs are excluded in clinical trials; and duration of clinical trials is of few years as compared to real practice. Therefore, there is a dire need to have a vibrant national pharmacovigilance centre to monitor the safety of drugs during its post marketing phase. Pharmacovigilance as defined by WHO is the science and activities relating to detection, assessment, understanding and prevention of adverse effect or any other drug related problem. Now, the scope of pharmacovigilance has been increased and it monitors the safety of drugs both in pre and post marketing phase and covers products other than drugs/medicines.

In line with international practices, the DRAP has established the Pakistan National Pharmacovigilance Centre (PNPC), under the Division of Pharmacy Services, DRAP, Islamabad, to monitor therapeutic goods' safety across the country. To this end, the Centre started National and International coordination for the development and promotion of pharmacovigilance in Pakistan. Pakistan becomes 134th Full member of World Health Organization Programme for International Drug Monitoring (WHO-PIDM) in 2018 with endeavours of DRAP. PNPC is supporting provincial governments and public health programmes in establishment of their pharmacovigilance centres. Moreover, PNPC is also coordinating with provincial governments to establish pharmacovigilance centres at the level of hospitals.

1.2 Legal Basis for Pharmacovigilance Activities in Pakistan.

The DRAP Act, 2012[XXI of 2012] is the law in Pakistan that govern the Pharmacovigilance activities in Pakistan. As per Section 2 (xxvi) and Section 4 (1) (g) of DRAP Act, 2012, the Division of Pharmacy Services has been given the mandate to develop, promote and regulate the pharmacovigilance activities in Pakistan.

1.3 Vision

To safeguard the health of Pakistani population by ensuring that the benefits of therapeutic goods outweigh the risk associated with their use. Further, in line with National Health Vision 2016-2025, the main vision of this programme is to establish a vibrant Pharmacovigilance centres at National Level and collecting points at provincial level.

1.4 Mission

To improve patient safety and the welfare of the Pakistani population by monitoring the safety of the therapeutic goods and accordingly reducing the risks associated with their use.

1.5 Scope of Pharmacovigilance Programme of Pakistan

The pharmacovigilance programme of Pakistan monitors the safety of therapeutic goods both in pre and post-marketing phase. The pharmacovigilance Programme of Pakistan collects and monitors the following reports:

- ✓ Detection, assessment, understanding and prevention of ADRs/AEs which are associated with the use of therapeutic goods in routine practice;
- ✓ AEFI reports associated with Vaccines and immunization errors;
- ✓ Lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical or life-threatening conditions;
- ✓ AEs with medication errors;
- ✓ AEs with quality problems (substandard and falsified medicines) of therapeutic goods;
- ✓ AE or ADR reports associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure of therapeutic goods.

Whereas, the products covered by the Pharmacovigilance Programme are therapeutic goods as per DRAP Act, 2012 and includes the following:

- ✓ Allopathic Medicines (Drugs/Medicines);
- ✓ Alternative Medicines (Ayurvedic, Chinese, Unani, Homeopathic and Biochemic system etc.);
- ✓ OTC Products/ Health products (Nutraceuticals and others etc.);
- ✓ Biologicals, Vaccines and other blood products.
- ✓ Medical Devices; and
- ✓ Other related products as may be defined by Authority.

1.6 Short Term Goals

- To strengthen the Pakistan National Pharmacovigilance Centre (PNPC) at DRAP, Islamabad;
- To coordinate with Provincial Health Departments for establishment of their Provincial Pharmacovigilance Centres (PPCs);
- To nominate Pharmacovigilance officers at PNPC;
- Coordinate with Provincial Health Departments for nomination of their Focal Persons/ Incharge Provincial Pharmacovigilance Centres;

- To constitute Pharmacovigilance Risk Assessment Expert Committee (PRAEC) at National level and coordinate with Provincial Centres for constitution of their Provincial Pharmacovigilance Committees;
- Encourage HCPs in reporting of AEs and ADRs; and
- Integrate Provincial Centres into National Centre database.

1.7 Medium Term Goals

- To coordinate with Provincial Pharmacovigilance Centres for establishment of their Regional (Divisional) Pharmacovigilance Centres and pharmacovigilance centres at the level of hospitals;
- To coordinate with public health programmes for establishment of their Pharmacovigilance centres;
- To coordinate with PHPs and PPCs for nomination of Focal Persons at the level of Hospitals, Regional (Divisional) Pharmacovigilance Centres and Public Health Programmes;
- Coordinate with Provincial Pharmacovigilance Centres for constitution of pharmacovigilance committees at the level of hospitals and regional pharmacovigilance centres;
- Coordinate with PHPs for constitution of Expert Safety Review Panel at the level of each public health programmes;
- Collection, analysis, data entry and causality assessment of collected data;
- Integration of public health programmes in National centre database; and
- Integration of regional and hospital pharmacovigilance centres in National centre database.

1.8 Long Term Goals

- To detect signals in Pakistan National pharmacovigilance database;
- Make ADRs and AEs reporting mandatory for HCPs;
- Expand Pharmacovigilance programme to all hospitals including Basic Health Units (BHUs); and
- Start active surveillance, cohort event monitoring and pharmacoepidemiological studies in Pakistan.

1.9 Overview of the System

The Drugs legislation in Pakistan has bipartisan shared responsibilities between Federal and Provincial Governments. The Drug Regulatory Authority of Pakistan working under the Ministry of National Health Services Regulations and Coordination is to provide for effective coordination and enforcement of the Drugs Act, 1976 and to bring harmony in

inter-provincial trade and commerce of therapeutic goods. The DRAP has the mandate to ensure access of safe, efficacious and quality therapeutic goods to the public of Pakistan.

The DRAP has established Pakistan National Pharmacovigilance Centre (PNPC), under the Division of Pharmacy Services, at DRAP headquarters, Islamabad, to monitor the safety of therapeutic goods across the country. PNPC collects reports from Healthcare professionals, Patients, Provincial Pharmacovigilance Centres, Public Health Programmes and Registration holders of therapeutic goods. In addition, PNPC is also responsible to communicate with national and global stakeholders. PNPC is responsible to detect signals; recommends regulatory actions; integrate provincial, public health programmes, hospitals and regional pharmacovigilance centres; issue safety communication; publish newsletter; and to perform other functions as elaborated in pharmacovigilance rules. Pharmacovigilance Risk Assessment Expert Committee [PRAEC] is the advisory committee working under the Division of Pharmacy Services at National level. PRAEC is responsible to evaluate risks associated with the use of therapeutic goods; signal detection, prioritization and assessment; risk management; risk minimization; failure mode effect analysis; and evaluation of periodic reports.

Provincial Pharmacovigilance Centres (PPCs) will be established by Provincial Health Departments of each province. These centres will collect pharmacovigilance data from therapeutic goods' sale points, public and private hospitals, regional centres, healthcare professionals and patients. Provincial Health Departments nominates Focal Persons/Incharge of PPC for coordination with PNPC. Provincial Pharmacovigilance committees will also be constituted by each Provincial Health Department under PPC that will evaluate the pharmacovigilance data of the province. PPC also notify and monitor the working of pharmacovigilance officers working at PPC and public hospitals of the province. For detailed functions of PPC, please refer pharmacovigilance rules.

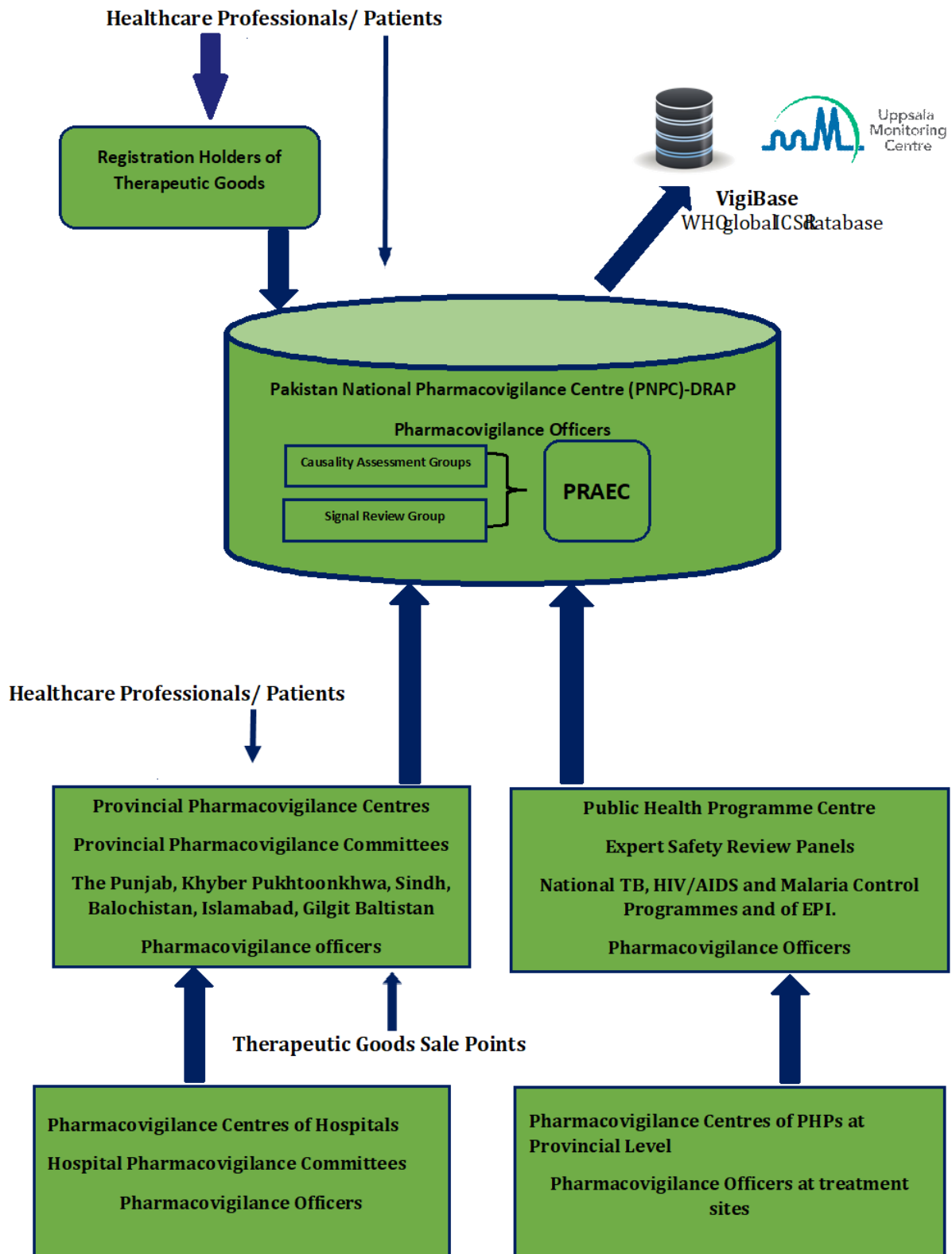
Pharmacovigilance centres will also be established by each Public Health Programme (PHP). Each PHP nominates Focal Person for coordination with PNPC and Pharmacovigilance officers for collection and assessment of data. PHPs will also constitute Expert Safety Review Panels (ESRP) for evaluation of pharmacovigilance data. PHPs will also conduct pharmacoepidemiological studies, cohort event monitoring and targeted spontaneous reporting.

At each public and private sector, secondary and tertiary care hospital, pharmacovigilance centres will be established by Provincial Health Departments and administration of private hospitals. Hospitals administration will nominate their Focal Persons for coordination with PPCs and regularly submit the pharmacovigilance data to PPC. Pharmacovigilance officers working in hospitals are responsible to collect and assess ADR/AE reports. Pharmacovigilance committees will also be established in hospitals for evaluation of data.

Registration holders of therapeutic goods will establish their pharmacovigilance system, nominate Qualified Person for Pharmacovigilance, maintain Pharmacovigilance

System Master File (PSMF), collect and evaluate pharmacovigilance data, submit the data regularly to PNPC, and perform other function as per Pharmacovigilance Rules.

1.10 Flow of Reporting



1.11 Pharmacovigilance Risk Assessment Expert Committee (PRAEC).

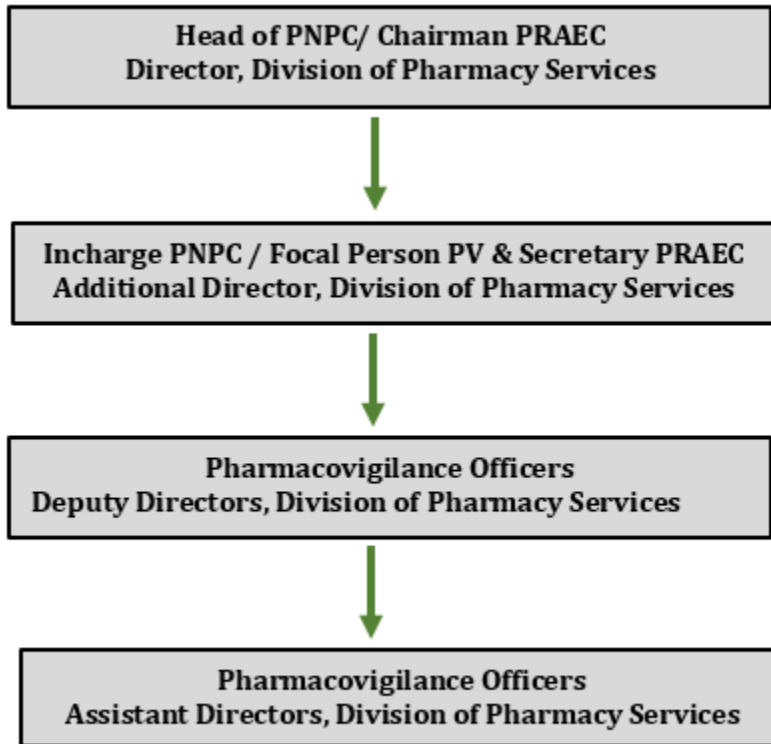
PRAEC constituted under Rule. 9 of Pharmacovigilance Rules, and is accordingly ratified by the Drug Regulatory Authority of Pakistan (DRAP) for evaluation of risks associated with use of therapeutic goods, signal assessment, risk management, risk minimization, failure mode effect analysis and evaluation of periodic reports. The composition of PRAEC is as under:

- a. Director, Pharmacy Services, who shall be its ex-officio Chairman;
- b. Additional Director, Pharmacy Services, or Pharmacovigilance who shall be its ex-officio Secretary;
- c. one professor of clinical pharmacy or pharmacy practice to be nominated by DRAP (member);
- d. one professor of clinical pharmacology to be nominated by DRAP (member);
- e. one representative from the Pharmaceutical Evaluation and Registration Division, DRAP (member);
- f. one representative from Quality Control and Lab Testing Division, DRAP (member);
- g. one representative from Medical Devices and Medicated Cosmetics Division, DRAP (member);
- h. one representative from Health and OTC Division, DRAP (member);
- i. one representative from Biological Drug Division, DRAP (member);
- j. one representative from the provincial pharmacovigilance centre of each province; and
- k. maximum eight expert members to be nominated by DRAP having at least five years' experience in the field of Clinical Pharmacology, Clinical Pharmacy (Clinical Pharmacist), Medicines (Physician), Epidemiology, Toxicology, Pharmacovigilance, Clinical Trials (drug research), and Biological safety.

As per Rule.10 of Pharmacovigilance Rules of Pakistan, the functions of PRAEC are summarized as under:

- ✓ prioritization and assessment of already detected signals;
- ✓ Recommendation of risk minimization actions/ regulatory actions;
- ✓ Recommend to PNPC to issue safety communication;
- ✓ Evaluation of periodic reports (DSUR and PBRER);
- ✓ Evaluation of Risk Management Plans;
- ✓ Recommendation for conduct of Post Authorization Safety and Efficacy studies;
- ✓ Considers or recognize and if deem appropriate implement within Pakistan the pharmacovigilance relevant decision of other countries;
- ✓ Nominate a team for Good Pharmacovigilance inspection of registration holders of therapeutic goods; and
- ✓ It can constitute subcommittees to carryout different activities of pharmacovigilance such as training of provincial centres and public health programmes or to launch an awareness campaign.

1.12 Organogram of Pakistan National Pharmacovigilance Centre.



1.13 Job Description of Staff at Pakistan National Pharmacovigilance Centre.

<p>Head of PNPC/ Chairman PRAEC</p>	<ul style="list-style-type: none"> •Chair the Meeting of PRAEC. •Supervise and execute the programmes on PV training. •Responsible for development and promotion of pharmacovigilance system in Pakistan. •Sign MOUs with PPCs, PHPs and other relevant organization. •Responsible for inter provincial coordination on PV and to chair meeting with them. •Execution of risk minimization measures through other Divisions of DRAP. •Present the rules, guidelines and procedures before Authority and Policy Board, and before Federal Government.
<p>Incharge PNPC/Focal Person PV Secretary PRAEC</p>	<ul style="list-style-type: none"> •Prepare agenda of PRAEC, convene its meeting and keep record of minutes. •Development of training plans for PNPC, PPCs and PHPs. •Responsible to communicate with PV stakeholders and arrange meeting with them. •Responsible to issue therapeutic goods safety alerts, newsletter and press releases. •Responsible for awareness campaign. •Evaluate the quality and causality of entered ADRs. •Chair the monthly meetings of Signal Review Group.
<p>Deputy Directors</p>	<ul style="list-style-type: none"> •Chair the weekly meeting of causality assessment groups. •Guide Assistant Directors on data entry, causality and signal detection. •Assist Incharge PV in his work. •Search Pakistan database for new signals along with Assistant Directors. •Review the material of training, therapeutic good safety alert, newsletter and press releases. •Help Incharge PV in awareness campaign.
<p>Assistant Directors</p>	<ul style="list-style-type: none"> •Collect, assess, enter and transfer ADRs. •Perform initial causality assessment or signal detection or review the causality of ADR received from PPC and PHPs. •Member of causality assessment and signal review groups •Prepare material of training, therapeutic good safety alert, newsletter and press releases. •Assist Deputy Directors and IC PV in their work. •Communicate with PPCs and PHPs in the follow-up of PV reports

Chapter No.2: Stakeholders of Pharmacovigilance in Pakistan.

2.1: Ministry of National Health Services Regulations and Coordination.

Ministry of NHSRC is the ultimate administrative body of health in Pakistan and perform the following function:

- To maintain and improve the health of the people of Pakistan.
- Formulate health and drug policies.
- Administrative controls of laws and rules relating to therapeutic goods;
- National and international coordination in the field of health.
- Supervise the working of Drug Regulatory Authority of Pakistan.

2.2: Drug Regulatory Authority of Pakistan (DRAP).

- The DRAP has the mandate to ensure the access of safe, efficacious and quality medicines to the people of Pakistan.
- Supervise the working of Pakistan National Pharmacovigilance Centre (PNPC), Division of Pharmacy Services.
- Allocation of budget to Pakistan National Pharmacovigilance Centre.
- Hiring/Appointment of personnel for PNPC.
- Implementation of the regulatory actions or any other risk minimization measures across Pakistan as follows: implementing the decisions by other Division of DRAP; implementing the decisions by the registration holders of therapeutic goods; and by coordination with provincial health departments.
- Implementation of the policies, legislation, rules approved by Ministry of NHSRC related to pharmacovigilance and any other aspect of therapeutic goods.
- Approve guidelines, procedures and reporting forms related to Pharmacovigilance.
- Coordinate with provincial health departments in respects of therapeutic goods safety and other matter of Drugs legislations.
- Notify pharmacovigilance officers working at PNPC.

2.3: Pakistan National Pharmacovigilance Centre (PNPC), Division of Pharmacy Services.

- Work as National Centre of Pharmacovigilance in Pakistan.
- Coordinate with World Health Organization and Uppsala Monitoring Centre.
- Coordinate with Provincial Pharmacovigilance Centres, Registration Holders of Therapeutic Goods and Public Health Programme.
- Coordination with hospitals and academia for the pharmacovigilance system development of Pakistan.
- Detect, manage, asses and confirm new signals in Pakistan ADRs database.
- With the approval of Pharmacovigilance Risk Assessment Committee recommend regulatory actions and risk minimization measures to concerned boards/committees/ Divisions of DRAP for implementation within Pakistan.

- Communication of risk minimization measures, regulatory actions and signal to concerned stakeholders.
- Implementation of post-authorization safety studies through registration holders of therapeutic goods if imposed by PRAEC.
- Maintain Pakistan's National ADRs database.
- Training of Pharmacovigilance officers of PNPC, PPCs and PHPs.
- Collection of ADRs/ AE from PPCs, PHPs, Registration Holders of Therapeutic goods, HCPs and Patients.
- Convene meeting of PRAEC.
- Encourage distributors, healthcare professionals and patients to report suspected adverse reactions and events to the PNPC.
- Frame standard operating procedures, guidelines, regulations, rules related to pharmacovigilance.
- Sharing of pharmacovigilance data of Pakistan to VigiBase.
- Issue therapeutic goods safety alerts.
- Publish news letters on pharmacovigilance activities.
- Conduct awareness campaign for HCPs and patients.

2.4: Provincial (Regional) Pharmacovigilance Centres & Provincial Governments.

PPCs are established by Health Departments of the respective Province, which at first nominate Focal Person of Pharmacovigilance for coordination with PNPC and then notify/constitute the Provincial pharmacovigilance committee. Following are the functions of PPC:

- Collection of reports from public and private hospitals, therapeutic goods' sale points such as (pharmacies, medical store, retailers and distributors).
- Sign Memorandums of Understanding with hospitals and academia of the province.
- Perform the causality assessment of AEs reports submitted to PPC and review causality assessment of collected ADRs reports
- Submission of pharmacovigilance data to PNPC on regular basis.
- Support hospitals and sub-provincial (Divisional) Pharmacovigilance centres in the province.
- Monitor the working of pharmacovigilance officers at PPC and in public sector hospitals.
- Pharmacovigilance training of hospitals and other sub-provincial (Divisional) pharmacovigilance centres in the provinces.
- Arrange awareness session/campaign for sensitization of HCPs of the province.
- Implement regulatory actions and risk minimization measures of PNPC in the province.
- Officer of PPCs participate in the meeting of PRAEC.

- Convene meetings of Provincial pharmacovigilance Committee.
- Participate in meeting, training, seminars, symposium arranged by PNPC.

2.5: Public Health Programmes (PHPs).

- Pharmacovigilance centres are established by each PHP at national level and integrate it with provincial chapter of the said public health programme.
- Effective coordination with PNPC by properly nominating a Focal Person for this purpose.
- Collection of pharmacovigilance data from provincial chapter of PHP and treatment sites.
- Regular submission of pharmacovigilance data to PNPC.
- Notification of POs at National, Provincial and site level of PHP.
- Constitution of an Expert Safety Review Panel (ESRP) at the National level, which shall perform the function such as causality assessment, signal detection, and establish procedures for pharmacoepidemiological studies and cohort event monitoring.
- Develop a system of active surveillance for all new drugs and other drugs that are specific to that public health programme and are associated with risks i.e. priority drugs.
- Training of POs of PHP and awareness campaign for patients.
- Signing of MOU with PNPC with respect to collection and submission of pharmacovigilance data.
- Public Health Programme such as Tuberculosis, HIV/AIDS, Malaria Control Programmes and Federal Expended Programme Immunization (EPI).

2.6: Registration Holders of Therapeutic Goods.

- Establish pharmacovigilance system for fulfilment of his pharmacovigilance activities in accordance with the directives of PNPC.
- Nomination of Qualified Person of Pharmacovigilance for communication with PNPC who is responsible for establishment and maintenance of the pharmacovigilance system.
- Maintenance of Pharmacovigilance System Master File and its submission to PNPC.
- Submission of ADRs/AEs to PNPC as per the timelines prescribed in Pharmacovigilance Rules.
- Conduct non interventional post authorization safety studies either voluntarily or if imposed by PNPC.
- Submission of Periodic Benefit-Risk Evaluation Reports as per the timelines prescribed in Pharmacovigilance Rules,
- Submission of Risk Management Plans to Registration Board and PNPC.
- Issuance of Dear Healthcare Professionals letters.
- Implementation of regulatory actions and risk minimization measures.

- Inform PNPC about the risk of their product detected during the self-assessment process.
- Submit adverse outcome reports to PNPC in case of abuse, misuse, overdose, off label use, medication errors, and occupation exposure of therapeutic goods.
- Submit reports of lack of efficacy of therapeutic goods to PNPC.

2.7: Academia.

- Inclusion of curriculum on pharmacovigilance in undergraduate and master level.
- Training and awareness campaign on pharmacovigilance
- Arrange Symposium and conferences of pharmacovigilance.
- Coordination with PPC and PNPC.
- Academia such as Pharmacy, Medical/Dental, Nursing councils and institutions.

2.8: Hospitals.

- Establishment of pharmacovigilance centre at hospital level.
- Nomination of Focal Person for coordination with PPC.
- Constitution pharmacovigilance committees at the level of hospital.
- Notification of POs at hospital level in case of private sector hospital or autonomous public hospital.
- Collection of AE and ADRs.
- Initial causality assessment of AEs.
- Regular submission of pharmacovigilance data to PPC.
- Signing of MOUs with PPC.
- Implement risk minimization measures of PNPC and PPC in hospital.

2.9: Therapeutic Goods' Sale Points (TGSP).

- TGSP includes distributors, wholesaler and retailer of therapeutic goods.
- Report the suspected ADR or AE to PPC, registration holders of therapeutic goods or PNPC. But, at a time a suspected ADR or AE shall be reported through one out of these three channels to avoid duplication of reports.
- Counselling of patients to immediately consult HCP if they experience AE.

2.10: Healthcare Professionals.

- Detect and manage adverse events associated with use of therapeutic goods.
- Document and immediately report all serious and non-serious suspected ADRs that known or unknown (un-expected) or which are due to interaction, abuse, misuse, medication errors, occupational exposure, and overdose. HCP shall also report lack of therapeutic efficacy.
- Perform the initial causality assessment of AEs.

- Report the suspected ADR or AE to PPC, registration holders of therapeutic goods or PNPC. But, at a time a suspected ADR or AE shall be reported through one out of these three channels to avoid duplication of reports.
- Counselling of patients to immediately consult HCP if they experience AE.

2.11: Patients/ Consumers.

- Reporting of adverse event immediately to their healthcare professionals, Pakistan National Pharmacovigilance Centre, Provincial Pharmacovigilance Centre or registration holder of therapeutic good. But, at a time an AE shall be reported thorough one out of these four channels to avoid duplication of reports. Support from national associations of consumers and patients may add to the general acceptance of pharmacovigilance.

2.12: Media

- Good relations with leading journalists may be helpful, e.g. for general public relations and as part of the risk management strategy whenever an acute drug problem arises. Special attention may be needed to explain to journalists the limitations of pharmacovigilance data. In addition, some AE are also reported in media, which can be further be followed up by national and provincial centres. Head of PNPC-DRAP or public relation officer nominated by DRAP is the only authorize people to engage with media. Press releases in print media and news on electronic media are some of the example of media coverage. Media should always consult DRAP for accurate and verifiable about the risk of therapeutic goods.

Chapter No.3: Basic Concepts of Pharmacovigilance.

3.1 Adverse Event (AE).

An AE is an untoward medical occurrence in a patient administered a pharmaceutical product or therapeutic good and which does not necessarily have a causal relationship with this treatment.

3.2 Adverse Drug Reaction (ADR)

An ADR is a response to medicines or therapeutic good 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.

Difference between ADR and AE

The difference between an ADR and an AE is crucial and yet these terms are widely confused, particularly within the pharmaceutical industry. In practice, determining whether or not a drug is responsible for a particular AE in an individual patient is often difficult and a judgment has to be made. When the judgment of a clinician caring for the patient is that the drug is a possible cause; this should be called a suspected ADR. Reports of such suspicions form the basis of spontaneous ADR reporting schemes. The term 'AE' properly should imply that a more systematic data collection process has been used so that events will be included regardless of whether or not anyone believes they might be caused by a drug.

So, we use:

An ADR: When it is generally accepted that drug x may cause effect y rather than in relation to individual cases. We qualify the term with 'possible' if there is doubt.

A Suspected ADR: When a health professional or investigator indicates that a drug *may* have been responsible for an event in an individual case. A valid case submitted as a spontaneous report to a company or regulatory authority is a suspected ADR by definition.

An AE: only in the context of systematic data collection when no element of judgment is involved in determining whether or not a case is counted

3.3 Classification of Adverse Drug Reactions.

ADRs are broadly classified in two categories: Type A and Type B

a. Type A (Augmented) reactions are generally:

- Dose-related
- Predictable from drug pharmacology
- Common
- Normally reversible
- Can be managed with dose adjustment.

Classic examples of Type A reactions are bleeding with warfarin, hypoglycaemia with sulphonylureas and headache with glyceryltrinitrate.

b. *Type B (Bizarre) reactions are generally:*

- Not dose-related
- Unpredictable
- Uncommon
- May be serious/irreversible
- Indicative that the drug needs to be stopped.

Classic examples of Type B reactions are anaphylaxis with penicillin's, hepatitis with halothane and agranulocytosis with clozapine.

There are four additional categories of ADRs, which are as follows:

- c. *Type C (Continuous):* – Reaction due to long term use, e.g. adrenal suppression with corticosteroids.
- d. *Type D (Delayed):* – e.g. tardive dyskinesia with neuroleptics and teratogenic or carcinogenic effects with drugs.
- e. *Type E (End of use):* – e.g. withdrawal reactions with benzodiazepines.
- f. *Type F (Failure of Therapy):* Treatment of Failure.

3.4 DOTS Classification of Adverse Drug Reaction:

This system is based on *dose-relatedness*, *time course* and *susceptibility*; this is known as 'DoTS'. The main ways in which ADRs may be classified within each of these three categories is given below:

Dose	Time	Susceptibility
Toxic Collateral Hyper susceptibility *'Toxic' means that reactions occur as a result of drug levels being too high; * 'collateral' means that reactions occur at drug levels which are in the usual therapeutic range; * 'hyper susceptibility' means	Independent Dependent: – rapid administration – first dose – early, intermediate, late – delayed – withdrawal * The terms early, intermediate and late have not been precisely defined; the main difference between 'late' and 'delayed' reactions is that the latter may occur long after treatment is stopped (e.g. cancer, which may occur years after exposure to a causal agent). * A withdrawal reaction means one that is specifically precipitated by stopping the	Age Gender Ethnic Group Genetic Disease

<i>that reactions may occur even at very low, sub-therapeutic doses.</i>	<i>drug.</i>	
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If suitable estimates of risk are available, it may be possible to draw three-dimensional DoTS diagrams of the probability of an ADR occurring in sub-groups over time and as a function of dose. When this is not possible, qualitative classification may still be useful, as shown by the following examples:

a. *Osteoporosis due to corticosteroids:*

This reaction occurs at therapeutic doses, usually after some months of treatment; females and older people are at the greatest risk. Hence it would be classified as:

Dose: collateral effect

Time: late

Susceptibility: age, sex

b. *Anaphylaxis due to penicillin:*

This reaction may occur with very small doses and within minutes of taking the first dose of a course, but true anaphylaxis only occurs when the drug (or a closely related agent) has been used previously. Hence it would be classified as:

Dose: hyper susceptibility

Time: first dose

Susceptibility: requires previous sensitization

The DoTS approach seems to be gaining acceptance because it addresses the limitations of the A/B scheme into which many ADRs do not clearly fit. Furthermore, it is useful in providing pointers as to how specific ADRs may be avoided.

3.5 Factors that Predispose Patients to ADRs

When seeking to recognize an adverse event, it is important to note that patients receiving the same drugs or treatment regimen can respond differently based on their individual characteristics. Certain factors tend to predispose some patients to ADRs, including:

- A. ***Age and gender:*** The elderly and the very young are more susceptible to ADRs, and gender also has an effect. Drugs that commonly cause problems in the elderly include hypnotics, diuretics, non-steroidal anti-inflammatory medicines, antihypertensive, psychotropic, and digoxin. All children, and particularly neonates, differ from adults in the way they respond to drugs. Some medicines are likely to cause problems in neonates but are generally tolerated in children.
- B. ***Concurrent illness:*** In addition to the condition being treated, the patient may also suffer from another disease, such as kidney, liver, or heart disease. Special precautions are necessary to prevent ADRs when patients have such concurrent illnesses.

- C. **Medicine interactions:** Drug interactions are among the most common causes of adverse effects. When two or more drugs are administered to a patient, they may either act independently or interact with one another. The interaction may increase or decrease the effects of the drugs and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious drugs interactions is likely to increase. Interactions may occur between drugs when:
- Drugs compete for the same receptor or act on the same physiological system.
 - One drug alters the absorption, distribution, or elimination of another drug so that the amount that reaches the site of action changes.
 - A drugs-induced disease or a change in fluid or electrolyte balance (physiologic change) indirectly alters the response to another medicine.
- D. **Other chemical interactions:** Interactions may also involve no medicinal chemical agents, social drugs such as alcohol, traditional remedies, and certain foods.
- E. **Genetics:** It is well known that the genetic make-up of individual patients may predispose them to ADRs.

Chapter No.4: Guidelines for Reporting of Suspected Adverse Drug Reactions/Events.

4.1 Suspected Adverse Drug Reaction Reporting Form

Pakistan National Pharmacovigilance Centre has designed “Suspected Adverse Drug Reaction Reporting Form for collection of suspected adverse drug reactions reports from healthcare professionals “Annex A”. Following are the points to be filled in the said reporting form.

A. Patient Information

1. Patient Initial or Name: here healthcare professionals can either write initials of patient name like for example “MA” for Muhammad Arif or can write full name. If Healthcare professional provide full name it would be kept confidential.
2. Identification Number: Here hospital or ward admission number can be provided so that Healthcare professional can easily access patient files in case follow up information is required.
3. Sex: Mention the gender of patient. If the patient is female, then healthcare professional must provide information, whether she is pregnant or not.
4. Age at the time of reaction: Age of patient should be provided in this section along with proper unit for example hours, days, weeks, month, years etc. Suppose an infant is of 8 hours then the reporter needs to mentioned hours unit with numerical value.

B. Suspected Drug (s)/Vaccine (s)/ Alternative Medicine(s)

1. Drug/ Vaccine/Alternative Medicine Name: Both generic and brand shall be provide.
2. Batch No: Batch number shall be provided in case the drug has quality problem, it would be helpful to trace the drug and recall it.
3. Manufacturer Importer: if the reporter has provided generic name then he must provide details of manufacturer/ importer.
4. Route of Administration and daily doses: Route through which the drug was given
5. Dosage and Strength:
6. Start date: administration date of the drug. It would be helpful to build relationship between the drug and event and will determine time to onset of reaction.
7. Stop Date: when the drug was withdrawn. It would also help in assessment of reports by providing information on Dechallenge of drug.
8. Prescribed for: the indication for which the drug was administered.

C. Suspected Reaction (s)

1. When Reaction started: Mention the date on which reaction started, it would be helpful to determine the casual relationship of reaction with drug and will determine the time to onset of reaction.
2. When Recovery Started: Mention the date on which the reaction ended or recovery started, it would be helpful to determine whether the reaction subside when the suspected medicine is stopped.
3. Describe the reaction(s): Complete narrative/ description of reaction should be provided; who the patient developed the reaction, nature, localization etc.

4. Other relevant history of the patient (Allergies, Smoking, Alcohol Use, Hepatic/Renal Problems, and Pre-Existing Medical Problems etc.): write the relevant history persistent to patient including pre-existing conditions (allergies, smoking, alcohol use, hepatic or renal dysfunction, surgical procedure, risk factors etc.) and current medical condition if any.
5. Relevant tests/Laboratory data with dates: write all tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate a non-drug cause.
6. Seriousness of the reaction: If the reporter consider the reaction to be serious then he must tick all that apply out of the following:
 - *Patient Died:* If the patient died due to adverse event. It would be appropriate to mention the cause of death in the reaction narrative along with date of death.
 - *Life Threatening:* If the patient was at substantial risk of dying at the time of adverse event.
 - *Involved or Prolonged In patient Hospitalization:* if due to adverse the patient was hospitalized or already hospitalized patient stay was prolonged.
 - *Disability or incapacity:* If due to adverse event the patient normal life function are affected.
 - *Congenital Anomaly/ Birth Defect:* when exposure of drug during pregnancy has resulted into adverse outcome in the infant in the form birth defect.
 - *Other serious event:* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
7. De-challenge details: Withdrawal of a medicine from a patient following an adverse event.
 - *Yes:* if reaction abate/ subside after the suspected drug is stopped or dose reduced.
 - *No:* if reaction does not abate/ subsides after the suspected drug is stopped or dose reduced.
 - *Does not apply:* If de-challenge is not applicable as in case of vaccines, anaesthesia, where a single dose is given, in case of death, or in case where treatment is completed prior to reaction or event. Dechallenge is also meaningless in case of myocardial infarction and stroke
8. Re-Challenge details: Reintroduction of the medicine under the same conditions as previously (same dose, form, route of administration), following withdrawal and recovery from the adverse event.
 - *Yes:* when the suspected drug is reintroduced the reaction again appeared.

- *No*: when the suspected drug is reintroduced the reaction does not appeared.
- *Does not apply*: if rechallenge is not applicable as in case of anaphylaxis.

9. Outcome:

- *Fatal*: if the patient dies.
- *Recovering*: If the patient is recovering from the reaction.
- *Unknown*: if the outcome is unknown.
- *Continuing*: if the patient is continuing to experience the reaction/event.
- *Recovered*: if the patient has completely recovered from the reaction/event.

10. Cause of the Reaction:

- *Quality problem*: if the reaction patient experience was due to quality problem. However, healthcare professional can also inform PNPC about the visible sign of quality defects.
- *Medication Error*: Inappropriate medication use or patient harm, when the medicine was in control of healthcare professional or consumer.
- *Adverse Event/ Reaction*: if the patient develop reaction or event in spite of the fact that medicine has no quality defect and the healthcare professional does not use the medicine inappropriately.

11. Causality Assessment: the reporter (if trained) must perform the causality assessment and justify the assessment.

D. Other Concomitant Drug(s)/ Vaccine (s)/ Alternative Medicines (s)

Information is same as suspected drug. But, here only the information about the additional medication the patient is using shall be written. For suspected drug “B “field shall be used.

E. Suspected Medical Devices (s)

1. Medical Device Common Name/ Brand Name: Brand name which is on a label attached to a durable device; on a package of a disposable device; or is on the labelling materials of an implantable device. The generic or common name of the suspect medical device or a generally descriptive name (e.g., urological catheter, heart pacemaker, patient restraint). Please do not use broad generic terms such as "catheter", "valve", "screw", etc.
2. Lot No/ Batch Name: This number can be found on the label or packaging material and help in tracking the devise in the market and its production record at the time of recall.
3. Manufacturer/ Importer:
4. Model No: The exact model number found on the device label or accompanying packaging.

Unique Identifier No: This number can be found on the device, its label, or accompanying packaging. The number is located below the barcode and begins with one of the following three elements: 01; +; or =. Record all numbers, letters, parentheses, and symbols included in the UDI Number

5. Serial No: it is assigned by the manufacturer, and should be specific to each device.
6. Implantation date:
7. Explantation date:

F. Reporter Details

1. Name of Reporter: Reporter needs to mention his name on the form.
2. Professional Address: The reporter must also mention his professional address for communication.
3. Specialty: such Clinician, Pharmacist, Nurse, Physiotherapist.
4. Telephone No: For the purpose of communication, if any information is required by the officers of PNPC.
5. Email Address: for communication
6. Date of this report: mention the date on which she/her report the adverse reaction/ event.
7. Signature: sing of the reporter
8. Reporting to other stakeholder: the reporter need to mention whether he or she has reported the same ADR/ AE to PPC and Registration holder of therapeutic good or is reporting directly to PNPC.

4.1.1 Mandatory Information and Essentially Required Information:

Healthcare professionals including pharmacovigilance officers should collect all the information required to be filled in the suspected adverse drug reaction reporting form. In case complete information is not available, fill all the essentially required fields. In case essentially required information are not available, then make sure that the reporting form contains all the mandatory information.

Mandatory Information	Essentially Required Information.
<ol style="list-style-type: none"> 1. Patient Information. 2. One or more suspected reaction (s). The reaction terms must be given. 3. One or more suspected drug (s). 4. Reporter Information. 	<ol style="list-style-type: none"> 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) 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.

4.2 Who Can Report?

Spontaneous reports can be directly submitted to the PNPC by the following:

- i. At All healthcare professionals (physicians or doctors, dentist, pharmacist, nurses and physiotherapist) including pharmacovigilance officers;
- ii. Patient and consumer of the therapeutic good or relative of the patient;

Whereas, the following which are part of the pharmacovigilance programme of Pakistan, also collect spontaneous reports from patients and healthcare professionals, and accordingly submit these reports to PNPC:

- i. Registration holder of therapeutic goods;
- ii. Provincial Pharmacovigilance Cent (PPCs);
- iii. Public health Programmes;

Hospitals and therapeutic goods; sale points (distributors, wholesaler and retailer) report the suspected ADR to respective PPC, which after assessment submit the report to PNPC.

4.3 What to Report?

In order to develop a positive reporting culture in the country, PNPC encourages HCPs and patient or consumer to report all type of reports, whether known or unknown, serious or non-serious. Although pharmacovigilance is primarily concerned with drugs/medicines and vaccines, the PNPC also encourages to report ADRs or AEs with all therapeutic goods (drugs, alternative medicines, biologicals, medical devices, OTC products). The suspected adverse drug reaction/event related information with the following should be reported to PNPC:

- ✓ Known or unknown serious spontaneous AEs or ADRs reports with therapeutic goods ;
- ✓ Known or unknown non-serious spontaneous AEs or ADRs report with therapeutic goods;
- ✓ AEFI reports with Vaccines and immunization errors;
- ✓ Lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening; and
- ✓ AEs with medication errors;
- ✓ AEs with quality problems.
- ✓ AE or ADR reports associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

PPCs, PHPs registration holders of therapeutic goods also collect the suspected ADR/AE of the above nature from healthcare professionals, patient or consumers and therapeutic goods' sale points. PPCs also encourage hospitals and therapeutic goods sale points to report ADR/AE of the above nature. PHPs also monitor the serious adverse events

(SAE) during the pharmacoepidemiological studies and cohort event monitoring and report these to PNPC.

4.4 Where and How to Report?

- a. Patient or Consumer of therapeutic goods: Patients or consumer of therapeutic goods should at first, report the adverse events of the above nature to his/her healthcare professional (pharmacist, nurse or doctor) by providing complete information of the event. Patient should always consult his/her healthcare professional in case of untoward event and ask the healthcare professional to report the adverse event to concerned quarters. If the patient doesn't have access to the healthcare professionals, then he can directly report the adverse event to Provincial Pharmacovigilance Centre of his/her province either via telephone or online through official website of the Provincial Pharmacovigilance Centre. Further, patient/consumer of therapeutic goods could also report the adverse event to Pakistan National Pharmacovigilance Centre by visiting the official website of DRAP. In some cases patient or consumer also report the adverse event to registration holder of therapeutic goods. But, the patient and consumer should keep one thing in mind that is to "report an adverse event through only channel only", in order to avoid duplication of reports.
- b. Healthcare professionals:
 - Healthcare professionals, who are working in hospital and are not pharmacovigilance officers, should at first report the suspected adverse drug reaction/ event to pharmacovigilance officer/ Pharmacovigilance Focal Person of the hospital, who document it and take further action. Healthcare professionals should also manage the adverse event/reaction to prevent harm to the patient.
 - Healthcare professionals who are working in private clinics or does not have access to pharmacovigilance officers/Focal Person of Pharmacovigilance can report the suspected adverse drug reaction/event to Pakistan National Pharmacovigilance centre (PNPC) by visiting the official website of Drug Regulatory Authority of Pakistan (DRAP):<https://www.dra.gov.pk/docs/Suspected%20Adverse%20Reaction%20Reporting%20Form%20for%20Health%20Care%20Professionals.pdf> This can be downloaded, filled in, and send to PNPC through post. In addition, PNPC also have online reporting system for healthcare professionals, wherein healthcare professionals can report the suspected adverse drug reaction/event online. The report can also be email on the following official email address of PNPC: npc@dra.gov.pk. The healthcare professionals should perform causality assessment of the adverse event as per WHO-UMC method (Annex- D) or Naranjo Method (Annex-C) if they are trained in this.
 - Healthcare Professionals can also report the suspected adverse drug reaction/event to Provincial Pharmacovigilance Centre (PPC) and registration holders of therapeutic goods. But, the healthcare professionals should keep one thing in mind that is to "report an adverse drug reaction/event through one channel only", in order to avoid duplication of reports.
- c. Pharmacovigilance Officer/ Focal Person: Those HCPs who are working in the hospitals as Pharmacovigilance officer/ Focal Person of PV should collect the

information from patient and from other HCPs of the hospitals, document it, present it before the pharmacovigilance committee, and accordingly shall submit it to respective PPC.

- d. PPCs and PHPs: PPCs and PHPs shall either transfer the collected report to PNPC if they have login of VigiFlow, or should manually send the report to PNPC in hard format.
- e. Registration holders of therapeutic goods: shall either send the report in hard format on CIOMS Form-I (**Annex-B**) on the postal address of PNPC, or the report can be submitted in E2B xml format on the official email of PNPC: npc@dra.gov.pk.
- f. Address of PNPC:

Incharge Pakistan National Pharmacovigilance Centre,
Division of Pharmacy Services
Drug Regulatory Authority of Pakistan
3rd Floor, TF Complex,
7-Mauve Area
Islamabad.
Phone No: +92519107413, +92-51-9262182
Email Address: npc@dra.gov.pk , pnpc.drap@gmail.com
Website: www.dra.gov.pk

4.5 When to Report?

Patient should report serious adverse event as soon as possible to healthcare professionals, Provincial Pharmacovigilance Centre, Pakistan National Pharmacovigilance Centre or registration holder of therapeutic goods. Sometimes, the adverse event might be unexpected and might be posing harm to other patient. An earlier reporting of adverse event by patient will be helpful to minimize harm to other patients. Further, non-serious adverse event should also be reported at the earliest through the above channel. The reporting form should be filled in by the HCP at the earliest and submit the report through the above mentioned channel. Pharmacovigilance officers/ Focal Persons of Hospitals shall submit the serious ADR/AE report to PPC within 15 calendar days and non-serious ADR/AE report within 30 calendar days to PPC. PPCs and PHPs should accordingly submit the serious ADR/AE report to PNPC within 15 calendar days and non-serious ADR/AE report within 30 calendar days to PNPC.

4.6 What Happened to Report?

1. Hospital: Pharmacovigilance officer (PO) working hospitals collect all serious and non-serious AE/ADR from patient and other healthcare professionals. At first the ADR/AE is documented by giving it proper number. The ADR/AE is checked for data quality that is essentially required and mandatory information. If follow-up information is required healthcare professionals and patient can be contacted. The pharmacovigilance officers perform the initial causality assessment of the report. The report is then presented before pharmacovigilance committee or pharmacy and therapeutic committee for assessment and action. When the causality of report is

reviewed by pharmacovigilance committee or pharmacy and therapeutic committee, it is sent to PPCs as per the reporting timeline. In case the hospital is sub-regional centre and is integrated in Pakistan VigiFlow; then, PO should enter the report into VigiFlow, by properly coding through terminologies such as MedDRA and WHO-Drug.

2. Provincial Pharmacovigilance Centres (PPC) Pharmacovigilance officer at PPC should at first document the ADR/AE report by assigning a unique identification number. Subsequently, should check the ADR/AE for mandatory and essentially required information. If information is missing, PO should contact the HCP, patient, therapeutic goods' sale point or PO in the hospital. Perform the initial causality assessment and present the case before the provincial pharmacovigilance committee, which review the casualty assessment. In other words, PPCs perform the complete assessment of individual reports that will be discussed in detail in the coming paragraph. If PPC is integrated in Pakistan VigiFlow database, the POs at PPC should accordingly enter the report into VigiFlow using terminologies such as MedDRA and WHO-Drug and transfer these report as reporting timelines. If PPC does not have the logins of VigiFlow, the reports should be submitted manually in hard format.
3. Public Health Programme (PHP): Pharmacovigilance officers (PO) of PHP working at the treatment site collect the reports and send it provincial chapter of PHP, which after assessment send these to Federal PHP. An Expert Safety Review Panel (ESRP) is constituted at the Federal Level of PHP, which consists of pharmacists, physicians, disease experts and other members which it may desire. This panel perform the causality assessment of the collected reports and signal detection of programme specific drugs. If PHP is integrated into Pakistan VigiFlow database, the data is entered into Pakistan VigiFlow database using terminologies. If the PHP is not integrated the reports are manually shared with PNPC.
4. Pakistan National Pharmacovigilance Centre (PNPC): PNPC collect ADR/AE reports from Healthcare Professionals, patients, Provincial Pharmacovigilance centres, Public health Programme, and registration holders of therapeutic goods. Pharmacovigilance officer at PNPC, at first check the report for mandatory and essentially required information. If the ADR/ AE have missing mandatory information, the reporter is contacted. The PO also contacts the reporter for more information of serious ADR/AE. The reports which are received through VigiFlow from PPCs, PHPs and via E2B through registration holders of therapeutic goods are also checked for data quality. Further, the reports which are received online form HCPs and patient are also properly coded and checked for data quality. The PO at PNPC also enter the report into VigiFlow using terminologies if the report is received in hard format from the reporter. The causality assessment group at PNPC either perform the casualty assessment of new reports or review the causality assessment of those reports which assessment has already been done at hospital, PPC or PHP level. In other words, PNPC perform complete assessment of individual reports that will be discussed in detail in the coming paragraph. The database is checked for new signals by signal review group and the case is presented in the meeting of PRAEC for its recommendation and final assessment of reports. The individual case safety report in

Pakistan VigiFlow database are accordingly transferred to VigiBase database of WHO-UMC.

4.7 Assessment of Individual Case Safety Reports (ICSRs):

The assessment of adverse reaction case reports needs combined expertise in clinical medicine, pharmacology and toxicology, and epidemiology. This expertise can be developed by training the centre staff and by the use of specialised consultants. In the assessment of case reports the following elements can be recognised:

1. **Quality of documentation:** e.g. completeness and integrity of data, quality of diagnosis and follow-up.
2. **Coding.** Drug names should be registered in a systematic way, for example by using the WHO Drug Dictionary (which is based on the INN nomenclature and the ATC classification). For the coding of the adverse events the recognised terminology (e.g. MedDRA) should be used.
3. **Relevance:** with regard to the detection of new reactions, drug regulation, or scientific or educational value. The following questions especially may be asked:
 - **New drug:** Products on the market less than five years are usually considered new drugs.
 - **Unknown reaction:** The reaction which is not listed/included in safety specification/prescribing information/package inserts/ SmPC of the drugs.
 - **Serious reaction:** Please refer to
4. **Identification of duplicate reports:** Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, etc.) may be used to identify duplicate reporting.
5. **Causality assessment:** see Chapter No.6

4.8 Use of Pharmacovigilance Data:

1. **Signal detection and Strengthening:**

A major aim of pharmacovigilance is the early detection of signals with regard to possible adverse reactions. A signal may be strengthened by combining the experiences reported in various countries. Therefore, international collaboration is important. Through VigiLyze statistics of Drug-ADR combination in VigiBase and other countries can be seen. It will help to build case series.
2. **Risk Management:**

Risk management is identification, characterization, assessment, prioritization of risks, followed by coordinated and economical application of resources to, minimize, monitor, control and prevent the probability and impact of unfortunate event is known as risk management.
3. **Drug Regulation:** After approval of a therapeutic good, all available domestic information is continuously monitored by the PNPC-DRAP, PPCs and registration holders of therapeutic goods. The pharmacovigilance data of Pakistan can be useful to update to prescribing information/package inserts, recall or withdraw a product, imposition of restriction in use, or cancellation of registration of therapeutic good.
4. **Risk Communication and Information:**

ADR Bulletin, newsletters or therapeutic goods safety alert are important source for dissemination of information to Healthcare professionals. In the case of an emergency, PNPC and registration holders of therapeutic goods may send direct healthcare professionals communication (DHPC) in the form of dear healthcare professional letter.

5. Education and Feedback:

The information from PNPC data is useful in updating the knowledge associated with the use of medication to healthcare professionals.

Chapter No.5: Types of Surveillance in Pakistan.

5.1 Passive Surveillance:

Passive surveillance means no active measures are taken to look for adverse effects other than the encouragement of healthcare professionals and others to report safety concerns. Reporting is entirely dependent on the initiative, motivation and goodwill of the potential reporters. It is the most common method used in pharmacovigilance. It covers entire population and monitor adverse effects in patient that occur in real time practice. Although it is easiest and least expensive method yet it is not devoid of weaknesses which are: total or heavy reliance on voluntary or spontaneous reporting, under reporting, and lack of quality of data in reports. However, it generates signals or alerts that can be further evaluated through active surveillance. Passive surveillance includes: spontaneous reporting; and case series etc.

5.2 Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. It can be achieved through sentinel sites, drug event monitoring and registries.

5.3 Spontaneous reporting:

A system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority. It is also defined as “an unsolicited communication by a healthcare professional or consumer to a company or national regulatory authority (PNPC or PPC in case of Pakistan) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme”.

Benefits of spontaneous reporting are that it is easy establish, least expensive, least labour intensive. It covers the whole population, includes all medicines, and continues throughout the life cycle of a medicine. In addition, it detects signal of new, rare or serious ADRs. Whereas, its disadvantages are: inherent under reporting; captures only suspected ADRs; difficult to detect delayed ADRs and ADR with high background incidence.

Passive surveillance is the primary method used in Pakistan. Spontaneous reporting, as the main mechanism for passive surveillance is used to generate signals/alerts of adverse events, which can then be investigated further.

5.4 Intensified/ Additional ADR monitoring:

It is an extension of spontaneous reporting programme and its objective is to enhance ADR reporting of specific drugs in early post-marketing phase. Drugs under additional

monitoring have a black inverted triangle displayed in their package leaflet and in the information for healthcare professionals in the package inserts, together with a short sentence explaining what the triangle means. Additional monitoring status is always applied to a drugs or medicines in the following cases:

- i. Drugs that contain a new active substance;
- ii. Biological: this applies to all biological including biosimilars;
- iii. Drugs for which the registration holder of therapeutic goods is required to carry out a post-authorisation safety study (PASS);
- iv. Drugs given conditional approval by Registration Board or authorised under exceptional circumstances; and
- v. drugs authorised with specific obligations on the recording or monitoring of suspected adverse drug reactions.

Registration Boards while registering the drugs of aforementioned classes will direct the registration holders of the said drugs to include inverted black triangle and other necessary information in the prescribing information/ package inserts of the drugs to promote intensified ADR monitoring.

Pharmacovigilance officers across Pakistan at the level of PPCs, PHPs, and Hospitals should actively monitor the safety of these drugs and reports accordingly. In addition, healthcare professionals who are not pharmacovigilance officer should also monitor the safety of these high risk drugs.

Registration holders of the above mentioned classes of high risk drugs/medicines would include inverted black triangle and other specific information in the package inserts/prescribing information of these classes of drugs in order to encourage intensified ADR reporting. In addition, registration holders of therapeutic goods shall also search lists of drugs under additional monitoring of reference regulatory authorities. If it comes to their knowledge that their drugs have been included in the list of drugs under additional monitoring by any reference regulatory authority, then they should accordingly implement the same in Pakistan.

5.5 Cohort Event Monitoring

A prospective, longitudinal, observational, cohort study of adverse events associated with one or more monitored medicines. Its objective is to gather more information on the safety profile of a new chemical entity in early post- marketing phase. Patients are enrolled into cohort and actively followed-up during treatment to record all adverse events (not just suspected ADRs). Its benefits are: to characterize known reactions; detect signals of unrecognized reactions; identify interactions with other medicines; detect inefficacy of medicine; assess safety in pregnancy & lactation; and identify risk factors for ADRs.

This type of monitoring will be used in public health programme such as National TB, HIV/AIDS, Hepatitis and Malaria Control Programmes.

5.6 Registration Holder of Therapeutic Goods' Sponsored Post Authorization Safety Studies.

See Chapter 11 and Module 6 for more details. Page 76.

Chapter No.6: Assessment of Adverse Events and Other Tools.

6.1 What is Causality Assessment?

“It is the evaluation of the likelihood that a medicine or therapeutic good was the causative agent of an observed adverse reaction”. In other way, it is structured approach to determine the relationship between reported event and suspected drug.

Rationale for the causality assessment is the following: to define relationship drug-ADR; help in signal detection process; risk minimizing actions are based on evidence of causality assessment.

What Causality Assessment can do	What Causality Assessment cannot do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
	Change uncertainty into certainty

6.2 Methods of Causality Assessment for Signal Case Safety Reports.

Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance. These systems are largely based on four considerations:

- The association in time (or place) between drug administration and event
- Pharmacology (including current knowledge of nature and frequency of adverse reactions).
- Medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings, mechanism).
- Likelihood or exclusion of other causes.

These systems mainly fall into three categories.

- i. Algorithms e.g. Naranjo, RUCAM;
- ii. ‘Global introspection’ qualitative (e.g. WHO-UMC) or quantitative (e.g. French imputability system); and
- iii. Probabilistic methods e.g. Bayesian.

6.3 Naranjo Algorithm for Causality Assessment.

Naranjo is one of the most widely used method. It is basically a questionnaire designed by Naranjo et al, to determine the likelihood of whether an ADR is actually due to the drug

rather than the result of other factors (**Annex C**). It uses a series of 10 questions and these questions can be answered as Yes, No or do not know. Answers are weighted with scores (-1 to +2) and total score is ranked on four probability scale:

- i. “*Definite*” (*Certain*): if scores is more than 9.
- ii. “*Probable*”: if scores is between 5 -8.
- iii. “*Possible*”: if scores is between 1-4.
- iv. “*Doubtful*” (*Unlikely*): if is less than 1.

6.4 WHO-UMC System for Standardised Case Causality Assessment.

The WHO-UMC system for standardised case causality assessment (**Annex D**) has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognised that the semantics of the definitions are critical and that individual judgements may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another.

WHO-UMC causality assessment system considers the following criteria: timing of event; alternative explanations (disease or drugs); response to de-challenge (withdrawal of drug); and response to re-challenge (re-exposure to drug). Based on the above criteria the ADR can be classified in to the following six categories:

- A. Certain
- B. Probable/Likely
- C. Possible
- D. Unlikely
- E. Conditional/ Unclassified
- F. Unassessable/ Unclassifiable

A. Certain.

The assessment criteria for certain categories are as under:

- Event or laboratory test abnormality, with *plausible time* relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to *withdrawal plausible* (pharmacologically, pathologically)
- Event *definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)*
- Re-challenge satisfactory, if necessary

Further Explanation of the terms of “Certain” Category.

1. Plausible time relationship: The "certain" classification requires the *timing of event to be "plausible."* "Plausible" is a stronger word than reasonable used in the "probable" category. It means believable and for that we need more information than for reasonable. The time to onset should fit in with the known pharmacokinetics of the drug, for example its half-life, or for a Type B reaction, the time to mount an observed immune response would be an example.
2. Plausible Response to Withdrawal: A "plausible" response to withdrawal would be, for example, a rapid resolution of a Type 1 allergic reaction such as urticaria and a longer time for hepatitis.
3. Recognized Pharmacological Phenomenon: A pharmacological phenomenon might be decreased prothrombin with warfarin leading to haemorrhage due to its effect on vitamin K activity; respiratory depression with morphine, or serotonin syndrome manifested as symptoms such as agitation, increase sweating and myoclonus due to drugs that inhibit serotonin reuptake by its receptors. With a new drug we may not be aware of all its pharmacological actions. Therefore, an unexpected reaction will rarely be classified as "certain".
4. Specific, Observable, Medical Disorder: This is an important difference compared with the "probable" category. To classify a suspected reaction as "certain" it needs to be something you can observe or measure. If you have definite evidence of, for example, hepatitis or tendonitis then that's an observable clinical condition. It's pathological. In contrast, for a "probable" reaction symptoms that are not observable, such as headache or abdominal pain, can be included.
5. Rechallenge Satisfactory: a final criterion in the "certain" category is rechallenge and it is rarely used since a rechallenge is almost always required and this is often unethical. There are strict criteria for a drug administration to be called a rechallenge. If rechallenge is carried out, the patient should have first recovered from the clinical event on stopping the suspect drug after the first occurrence. The rechallenge should be with the same drug, at the same dose, and by the same route. Skin prick testing for allergy is an accepted form of confirmation although there are false positives. Rechallenge may not be needed for a "certain" classification in a small number of situations such as when a cytotoxic drug extravasates and causes tissue damage. Rechallenge may well be dangerous and the majority of reports that have rechallenge data arise from lack of recognition that an illness following the exposure to the drug previously was an adverse reaction until it happened again or a lack of a proper record of the previous reaction.

B. Probable/Likely.

The assessment criteria for "probable/likely" category are as under:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not require

Further Explanation of the term of "Probable" Category.

1. **Reasonable Time Relationship:** Some examples of reasonable time relationships are, firstly and obviously, when the onset of the clinical condition was after the drug was started and not before; or secondly, a drug suspected of causing a congenital cardiac defect, for example, was taken in the first trimester of pregnancy when the heart is developing and not just in the last trimester when it couldn't affect the developing heart.
2. **Alternative Causes:** to determine if the patient's clinical conditions are likely to be alternative causes, we need first to identify them from the medical history if it is provided. They can also often be identified from the indications for the medicines the patient is taking, including the indication for the suspect medicine. Other drugs the patient was taking, the concomitants, should be considered. Is the clinical condition a recognised adverse reaction to any of them? If so, is there a reasonable time relationship with their intake in this case? If the patient recovered when only the suspect drug was withdrawn then concomitant drugs are unlikely to be alternative explanations.
3. **Dechallenge:** the response to withdrawal, that is, dechallenge, and should be clinically reasonable. That is, the patient recovered after the drug was stopped or the dose reduced, within an expected time period for the particular adverse reaction. Not applicable when irreversible tissue damage has occurred. Changes in tissue function might mimic natural disease so time to improvement follows natural evolution.

C. Possible.

The assessment criteria for “possible” category are as under:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Further Explanation of “possible” category:

A "possible" ADR report may be explained by other drugs or diseases. Like a "probable" reaction, we have an event or a laboratory test abnormality with reasonable time relationship to drug intake. Beyond that there are several reasons for classifying a reaction as "possible". The suspected reaction could also be explained by other drugs the patient was taking. Disease might also be an explanation. For example, if we have a report of pancreatitis with a drug used to treat diabetes there is a problem because diabetes itself can lead to pancreatitis. Furthermore, a "possible" ADR report does not require dechallenge. Another reason for a "possible" classification is lack of information about outcome when the suspect drug was stopped, that is on dechallenge. In some cases that information will never be available. Stopping the suspect drug does not always lead to recovery even if it did cause the clinical event. Maybe it was so serious the patient died or was permanently harmed. Maybe the event was pregnancy due to an interaction with an oral contraceptive. The pregnancy will of course continue even if the drug is stopped.

D. Unlikely.

The assessment criteria for “Unlikely” category as under:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations.

Further Explanation of “Unlikely” Category.

An "unlikely" ADR report may have an improbable time to onset or a more likely alternative explanation. An event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable for example before for example the drug was started, or too long after it was discontinued, or it was not in keeping with the known time to onset for a recognised adverse reaction. For example it would take longer than one day for hepatic failure to occur after exposure to a drug. And then disease or other drugs provide plausible explanations that are more likely than the suspect drug.

E. Conditional/Unclassified.

The assessment criteria for “Conditional/Unclassified” category as under:

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Further Explanation of “Conditional/ Unclassified” category.

"Unclassified" ADR reports usually contain very little information. Sadly, we receive a number of reports that really have very little information in them. For example, we might have reports that say that the patient took the drug on an unknown date, they had the event on an unknown date. We don't even know if the event occurred before or after starting the drug. We suspect it occurred afterwards, because it was reported, but we can't be sure. So we say these are "unclassified". Some people also use this as a "conditional" category for unexpected reactions that don't fit with our knowledge about the drug and the information in the reports is limited. They may add to evidence later if similar reports are submitted.

F. Unassessable/Unclassifiable.

The assessment criteria for “Unassessable/Unclassifiable” category as under:

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

"Unclassifiable" reports have insufficient information and no more is expected.

6.5 Method of Causality Assessment for Case Series.

Case series is a group of patients with similar exposure (drug) and similar outcome (suspected ADR).

Problems with single case assessment are the following: plausible timing, may not be known; de/re-challenge may not have occurred; difficult to exclude other causes or recognize

contributory causes; have only small list of typical ADRs; and some time event is known, not useful for signal detection

A case series is likely to supply additional information that is missing or hard to assess in individual case reports. A logical analysis is applied that is a development from single case assessment. However, it is important to first carry out single case assessment of the reports in the case series.

A set of criteria proposed by Sir Austen Bradford Hill in order to indicate in what circumstances an observed association between an exposure and an outcome could be considered a causal association. These criteria are applied most often to the findings from epidemiological studies; but, now it is also used for the causality assessment of case series.

The criteria are as under:

1. Strength of Association: relates to the observed number of reports compared with the expected number. If observed reports are more than expected, then is there is disproportionality.
2. Temporal relationship: the event should commenced after drug was started and Fits with pharmacology of drug or host responses (Reasonable time to onset.)
3. Consistency: It means that reports are received from a range of reporters in case of national database or, in international databases form a range of countries.
4. Biologic plausibility: biologic plausibility means that the suspected reaction fits in with what we know about the drug's actions. For example f a new drug is reported to cause urinary retention then it would be “biologically plausible” if it has some anticholinergic activity.
5. Coherence– It means suspected reaction fit with existing knowledge. For example, we know that furosemide can cause loss of potassium but could not retain it. So if someone has reported high blood potassium levels with furosemide, then there would be other caused of high potassium level. It would also not be coherent with existing knowledge for a drug that is not absorbed from the gastrointestinal tract to cause organ damage
6. Dose-response relationship: Recovery of event on dose decrease and onset of event on dose increased. It good evidence of causality but may not be observable in some situations
7. Specificity: Specific ADR not the cause of ADR. Many adverse reactions have multiple causes, for example headache, abdominal pain, renal failure. Generally drugs cause ADRs through specific mechanisms so that an adverse reaction is more likely if a specific cause of the condition is reported such as interstitial nephritis occurring in the reports of renal failure.
8. Experimental evidence: Experimental evidence may be from previous animal or human studies. For example many drugs are now checked for prolonged QT interval.
9. Analogy: Analogy is when similar reactions have been observed with other members of the suspect drug's ATC group. For example: combined oral contraceptives and venous thrombosis; and angiotensin converting enzyme (ACE) inhibitors and angioedema.

6. 6 Causality Assessment by Each Stakeholder

Healthcare Professionals: HCPs, if trained, should perform the initial causality assessment of individual report either by WHO-UMC or Naranjo method, when submitting report to PNPC, PPCs or Registration Holders of Therapeutic goods.

Hospital: Pharmacovigilance officers, at hospital perform the initial causality assessment of AE. The causality assessment of each report is reviewed by pharmacovigilance committee or pharmacy and therapeutic committee by using WHO-UMC method. Subsequently, these reports are submitted to PPCs.

Provincial Pharmacovigilance Centre: Pharmacovigilance officer perform the causality assessment of reports received directly from therapeutic goods' sale points, HCPs and patient. Whereas, causality of reports received from hospital is reviewed. Accordingly, it is reviewed by provincial pharmacovigilance committee and submitted to PNPC. PPCs also perform the causality assessment of case series as per Bradford Hill Criteria.

Public Health Programme: Perform the causality assessment as per WHO-UMC method. This is accordingly reviewed by Expert Safety Review Panel (ESRP) and submitted to PNPC.

Pakistan National Pharmacovigilance Centre: At PNPC causality assessment groups are constituted for different types of reports which consist of three pharmacovigilance officers each. This group meet on weekly basis and perform the initial causality assessment of directly received reports and reviewed the causality of reports received from PPCs, PHPs and registration holders of therapeutic goods. PNPC also perform the causality assessment of case series as per Bradford Hill criteria. Once done, the reports are then transferred to WHO-UMC VigiBase (Global database).

6. 7 Tools for Pharmacovigilance.

1. ***Suspected Adverse Drug Reaction Reporting Form:*** Refer to Chapter 4, and topic 4.1 along with “Annex A”
2. ***CIOMS Form-I:*** “See Annex B”
3. ***Naranjo Algorithm for Causality Assessment:*** Refer to Chapter 6 and topic 6.3 and “Annex C”
4. ***WHO-UMC System for Standardised Case Causality Assessment:*** Refer to Chapter 6 and topic 6.4 and Annex “D”
5. ***Bradford Hill Criteria for Causality Assessment of case series:*** Refer to Chapter 6 and topic 6.5
6. ***National Database in the Form of VigiFlow:*** Refer to Chapter 10 and topic 10.2.3
7. ***VigiLyze for Signal Detection:*** Refer to Chapter 10 and topic 10.2.4
8. ***Medical Dictionary for Regulatory Activities.*** Refer to Chapter 10 and topic 10.3
9. ***WHO-Drug:*** Refer to Chapter 10 and topic 10.2.1

Chapter No.7: Signal Detection and Evaluation.

7.1 Definition of Signal

World Health Organization define 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 signal is given by CIOMS Medical Sciences working group in its report of 2010 which is defined it 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”.

7.2 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 medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The PNPC and registration holders of therapeutic good should continuously monitor the safety of therapeutic goods for any new information that might have an impact on the registration of therapeutic goods.

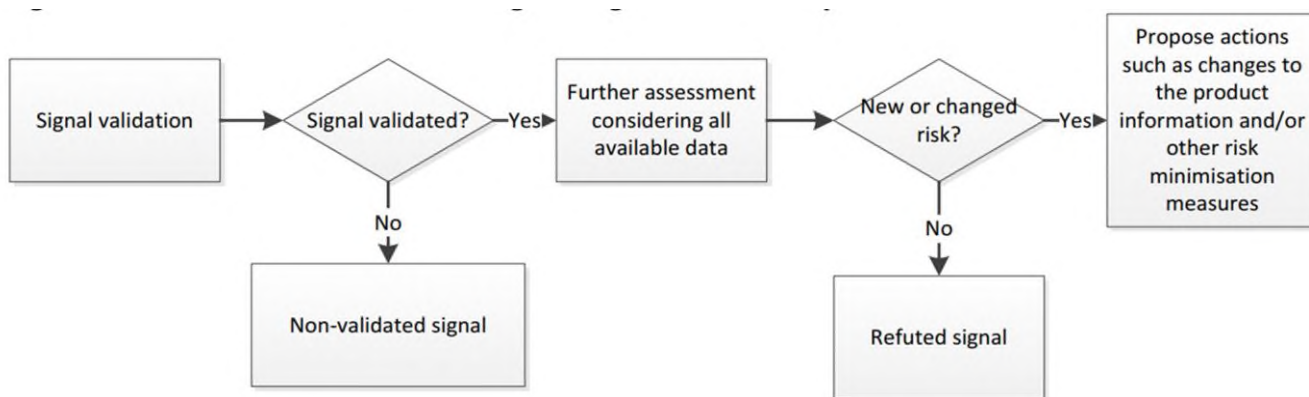
The signal management process concerns all stakeholders involved in the safety monitoring of therapeutic goods including patients, healthcare professionals, registration holders of therapeutic goods, and PNPC-DRAP. Whereas the ADRs database will be a major source of pharmacovigilance information, the signal management process covers signals arising from any source, only signals related to an adverse reaction shall be considered.

7.3 Steps in Signal Management Process

Signal management process covers all steps from detecting signals to recommending action(s) as follows:

- i. **Signal Detection:** The process of looking for and/or identifying signals using data from any source
- ii. **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 and the previous awareness of the association.
- iii. **Signal Prioritization:** The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay
 - iv. **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 medicinal product 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.
 - v. **Recommendation for action:** The effect of the new identified risk shall be evaluated on the benefit-risk ratio of the therapeutic goods and subsequent risk minimization action shall be initiated by PNPC-DRAP and the registration holders of therapeutic goods.
 - vi. **Exchange of information:** PNPC-DRAP and registration holders of the therapeutic goods shall accordingly communicate with healthcare professionals, media and patient etc. about the new signal.



7.4 Signal Detection

Signal detection can be of two types: hypothesis driven signal detection wherein an assessor proposes either new causal relationship between drug and event or new aspect of known relationship; and Data mining-data driven signal detection, wherein signal is either automatically or manually find in large database. Signal are triggered by the following:

- ADR reported is un-expected;
- Unusual aspects of expected ADRs;
- Fatal outcome or life threatening course;
- Specific ADRs: SJS, TEN, Agranulocytosis; and

- Cluster.

Various methods have been used to detect signals using spontaneous reporting data. Based on different statistical methodologies such as Bayesian or Frequentist approach, the basic concept behind these methods is measurement of disproportionality that determines to what extent the number of observed cases differs from the number of expected cases. When all drugs are considered together, large ADR databases tend to have fairly stable proportions of particular reactions over time. That proportion is used as a baseline for comparison to determine what would be expected if there was no signal

In the BCPNN methodology, computation of the information component (IC) is based on prior and posterior probabilities. According to WHO-UMC, the IC measures the disproportionality in the reporting of a drug-ADR combination in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. However, a review of signals generated with this methodology must be analysed by clinicians and drug safety experts before any conclusion is made. Each method used for signal detection has its advantages and disadvantages, and no one method can be considered the gold standard.

7.5 Signal Validation and Assessment

When new signal is detected, first it is validated in order to verify that the available data support the new causal relationship. It is then followed by complete assessment of the signal. In case of spontaneous adverse drug reaction reports it important to have basic information of the following before going into signal detection and making a decision.

- Information about the Drug (Mechanism of Action, its ADRs profile, Pharmacokinetics, Pharmacodynamics, indication, dosage, ATC group, start date, stop date, route of Administration, Re-challenge, de-challenge, concomitant medication)
- The ADR (mechanism, risk factor, System Organ Class group, outcome, onset date, recovery date);
- Information about Patient (s) (Age, Sex, current and past medical condition, genetics, pregnancy, lifestyle factors, allergy, previous major illness);
- History of the registration of drugs/ class across the globe;
- Case series data in case of case series (demographic, pattern, age, re-challenge, de-challenge);
- Information on causal relationship from literature/ studies
- Information from Clinical Trials;
- Data from Risk Management Plan and PBRER; and
- Action taken by other regulatory authorities.

7.6 Signal Review Group

Signal review group at PNPC perform the whole process of signal detection and assessment. This group meets on monthly basis and search the database through VigiLyze for any rise in

IC value (data mining driven signals), or if any new information of possible causal relationship has been found (hypothesis driven signal). The signal is further evaluated by finding information of the possible causal relationship through the above mentioned steps. If signal poses serious threat to the public health it is prioritize. The case is then presented in the forthcoming meeting of PRAEC, which after deliberation and final assessment either refute the signal or confirm it with necessary recommendation in the form of regulatory actions or risk minimization measures.

Chapter No.8: Risk Management, Risk Minimization and Safety Communication.

8.1 Risk Management

Risk management is the identification, assessment, and prioritization of risks associated with the use of a therapeutic good, followed by the coordinated and economical application of resources to minimize, monitor, and control the probability and impact of new ADRs or new aspect of known ADR. At the time of registration, the safety of drugs is established only in few thousand people. When the benefit of drug 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 that leads to risks of new type. Risk management has three inter-related stages:

- i. Characterizing the safety profile of the medicinal product, including what is known or not known;
- ii. Planning of PV activities to characterize and identify new risks and increase knowledge about the safety profile of the medicinal product; and
- iii. Planning and implementing risk minimization and mitigation activities and assessing the effectiveness of these activities.

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

The PNPC-DRAP is responsible for the development of risk minimization strategies; whereas, other Divisions of DRAP, PPCs and Registration holders of therapeutic goods are responsible for implementing these strategies.

8.2 Risk Minimization Measures

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient. 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 a 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.

When it is confirmed that the risk of medicines outweigh its benefit, or when new ADR has been detected, PRAEC recommend risk minimization measures for implementation within Pakistan. These measures are applicable to all therapeutic goods and involve the use of the following tools as describe in the said module.

1. Prescribing information/Package inserts Updatation:
 - Addition of new ADRs;
 - Removal of Indications;
 - Addition of Contraindication (patient, age, disease, pregnancy);
 - Reduction in dose;
 - Addition/Updatation of warnings and precaution section; and
 - Addition of Box Warning.
2. Safety Communication to target audience;
3. Imposition of Post Market Authorization Safety Studies (see chapter 11 and Module 6);
4. Recommendation to submit Risk Management Plan and PBRER (see chapter 11 and Module 4 and 5);
5. Educational programme for healthcare professionals and patients (brochures, checklists, flyers, bulletins, posters, media, patient alert card, campaign of sensitization)
6. Control access programme such as “prescription only drug”
7. Pregnancy prevention programme
8. Recall of the product (due contamination or quality);
9. Suspension or cancellation of market authorization/Registration;

Other Divisions of DRAP, PPCs and Registration holders of therapeutic goods are responsible to implement the risk minimization measure in Pakistan.

8. 3 Safety Communication

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).

All communication with WHO-UMC and WHO headquarters will be managed by PNPC-DRAP. The PNPC-DRAP is responsible to publish/communicate any finding from Pakistan ADR database to media; whereas, other stakeholder are required to get prior approval from PNPC-DRAP to publish or communicated any data of information originating from Pharmacovigilance programme of Pakistan.

A 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 risk minimization; help HCPs and patients to make wise decisions in their choice of therapeutics; foster trust in Regulatory Authorities, Provincial Centres and Registration holders of therapeutic goods.

8.3.1 Target Audiences

The primary target audiences for safety communication issued by PNPC and registration holders of therapeutic goods 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 medicines 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 concern at the same time.

Patients, consumers and healthcare professional's 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.

8.3.2 Means of Safety Communication.

Following are some of the means adopted for the safety communication:

- i. Direct healthcare professionals 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 of therapeutic or PNPC, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. Dear healthcare professional letter is the form of direct health care professional communication.
- ii. 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 of therapeutic goods should contain the PNPC's

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

- iii. Press communication:** Press communication includes press releases and press briefings which are primarily intended for journalists. Head of PNPC-DRAP or public relation officer nominated by DRAP is the only person authorize to engage with media. PNPC 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 of therapeutic goods. Their press releases should make reference to the regulatory action taken by the PNPC-DRAP. Relevant on-going reviews should be mentioned in any communication by the marketing registration holders of therapeutic goods.
- iv. 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. PNPC-DRAP as well as registration holders of therapeutic good 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.
- v. Therapeutic good safety alert:** When new safety concern is detected, it is promptly issued in the form of therapeutic goods safety alert. The therapeutic good safety alerts is communicated either through media or uploaded on DRAP website as public safety information for healthcare professionals and patients.
- vi. 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. PNPC 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. PNPC issue /publish quarterly newsletters. The newsletter is for everyone concerned with the issues of PV and provides practical information and advice on drug safety and information about emerging safety issues.
- vii. Communication with Provincial Pharmacovigilance Centres:** PNPC-DRAP shall inform the provincial pharmacovigilance centres about the regulatory action taken at the level of national level with regards to the new safety concern.
- viii. Advisories:** PNPC and other Divisions of 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.

- ix. Responding to enquires from the Public:** PNPC and registration holders of therapeutic goods should have systems in place for responding to enquiries about therapeutic goods from individual members of the public. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by PNPC-DRAP. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

Chapter No.9: Training, Capacity Building and Awareness Campaign.

9.1 TRAINING AND CAPACITY BUILDING.

Pakistan National Pharmacovigilance Centre (PNPC), Division of Pharmacy Services, at first, conduct necessary trainings of pharmacovigilance officers working at PNPC on causality assessment, signal detection, signal management, and risk communication. PNPC also identify other key areas where training is required at National level. To this end, DRAP can either invite international trainers for training in Pakistan, or send their pharmacovigilance officers abroad for participation in international training. PNPC develop pharmacovigilance training plan and update it at least once a year and keep record of staff training.

The pharmacovigilance officers of PNPC, once trained provide further training to stakeholders such as provincial pharmacovigilance centres (PPCs), public health programmes (PHPs), healthcare professionals and registration holders of therapeutic goods. The training provided to provincial pharmacovigilance centres and public health programme is focused on collection, assessment, and data entry of adverse events/ reactions. In addition, Pakistan National Pharmacovigilance would help PPCs and PHPs in the establishment of their pharmacovigilance centres. To this end, DRAP arrange training sessions at DRAP headquarters, Islamabad, wherein pharmacovigilance officers (POs)/ Focal Persons from PPCs, and PHPs are trained on different aspects of pharmacovigilance such as pharmacovigilance centres establishment, data collection, causality assessment and data entry. In addition, PNPC-DRAP also arranges training session for registration holders of therapeutic goods, wherein necessary training is provided on pharmacovigilance system establishment in line with good pharmacovigilance practices.

PNPC-DRAP also arrange different workshops, seminars, symposium, conferences and meetings at National level, wherein pharmacovigilance officers of PNPC, PPCs, and PHPs along with other stakeholders such registration holders of therapeutic goods, healthcare professionals, people from academia, distributors etc. are trained on different process of pharmacovigilance in order to strengthen the pharmacovigilance system of Pakistan.

PPCs also arrange training session for pharmacovigilance officers, hospitals and healthcare professionals of the provinces on identification, assessment and reporting of ADR and AEs. Officers of PNPC also participate in these training which are provided at provincial level. In addition, PPCs also utilizes the expertise of potential hospitals, and with their collaboration conduct training of other hospitals.

PHPs are mostly well funded by international donors, therefore, they can either invite international trainers to conduct training of their pharmacovigilance officers in Pakistan or send their pharmacovigilance officers/Focal Persons abroad for participation in international training. However, necessary training/guidance to PHPs is provided by PNPC-DRAP. Pharmacovigilance officers of DRAP also participate in training session arranged by PHPs in Pakistan.

Registration holders of therapeutic goods should also properly train their Pharmacovigilance staff on different pharmacovigilance activities. In addition, healthcare professionals should also be trained. Awareness campaign for healthcare professionals and patients should also be launched by registration holders of therapeutic goods.

9.2 AWARENESS CAMPAIGN:

PNPC and PPCs are responsible for raising awareness among healthcare professionals, patients and distributors. Both PNPC and PPCs should resort to different means of awareness campaign in order to build a positive reporting culture in the country.

On world patient safety day, the 17th September each year, awareness campaigns for healthcare professionals and public should be launched by PNPC and PPC. Different mean of awareness campaign for healthcare professionals and patients should be adopted. Academia, public health programme, hospitals and registration holders of therapeutic goods should launch their awareness campaign on world patient safety day

Routine awareness among healthcare professionals can be raised through meeting, symposium, face to face training. Pamphlets and posters that encourage reporting should also be circulated in the hospitals to sensitize the healthcare professionals. Those healthcare professionals who reports more frequently should be appreciated either through a letter of appreciation or by awarding a shield. Regular feedback to healthcare professionals is also one of the means to encourage them to report ADRs. PNPC and PPCs should also run awareness campaign for healthcare professionals through print and electronic media, in the form of press-note in newspapers highlighting the importance of reporting or in the form of short documentary/videos in electronic media.

Healthcare professionals in hospitals can play a crucial role to increase awareness among patients. The Nurse, Pharmacist, and Doctor shall properly counsel their patients about the risk of medicines and should encourage patients to consult them in case they experience any untoward event. PNPC and PPCs should launch social mobilization and public awareness campaign both in print and electronic media. Circulation of pamphlet at the times of public gathering is another effective way to increase awareness among public. In addition, the awareness among general public can also be raised through posters, billboards or educational campaign. Coordination shall also be made with civil society of Pakistan to arrange marathon, walks or rally to raise awareness among general public on world patient safety day.

Chapter No.10: Collaboration with International Stakeholders.

10. 1 World Health Organization

World Health Organization (WHO) is the custodian of World Health Organization Programme for International Drug Monitoring (WHO-PIDM) that was started in 1968 in the aftermath of thalidomide tragedy. Membership of this programme is only provided to WHO members countries. Uppsala Monitoring Centre (UMC), Sweden is responsible to provide operational support to WHO-PIDM, whereas, WHO retained full responsibilities of the policy, coordination, and dissemination of information. The WHO Essential Medicines and Health Products (EMP) department works with countries to promote affordable access to quality, safe and effective medicines, vaccines, diagnostics and other medical devices. Under the EMP safety and vigilance section is responsible to increase knowledge of real life adverse events and coordinate actions taken against adverse events, mitigate risks and protect against substandard / falsified products. Work areas of Safety and Vigilance are Medicine safety, Vaccines safety and Substandard and Falsified medicines. WHO arrange annual meeting of representative of National Pharmacovigilance Centres, issue drug safety alerts among the national centres, and convene meeting of Advisory Committee on Safety of Medicinal Products (ACSoMP). The WHO also issue pharmaceutical newsletters, wherein new information on the safety and efficacy of medicines, new signals detected and regulatory actions taken by countries are shared published. WHO have also issued guidelines on different aspect of pharmacovigilance. In Pakistan, PNPC-DRAP is responsible to coordinate with WHO on the matter of Pharmacovigilance. There are different collaborating centres of WHO, those are also contributing to pharmacovigilance. Uppsala Monitoring Centre (UMC), Sweden is WHO collaborating that is responsible to the lead operations, act as a technical partner, database management, analysis, communication, research and training. WHO collaborating Centre (WHO-CC) at Oslo, Norway is responsible for ATC/ DDD training, whereas, WHO-CC Morocco supporting in medication errors, training, country support (Francophone, Arabic), and convergence of pharmacovigilance systems. The last one is WHO CC Lareb, in Netherlands working on pharmacovigilance in education and patient reporting.

10. 2 Uppsala Monitoring Centre (UMC)

The Uppsala Monitoring Centre (UMC) is an independent, non-profit foundation and a centre for international service and scientific research that is dedicated to promoting safer use of medicines for patients everywhere, using the science of pharmacovigilance to explore and understand the risks and benefits of medicines. UMC was established in Uppsala, Sweden in 1978 as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. UMC operates the technical and scientific aspects of the WHO's worldwide pharmacovigilance network. It provides scientific leadership and operational support to the WHO Programme for International Drug Monitoring (WHO-PIDM). UMC main areas of work are scientific development (*thinking*), provision of technology and support tools (*tools*), and teaching, training and advocacy (*teaching*). It is custodian of tool such as VigiBase (global database), WHO-Drug, VigiFlow (National database), and VigiLyze. A national centre need

to contact WHO-UMC in order to get access to VigiBase. Further, UMC also provides VigiFlow, VigiLyze and WHO-Drug subscription to National Centre after agreement between the two parties. UMC also detects signals in VigiBase, which are at first shared with national centres and subsequently are published in WHO pharmaceutical newsletter. UMC conducts annual pharmacovigilance course at Uppsala, and also conduct some pharmacovigilance courses in collaboration with pharmacovigilance partners in other parts of the world. In addition, UMC also provide specific training course on the request of National Centres. UMC also have distance learning training programme where free on-line training course is provided. National Centre of the country is responsible to coordinate with WHO-UMC for the provision of VigiFlow, VigiLyze and WHO-Drug. The tools of the WHO-UMC are further elaborated as under:

10. 2. 1 WHO-DRUG Dictionary.

The world's most comprehensive dictionary enabling grouping of reported drugs with: same active substance(s); same active moiety (ies); and same Anatomical Therapeutic Pharmacological Chemical classification. WHO-Drug is used by Regulatory Authorities, Pharmaceutical companies, Clinical Research Organization, PV centres and UMC. WHO-Drug data covers both conventional medicines and herbal remedies. The conventional medicines include prescription-only products, over-the-counter (OTC) and pharmacist-dispensed preparations, as well as biotech and blood products, diagnostic substances and contrast medication. WHO-Drug has more than 500 000 unique drug names and more than three million medicinal products from 150 countries. The National Centre has to sign agreement with WHO-UMC in order to use WHO-Drug. The drugs in the VigiFlow are coded through WHO-Drug while entering the data into VigiFlow.

10.2. 2 VigiBase

VigiBase is the WHO global ICSR database and consists of reports of adverse reactions submitted by member countries since 1968. The VigiBase data resource is the largest and most comprehensive in the world and it is developed and maintained by the UMC on behalf of WHO since 1978. At present, 130 countries are contributing to VigiBase. VigiBase includes linked databases (WHO-ART/MedDRA, WHO ICD, and WHO-DD) that contain medical and drug classifications. It is a computerized PV system in which information is recorded in a structured, hierarchical form to allow for easy and flexible data retrieval and analysis. Its purpose is to provide evidence from which potential medicine safety hazards may be detected and communicated. As of 2019, VigiBase has over 20 million anonymized reports of suspected adverse effects of medicines suffered by patients.

10. 2. 3 VigiFlow

A web-based ICSR data management system available to the national pharmacovigilance centres of the member countries of the WHO Programme for International Drug Monitoring. VigiFlow is compliant with international ICH E2B standard and maintained by Uppsala Monitoring Centre in Uppsala, Sweden. Since it is web based system, therefore, no local installations, back-ups or maintenance are required, except internet connection. VigiFlow

enables to: collect ADRs and AEFIs; structure and evaluate these; and accordingly share these with other stakeholders. It is equipped with international standards such ICH-E2B and terminologies such as MedDRA and WHO-Drug. ADRs can be either manually entered by using these terminologies or can be uploaded via E2B upload. It is also equipped with e-reporting wherein healthcare professionals and patient can directly report to National Centre. The data entered has complete record in the form of audit and traceability. At the national pharmacovigilance centre, the entered ADRs are saved and after assessment are transferred via one click to Vigibase. The VigiFlow captures results from three causality assessment methods: WHO-UMC causality; Naranjo Algorithm; and WHO-AEFI. The new VigiFlow is focused more on decentralization by giving more autonomy to national centres. There are three level hierarchies in new VigiFlow i.e. national, regional and sub-regional. Furthermore, ADRs can also be assigned by national centres to regional centres.

10. 2. 4VigiLyze.

VigiLyze is a powerful search and analysis tool that provides access to more than 20 million ICSRs in VigiBase, submitted by over 130 countries. VigiLyze includes data on allopathic medicines, traditional medicines (herbals), as well as biological medicines, including vaccines. Results from VigiLyze are generated instantly in tabular and graphical formats. VigiLyze is available to PV national centres in all member countries of the WHO Programme for International Drug Monitoring. It is web based, easily assessable and user friendly and it can be accessed only through secure logins. VigiLyze can provide global, regional or national view of the suspected adverse effects of a medicine. It is equipped with terminologies such as MedDRA and WHO-Drug which make the search standardized in VigiLyze. The new VigiLyze provides two view i.e. qualitative view and quantitative view. In qualitative view, the ICSRs can be viewed in tabular and charts form, filtered by country, regions, gender, ages etc., and these ICSRs can be exported to excel sheet and further search by applying different filters. Whereas, Quantitative view is equipped with data mining tools such Information Component (IC) and IC 0.25, that measure disproportionality of drug-ADR combination in VigiBase. It helps in signal detection by applying powerful filters that enables the assessor to view the drug-ADR combination in different countries and by going higher up in the hierarchy of MedDRA and WHO-Drug to increase the span of search.

10.3 Medical Dictionary for Regulatory Activities (MedDRA).

MedDRA is not a dictionary rather a clinically-validated international medical terminologies used by regulatory authorities and regulatory biopharmaceutical industry through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evolution, and presentation. MedDRA was developed under the auspices of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA management committee. Since ADRs and other clinical terms are coded into standardized terms while entering the data into VigiFlow, therefore, the license of MedDRA-MSSO is obtained by the National Pharmacovigilance Centre of the country. All the terms are divided into 27 System Organ Class (SOC); that are

further sub divided into 337 High Level Group Term (HLGT); 1737 High Level Term (HLT); 23, 708 Preferred Term (PT); and 80, 262 Lowest Level Term (LLT). In addition, there are 104 Standardized MedDRA Queries (SMQs) constructed at the level of preferred term level, wherein terms from one or more MedDRA SOCs related to medical condition or area of interest are grouped together to help in signal detection and other screening purpose. More information about MedDRA and online training can be accessed through the following link: <https://www.meddra.org/>

Chapter No. 11: Responsibilities of Registration Holders of Therapeutic Goods.

MODULE.1: PHARMACOVIGILANCE SYSTEM

A pharmacovigilance system is defined as the system used by the manufacturer or registration holder of therapeutic goods to fulfil the tasks and responsibilities listed in these guidelines and is designed to monitor the safety of therapeutic good and detect any change to their risk-benefit 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 this chapter.

Manufacturers or registration holders of therapeutic goods establishes their pharmacovigilance system for fulfilment of their pharmacovigilance activities in accordance with Rule.11 (1) of Pharmacovigilance Rules. They evaluate all information scientifically, consider options for risk minimization or prevention and take appropriate measures. The manufacturer or registration holder of therapeutic goods collect, record, store, maintain and analyse the adverse events or adverse drug reactions of all therapeutic goods registered in their name, in order to monitor their safety. Accordingly, they report pharmacovigilance data including zero events to PNPC, as per timelines provided in the Pharmacovigilance Rules. Manufacturers or registration holders of therapeutic goods has to follow or perform all the guidelines provided in this documents which are relevant to them.

When submitting an application for new therapeutic good registration, the registration holder of therapeutic goods need to submit a description of the pharmacovigilance system, and a proof-document stating that the services of the QPPV are in place. These document are submitted to Registration Board and a copy is also send to PNPC.

1.1. Qualified Person for Pharmacovigilance (QPPV).

1.1.1 Requirement of QPPV: Manufacturers or Registration holders of therapeutic goods shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance (QPPV), who shall reside and operate in Pakistan. In case of multinational manufacturers or registration holders of therapeutic goods, a local safety officer may be accepted if he/she is based in Pakistan. However, in case of local manufacturers or registration holders of therapeutic goods there should be a dedicated QPPV and she/she should reside in Pakistan.

Each pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one manufacturers or registration holder of therapeutic goods, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same manufacturer or registration holder of therapeutic goods, provided that the QPPV is able to fulfil all obligations.

The registration holders of therapeutic goods shall provide following requirements to the PNPC in order to get approval:

- i. Letter of appointment from the registration holders of therapeutic goods;
- ii. Copies of degree(s) of the QPPV;
- iii. Training certificate in PV;
- iv. Experience certificate in PV;
- v. List of products covered by the registration holder of therapeutic goods PV system; and
- vi. SOP of the PV officer.

1.1.2 Responsibilities of QPPV: The QPPV shall be responsible for the establishment and maintenance of the registration holder of therapeutic goods' 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 pharmacovigilance system master file 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 responsibility for the pharmacovigilance system means that the QPPV has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, 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).

In relation to the therapeutic goods covered by the pharmacovigilance system, specific additional responsibilities of the QPPV 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 the Pakistan or pursuant to a risk management plan agreed in the 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 PNPC;
- ix. Ensuring a full and prompt response to any request from PNPC and DRAP for the provision of additional information necessary for the benefit-risk evaluation of a therapeutic goods;
- x. Providing any other information relevant to the benefit-risk evaluation to the PNPC or any other board or committee of the DRAP; and
- xi. Providing input into the preparation of regulatory actions in response to significant safety issue (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals).

1.1.3 Qualification of QPPV: The registration holder of therapeutic goods shall ensure that the QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPV should have a minimum of bachelor degree in pharmacy or medicines; a basic training in epidemiology and biostatistics is desirable. The registration holder of therapeutic goods should provide the QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the therapeutic goods covered by the pharmacovigilance system.

MODULE-2: PHARMACOVIGILANCE SYSTEM MASTER FILE (PSMF).

2.1 Definition: “It is a detailed description of the Pharmacovigilance system used by the manufacturer or registration holder of therapeutic goods with respect to one or more authorized therapeutic goods.”

The legal requirement for manufacturer or registration holder of therapeutic goods for maintenance and submission of pharmacovigilance system master file (PSMF) is laid down in Rule.11 (4) of the Pharmacovigilance Rules.

2.2 Objective of Pharmacovigilance System Master File.

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

2.3 Submission of Pharmacovigilance System Master File.

Manufacturer or registration holder of therapeutic goods shall maintain the pharmacovigilance system master file (PSMF) and submit it to PNPC within forty-five calendar days when directed. In addition, a notification letter showing amendment or update shall also be submitted to the PNPC when there is any update in QPPV or location of PSMF.

Manufacturer or registration holder of therapeutic goods is also required to submit to the registration board the summary of the PSMF at the time of registration of therapeutic goods.

2.4 Location of Pharmacovigilance System Master File.

The PSMF shall be located (physically) either at the site where the main pharmacovigilance activities of the registration holder of therapeutic goods are performed or at the site where the QPPV operates.

2.5 Contents of Pharmacovigilance System Master File.

The content of the pharmacovigilance system master file should reflect global availability of safety information for therapeutic goods authorized for the manufacturer or registration holder of therapeutic goods, with information on the pharmacovigilance system to the local or regional activities. Multinational manufacturer or registration holder of therapeutic goods should provide clear illustration of the key elements of both global pharmacovigilance system and national pharmacovigilance sub-system, highlighting the role of QPPV, which pharmacovigilance activities are carried out in the Pakistan, which are carried out in the

headquarter/globally and how they integrate together. For the Multinational manufacturer or registration holder of therapeutic goods the following two documents are required to have:

- i. **The PSMF** (according to European Good Pharmacovigilance Practice) and/ or,
- ii. **National pharmacovigilance system file (National PVSF)** which describes the key elements of pharmacovigilance activities in the Pakistan.

In accordance with Rule.11 (4) of the Pharmacovigilance Rules, following shall be the content of the PSMF:

- i. details of the qualified person responsible for pharmacovigilance;
- ii. details of the organization structure of the company that actually holds the registration;
- 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 control systems.

In addition to the above requirements, the PVSF may also contain the following additional information included in the Annexes, namely:

- i. A list of therapeutic goods covered by the PSMF;
- ii. A list of performance indicators;
- iii. A list of all completed audits, for a period of five years, and a list of audit schedules; and
- iv. 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.

2.6 Format and Layout.

The PSMF may be in PDF or hard format. 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 cover page shall include the name of the registration holder of therapeutic good along with the name of the QPPV and date of preparation or last update date. The heading to be used in the PSMF along with further details may be prepared as under:

1. The qualified person responsible for pharmacovigilance, Annex A
 - *the list of tasks that have been delegated by the QPPV, or the applicable procedural document;*
 - *the curriculum vitae of the QPPV and associated documents; and*
 - *contact details.*

2. The Organisational Structure of the manufacturer or registration holder of therapeutic goods, Annex B
 - *the lists of contracts and agreements.*
3. Sources of safety data, Annex C
 - *Lists associated with the description of sources of safety data e.g. affiliates and third party contacts.*
4. Computerised systems and Databases, Annex D
5. Pharmacovigilance Process, and written procedures, Annex E
 - *Lists of procedural documents.*
6. Pharmacovigilance System Performance, Annex F
 - *Lists of performance indicators; and*
 - *Current results of performance assessment in relation to the indicators.*
7. Quality System, Annex G
 - *Audit schedules; and*
 - *List of audits conducted and completed.*
8. Products, Annex H
 - *List(s) of therapeutic goods covered by the pharmacovigilance system; and*
 - *any notes concerning the manufacturer or registration holder of therapeutic good as per therapeutic goods.*
9. Logbook
10. Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself.

MODULE-3: COLLECTION, MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE DRUG REACTIONS

3.1 Collection of Adverse Events or Adverse Drug Reactions:

Manufacturer or registration holder of therapeutic goods shall record all adverse events or adverse drug reactions with therapeutic goods registered on their name in the country which are brought to their attention, whether reported spontaneously by patient or health care professional, or occurring in the context of a post-authorization study and shall not refuse to consider reports of suspected serious and non-serious adverse reaction received through email or by telephone from patients and healthcare professionals.

Manufacturer or registration holder of therapeutic goods shall collect adverse events or adverse drug reactions in the following conditions, namely:-

- (i) passive surveillance;
- (ii) stimulated reporting;
- (iii) active surveillance;
- (iv) comparative observational studies (cross-sectional study, case-control study, and cohort study);
- (v) targeted clinical investigations; and
- (vi) Descriptive studies (nature history of the disease and drug utilization study).

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.

3.2 Unsolicited Reports

3.2.1 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 medicinal products and that does not derive from a study or any organized data collection scheme. It does not derive from a study or any organised data collection systems.

3.2.2 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 medicinal products, particularly in relation to the detection of new safety signals or safety issues. Reports 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 of therapeutic goods to identify and record ICSRs. In addition, registration holder of therapeutic goods should have

procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have registration, and to bring them to the attention of the company safety department as appropriate.

3.2.3 Report from non-medical sources

If a registration holder of therapeutic goods 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.

3.3 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.

3.4 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 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 reaction.

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 of therapeutic goods should validate the reports, accordingly.

Furthermore, maximum efforts should be taken to ensure that report contain essentially required information as enumerated in in chapter 4 and head 4.1.1 for better assessment and quality of ICSRs.

3.5 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 in chapter 4 and head 4.1.1. 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.

3.6 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 of therapeutic goods and PNC 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 non-corruption of data during data transfer.

Registration holder of therapeutic goods 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 identification and management of duplicate cases at data entry and during the generation of aggregated reports.

3.7 Quality Management:

Registration holder of therapeutic goods 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.

3.8 Special Situation

3.8.1 Use of therapeutic goods during pregnancy

Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure and/or if the suspected medicinal product 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 medicinal products 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 PNPC.

3.8.2 Use of therapeutic goods in paediatric 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 history of the elderly patients shall be properly included in the report.

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

Reports with no associated suspected adverse reaction 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 associated with suspected adverse reactions 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, context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

3.8.4 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.

3.9 Submission of Reports

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 holders of therapeutic goods. 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 of therapeutic goods shall submit the ICSRs in E2B xml format on the following official email address of the PNPC: npc@dra.gov.pk.

However, the PNPC may waive-off the online email submission for some local registration holders of therapeutic goods if they have not yet develop the pharmacovigilance system in line with this guideline. These local registration holders of the therapeutic goods shall submit

the reports on CIOMS form-I (**Annex-B**) manually in hard format on the following mailing address of the DRAP:

In-charge Pakistan 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, +92-51-9262182

3.9.1 Submission time frames:

In accordance with Rule.11 (5), of Pharmacovigilance Rules, the registration holder of therapeutic goods shall submit the ADRs or AEs originating from spontaneous reporting or from post authorization safety or efficacy studies as per the following timeline to the PNPC:

- (i) submit to PNPC database domestic serious suspected adverse reactions within fifteen calendar days following the day on which manufacturer or registration holder of therapeutic goods concerned gained knowledge of the event;
- (ii) submit to PNPC database non-serious suspected adverse reactions that occur in the country, within ninety calendar days following the day on which the manufacturer or registration holder of therapeutic goods concerned gained knowledge of the event;
- (iii) submit to PNPC database zero event report within ninety calendar days; and
- (iv) Manufacturer or registration holder of therapeutic goods shall not be required to report to PNPC database the adverse event recorded in the listed medical literature. However, they shall monitor all other literature and report any suspected adverse reaction within ninety calendar days.

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

- (i) In accordance with Rule.11 (12) of Pharmacovigilance Rules, manufacturer or registration holder of therapeutic goods shall report any identified significant safety issue as soon as possible within fourteen calendar days of the awareness of the issue by sponsor or manufacturer or registration holder of therapeutic goods to PNPC and concerned board or committee.
- (ii) In accordance with Rule.11 (13) of Pharmacovigilance Rules, manufacturer or registration holder of therapeutic goods shall forward to PNPC those reports which are associated with adverse outcomes as result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods within fifteen calendar days of its awareness.
- (iii) In accordance with Rule.11 (14) of Pharmacovigilance Rules, Lack of therapeutic efficacy in case of vaccines, contraceptives, antibiotics, and

medicines used in critical conditions or life-threatening situations shall be reported to PNPC within fifteen calendar days.

MODULE 4: RISK MANAGEMENT SYSTEM (RMS)

Risk management system is a set of pharmacovigilance activities and intervention designed to identify, characterize, prevent or minimized risks relating to therapeutic good including the assessment of the effectiveness of those activities and interventions. Whereas, Risk Management Plan (RMP) is a detailed description of the risk management system.

4.1 Responsibilities of the Manufacturers or Importers of Drugs with Regards TO Risk management Plan.

Manufacturer or importers of drug is responsible for:

- i. Having an appropriate risk management system in place;
- ii. Ensuring that the knowledge and understanding on the drug's safety profile, following its use in clinical practice, are critically reviewed;
- iii. Ensuring that they constantly monitor the risk of their drugs in compliance with Pharmacovigilance Rules and report the results as required by PNPC; and
- iv. Taking all appropriate actions to minimize the risks of their medicines 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.

4.2 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 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: Annex.

4.3 Submission of Risk Management Plan.

In Pakistan Rule 11 (11) of Pharmacovigilance Rules regulate the submission of Risk Management Plans. Risk Management Plan shall be submitted by the manufacturers or drug

registration holders for all new drugs in their application dossier to the Registration Board at the time of registration of drug. The copy of said RMP may also be submitted to the PNPC. Moreover, PNPC, at later stage of the drug's life may direct the drug registration holder to submit an ad-hoc RMP, if so desired. The ad-hoc RMP may also be voluntarily submitted by the drug registration holder new safety information has come to knowledge due to their own assessment. The RMP is a dynamic document that should be updated throughout the life cycle of the product(s). This includes the addition of safety concerns where required, but also, as the safety profile is further characterized, the removal or reclassification of safety concerns.

Module 5: PERIODIC BENEFIT RISK EVALUATION REPORT (PBRER).

5.1 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 the registration holder of therapeutic goods 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 of therapeutic goods 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.

5.2 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.

5.3 Format of PEBRER

The required format and contents of PBRERs are those described in the ICH-E2C (R2) guidelines that can be assessed by clicking the following link: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2_Step4.pdf . However, PSUR developed in accordance with European Good Pharmacovigilance practices will also be accepted, if 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 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.

5.4 Obligations of Registration Holders of Therapeutic Goods in Pakistan.

1. As general practice PBRRER is submitted across the globe for all new drugs after their registration by market authorization holders as per the following frequency: every six month 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 PBRRER submission which state that: “manufacturer or drug registration holder shall submit PBRRER for all new drugs as per International Council on Harmonization (ICH) format E2C (R2), after its registration in Pakistan in line with International frequency that is based on its IBD”.

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: “manufacturer or drug 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 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 Drug Registration Board or PNPC 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 manufacturer or registration holder of therapeutic goods.”
3. As per Rule.11 (10) of the Pharmacovigilance rules, manufacturer or registration holder of therapeutic goods 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 concerned board or committee or PNPC on the basis of concern relating to pharmacovigilance or due to lack of periodic safety reports relating to an active substance after the registration has been granted.
4. Rule.12 (9) of the Pharmacovigilance rules state that: If the investigational drug has received accelerated approval or registration, and clinical trials continue or are initiated, both a PBRER and a DSUR should be prepared in accordance with directions from PNPC. The sponsor shall change the DSUR’s DLP to coincide with the IBD so that the DSUR and the PBRER can be synchronized. In synchronizing the DLP for the DSUR and PBRER, the period covered by the next DSUR should be no longer than one year.

MODULE 6: POST-AUTHORIZATION SAFETY STUDIES (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:

“Manufacturer or drug 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 under Rule. 10 (1) (f) of the Pharmacovigilance Rules may also recommend to the registration holders of therapeutic goods to conduct post authorization safety studies, if it is found that during the evaluation of data, there is a safety concern with the use of 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.

If PASS is Phase-IV Interventional Studies, then the registration holder of therapeutic goods/ investigator would apply to Division of Pharmacy Services as per relevant provision of Bio Study Rules, 2017 for the approval of trial sites and interventional study.

For non-interventional PASS studies, the registration holder of therapeutic good or the investigator on his behalf need to inform the Division of Pharmacy Services about the duration, design and protocols of the PASS study. All the AEs/ ADR shall be reported to PNPC as per the provision of Pharmacovigilance Rules. Progress report of the study shall also be submitted to PNPC on regular basis. The final report should be submitted within 12 months after the end point and it should contain information on the outcome of study and its effect on safety of drugs.

If PRAEC is not satisfied with results of PASS after submission of PASS study final report, then it would recommend any other regulatory action/risk minimization measures for implementation in Pakistan.

6.1 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
4. Drug Utilization Studies

6.2 Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. It can be achieved through Intensive Monitoring Scheme (Sentinel sites) Prescription/ Drug Event Monitoring and Registries

6.2.1 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.

6.2.2 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.

6.2.3 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.

6.3 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 programme or case series. Major types of these designs are cross sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

6.3.1 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 a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilised when exposures do not change over time.

6.3.2 Case-Control Study

In a case-control study, cases of disease (or events) are identified and patients from the source 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.

6.3.3 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

6.4 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 the study is a clinical trial, 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.

6.5 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 determining rates of adverse events. DUS have 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 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 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 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

Chapter No.12: Performance Evaluation of Pharmacovigilance Activities.

In order to measure the existence and performance of key pharmacovigilance structures and processes and are able to identify the strengths and weaknesses, as well as revealing the achievements, growth or lack of growth of the pharmacovigilance systems and to measure the degree of attainment of set strategic objectives, it is necessary to continuously monitor and evaluate the pharmacovigilance activities. To this end, PNPC have established some key performance pharmacovigilance indicators to regularly calculate, analyse, and evaluate the output of pharmacovigilance activities against the set targets.

The Key Performance Indicators for Pharmacovigilance System of Pakistan are as under:

- Numbers of ADRs/AEs reports received in a year from all stakeholders;
- Number of ADRs/AEs reports entered in a year in Pakistan VigiFlow database both at National and Provincial level;
- Numbers of AEs reports whose causality assessment is performed or reviewed.
- Number of reports transferred to WHO-UMC VigiBase;
- Percentage of reports submitted by healthcare professionals;
- Numbers of registration holders of therapeutic goods having functional pharmacovigilance system;
- Numbers of nomination of Qualified Person for Pharmacovigilance received from registration holders of therapeutic goods;
- Number of Focal Person nomination made at Provincial and Public Health Programme level;
- Numbers of Focal Person and Pharmacovigilance Officers nomination made at hospital level;
- Number of healthcare professionals trained on pharmacovigilance;
- Number of signals detected and confirmed;
- Numbers of meeting of Pharmacovigilance Risk Assessment Expert Committee (PRAEC) convened;
- Numbers of Post Authorization Safety Studies (PAES) imposed by PRAEC.
- Numbers of Periodic Benefit-Risk Evaluation Reports (PBRERs) submitted by registration holders of therapeutic goods;
- Numbers of Risk Managements Plan (RMPs) submitted by registration holders of therapeutic goods;
- Number of therapeutic goods withdrawn in the country due safety reason;
- Number of prescribing information/labels/ package inserts updated due new safety reason;
- Number of healthcare professionals' advisories/ Dear Health Care Professionals letters, press release issued;
- Numbers of newsletters issued; and
- Numbers of therapeutic goods safety alerts issued.

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Glossary

1. **Abuse of Therapeutic Good:** It is persistent or sporadic, intentional excessive use of therapeutic good which is accompanied by harmful physical or psychological effects.
2. **Adverse Event (AE):** An AE is an untoward medical occurrence in a patient administered a pharmaceutical product or therapeutic good and which does not necessarily have a causal relationship with this treatment.
3. **Adverse Drug Reaction (ADR):** An ADR is a response to medicines or therapeutic good 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.
4. **Adverse Event Following Immunizations (AEFI):** It is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.
5. **Benefit-Risk Assessment:** It is the continuous examination of the favourable and unfavourable results of a specific treatment (therapeutic good) to determine whether its benefits outweigh its risks in a specific condition
6. **Causality Assessment:** It is the evaluation of the likelihood that a medicine or therapeutic good was the causative agent of an observed adverse reaction.
7. **Data Lock Point:** It is the date designated as the cut-off for data to be included in Development Safety Update Report (DSUR) and Periodic Benefits-Risk Evaluation Report (PBRER) based on their Development international birth date (DIBD) and International Birth Date (IBD) respectively.
8. **Development Safety Update Reports (DSUR):** It is a document intended to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation.
9. **Development International Birth Date (DIBD):** It is the date of sponsor's first authorization or approval to conduct a clinical trial in any country worldwide.
10. **Data mining:** A general term for computerised extraction of potentially interesting patterns from large data sets often based on statistical algorithms. A related term with essentially the same meaning is 'pattern discovery'. In pharmacovigilance, the commonest application of data mining is so called disproportionality analysis, for example using the Information component (IC).
11. **De-challenge:** The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.
12. **Disproportionality analysis:** Screening of ICSR databases for reporting rates which are higher than expected. For drug-ADR pairs, common measures of disproportionality are the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), The Information Component (IC), and the Empirical Bayes Geometrical Mean (EBGM). There are also disproportionality measures for drug-drug-ADR triplets, such as Omega (Ω).
13. **Immunization Error:** Immunization errors result from errors in vaccine preparation, handling, storage or administration. They are preventable and detract from overall benefit of immunization programme. Immunization errors often constitute the greatest

proportion of AEFIs. Example of Immunization errors includes: administration of non-sterile injection, reconstitution errors, injection at incorrect site, vaccines transported/stored incorrectly, and when the contraindication is ignored.

14. **Individual Case Safety Report (ICSR):** A report describing a suspected adverse drug reaction related to the administration of one or more medicinal products or therapeutic good to an individual patient.
15. **Information component (IC):** The Information component (IC) measures the disproportionality in the reporting of a drug-ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. The IC has also been implemented on electronic health records, to detect interesting temporal relationships between drug prescriptions and medical events.
16. **International birth date (IBD):** It is 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.
17. **Medication Error:** It is 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.
18. **Misuse of Therapeutic Good:** It is a situation where the therapeutic good or drug is intentionally and inappropriately used not in accordance with the registered therapeutic good information.
19. **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
20. **Occupational Exposure:** For the purpose of reporting cases of suspected adverse reactions, means an exposure to a therapeutic good as a result of one's professional or non-professional occupation.
21. **Off Label Use:** It is 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.
22. **Periodic Benefit-Risk Evaluation Report (PBRER):** It is a document intended to present a periodic, comprehensive, concise and critical analysis of new or emerging information on the risks of the health product or a drug, and on its benefits in approved indications, to enable an appraisal of the product or drug's overall benefit-risk profile.
23. **Pharmacovigilance (PV):** It is science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
24. **Pharmacovigilance officer (PO):** An officer, who is an employee of the Authority, Federal government, Provincial governments, Public Health Programmes, public sector autonomous hospitals, or private sector hospitals, being notified by the Authority, Federal Government, respective Provincial Governments, Public Health Programmes and administration of public and private sector hospitals to collect therapeutic goods safety data, monitor for potential occurrence of ADRs, report such

- ADRs to the PNPC, Public Health Programmes or respective Provincial Pharmacovigilance Centres and perform causality assessment and investigation when required. Pharmacovigilance officer may be a Pharmacist or Doctor.
25. **Pharmacovigilance System:** It is a system used by the manufacturer or registration holder of therapeutic goods to fulfil the tasks and responsibilities listed in these rules and is designed to monitor the safety of therapeutic good and detect any change to their risk-benefit balance.
 26. **Pharmacovigilance System Master File (PSMF):** It is a detailed description of the Pharmacovigilance system used by the manufacturer or registration holder of therapeutic goods with respect to one or more authorized therapeutic goods.
 27. **Post-Authorization Safety Study (PASS):** 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.
 28. **Public Health Programmes (PHPs):** these health programmes at the Federal and Provincial government level that are designed for prevention and eradication of disease and prolonging health through organized efforts of the society.
 29. **Risk-Benefit Balance:** An evaluation of the positive therapeutic effects of the therapeutic good in relation to the risks i.e. any risk relating to the quality, safety or efficacy of the therapeutic good as regards patients' health or public health.
 30. **Risk Management Plan (RMP):** a detailed description of the risk management system which includes a set of Pharmacovigilance activities and interventions which are designed to identify, characterize, prevent or minimize risks relating to a medicinal product including the assessment of the effectiveness of these activities and interventions. The RMP consists of a safety overview of the medicinal product, and the proposed Pharmacovigilance activities and risk minimization activities.
 31. **Serious Adverse Reaction or Serious Adverse Event:** It is an untoward medical occurrence that at any dose result in:
 - i. Patient death;
 - ii. is life-threatening;
 - iii. require inpatient hospitalization or result in prolongation of existing hospitalization;
 - iv. result in persistent or significant disability or incapacity;
 - v. is a congenital anomaly or birth defect; or
 - vi. Is judged to be medically important event or reaction.
 32. **Side Effect:** A side-effect is an unintended effect of a medicine. Normally it is undesirable but it could be beneficial (e.g. an anxiolytic effect from a beta-blocker prescribed for hypertension).
 33. **Signal:** 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.

34. **Spontaneous Reporting:** a system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.
35. **Re-challenge:** The point at which a drug is again given to a patient after its previous withdrawal.
36. **Therapeutic Good Safety Alerts:** these are safety information as an alert for specific audience issued by PNPC or PPC.
37. **Therapeutic Good Sale Point (TGSP):** It is a point of sale of drugs or therapeutic goods, defined in individual sale rules of respective provinces, e.g. medical stores, pharmacy or wholesale.
38. **Unexpected Adverse Drug Reaction:** An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.
39. **Zero Event Report:** A report or statement showing that no adverse drug reaction/event has been reported to an organization or occurred in an institution.

Annex A

Suspected Adverse Drug Reaction Reporting Form



SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

This form is for voluntary reporting of adverse drug reactions caused by therapeutic goods marketed in Pakistan.
For Health Care Professionals

Pakistan National Pharmacovigilance Centre (PNPC)
Pharmacy Services Division, Drug Regulatory Authority of Pakistan (DRAP)
Ministry of National Health Services, Regulation & Coordination,
3rd Floor, TF-Complex, 7-Mauve Area, G-9/4, ISLAMABAD.
Telephone No: +92519262087

For DRAP's Office Use Only

Report No. _____

A. PATIENT DETAILS

Patient's Initials or Name: _____ Identification Number (Medical/Hospital Ref): _____
Sex: Male / Female: _____, If Female, pregnant or not: _____ Age (at the time of reaction): _____ Weight (kg) _____

B. SUSPECTED DRUG(S)/VACCINE(S)/ALTERNATIVE MEDICINE(S) (use additional pages if necessary):

Drug/Vaccine/Alternative Medicine (Brand Name & Generic Name)	Batch No:	Manufacturer / Importer	Route of Administration & Daily Doses	Dosage & Strength	Start Date	Stop Date	Prescribed For

C. SUSPECTED REACTION(S) (use additional pages if necessary):

1. When reaction started (DD/MM/YY): _____ 2. When recovery started (DD/MM/YY): _____

<p>3. Describe the reaction(s): (use additional pages if necessary):</p> 	<p>6. Do you consider the reaction(s) to be serious? Yes/No If yes, please tick all that apply of the following:</p> <p><input type="checkbox"/> Patient died due to reaction:</p> <p><input type="checkbox"/> Life Threatening:</p> <p><input type="checkbox"/> Involved or prolonged inpatient hospitalization:</p> <p><input type="checkbox"/> Involved persistent or significant disability or incapacity:</p> <p><input type="checkbox"/> Congenital anomaly/Birth Defects:</p> <p>Other Serious (Medically Important Condition): please give details: _____</p>
<p>4. Other relevant history of the patient (Allergies, Smoking, Alcohol Use, Hepatic/Bleed Problems, and Pre-Existing Medical Problems etc.):</p> 	<p>7. Reaction abated after use stopped or dose reduced? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply</p> <p>8. Reaction reappeared after reintroduction? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't apply</p>
<p>5. Relevant tests/Laboratory data with dates: (use additional pages if necessary):</p> 	<p>9. Outcomes: <input type="checkbox"/> Fatal <input type="checkbox"/> Recovering <input type="checkbox"/> Unknown <input type="checkbox"/> Continuing <input type="checkbox"/> Recovered Other _____</p>
<p>10. You consider the problem related to which of the following: <input type="checkbox"/> Quality Problem <input type="checkbox"/> Medication Error <input type="checkbox"/> Adverse Event/Reaction If other, please specify: _____</p>	

D. OTHER CONCOMITANT DRUG(S)/VACCINE(S)/ALTERNATIVE MEDICINE(S) (use additional pages if necessary):

Drug/Vaccine/Alternative Medicine (Brand Name & Generic Name)	Batch No:	Manufacturer / Importer	Route of Administration & Daily Doses	Dosage & Strength	Start Date	Stop Date	Prescribed For

E. SUSPECTED MEDICAL DEVICE(S) fill this area for suspected Device only (use additional pages if necessary):

Medical Device Common Name / Brand Name	Lot No/ Batch No:	Manufacturer / Importer	Model No:	Unique Identifier No:	Serial No:	If Implanted enter date	If Explanted enter date

F. REPORTER DETAILS

Name: _____	Professional Address: _____
Specialty: _____	Tel No: _____, Email Address: _____
Date of this report: _____	Signature: _____
Have you reported this problem to Provincial Pharmacovigilance Centre or Manufacturer? If yes, please specify: _____	

"This form neither has any legal value nor can be presented before any Court of Law as an Evidence."

SECOND FOLD HERE

GUIDELINES FOR ADVERSE DRUG REACTION (ADR) REPORTING

"ADVERSE DRUG REACTION (ADR) REPORTING IS ETHICAL AND MORAL DUTY OF HEALTH CARE PROFESSIONALS"

Please use this form for reporting:

- Suspected Adverse Drug Reactions for **ALL MEDICINES**
- Suspected Adverse Drug Reactions for **NEW MEDICINES**
- Suspected Adverse Drug Reactions for **ALL VACCINES**
- Serious* Suspected Adverse Drug Reactions for **ALL UNREGISTERED MEDICINES**
- Serious* Suspected Adverse Drug Reactions for **ALL ALTERNATE REMEDIES** used in Homeopathic/ Herbal/ Unani/ Ayurvedic Treatment

✓ Reactions which are fatal, life threatening, disabling or incapacitating, result in or prolong hospitalization, congenital anomaly or birth defect and other serious medically important conditions are considered serious.

✓ Health care professionals shall comment on the causal relationship of each suspected drug/vaccines/alternative medicine with each reaction as per World Health Organization (WHO) causality assessment scale which comprises of the following six categories, namely:

- i. Certain ii. Probable iii. Possible iv. Unlikely v. Unclassified vi. Unclassifiable

For the Greater Good & in Public Interest, Please Report ADRs to DRAP even if you are unsure.

For More Information/Queries, please contact:

*Pakistan National Pharmacovigilance Centre (PNPC), Drug Regulatory Authority of Pakistan, Telecom Foundation (TF)
Complex, 7-Mauve Area, G-9/4, ISLAMABAD, Pakistan.
Website: www.dra.gov.pk Email: pnpc.drap@pmail.com.*

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SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

This form is for voluntary reporting of adverse drug reactions caused by therapeutic goods marketed in Pakistan.
 For Health Care Professionals (Additional page)

B. SUSPECTED DRUG(S)/VACCINE(S)/ALTERNATIVE MEDICINE(S) (continued):

Drug/Vaccine/Alternative Medicine (Brand Name & Generic Name)	Batch No:	Manufacturer /Importer	Route of Administration & Daily Doses	Dosage & Strength	Start Date	Stop Date	Prescribed For

C. SUSPECTED REACTION(S) (continued):

3. Describe the reaction(s) (continued):

4. Other relevant history of the patient (Allergies, Smoking, Alcohol Use, Hepatic/Renal Problems, and Pre-Existing Medical Problems etc. (continued) :

5. Relevant Tests/Laboratory Data with Dates (continued):

D. OTHER CONCOMITANT DRUG(S)/VACCINE(S)/ALTERNATIVE MEDICINE(S) (continued):

Drug/Vaccine/Alternative Medicine (Brand Name & Generic Name)	Batch No:	Manufacturer /Importer	Route of Administration & Daily Doses	Dosage & Strength	Start Date	Stop Date	Prescribed For

E. SUSPECTED MEDICAL DEVICE(S) (continued):

Medical Device Common Name / Brand Name	Lot No/ Batch No:	Manufacturer /Importer	Model No:	Unique Identifier No:	Serial No:	If Implanted enter date	If Explanted enter date

Annex B

CIOMS Form-I

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT												

I. REACTION INFORMATION

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

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA	
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> 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 <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

Annex C

The Naranjo Algorithm for Causality Assessment

The Naranjo algorithm				
Questions	Yes	No	Don't know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse events appear after the suspected drug was given?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	
Did the adverse reaction appear when the drug was readministered?	+2	-1	0	
Are there alternative causes that could have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Source: Wikipedia.

Naranjo scores of 9 or 10 indicate that an event was "definitely" an ADR; scores of 5-8 rate the likelihood as "probable"; scores of 1-4 are "possible"; and scores of less than 1 are "doubtful."

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions.

Clin Pharmacol Ther. 1981;30:239-245.

Annex D

The WHO-UMC System for Standardized Case Causality

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

(Annex-E)

REPORTING GUIDELINES FOR PATIENTS/ CONSUMERS

1. Why to Report?

Drugs and therapeutic goods are tested in limited number of patients and healthy volunteers during the clinical trials when the drug is in the phase of development. Therefore, everything about the safety of drugs and therapeutic goods could not be known from these trials until the drug is registered and used by people for many time. By reporting adverse events, you can help to provide more information about drugs and therapeutic goods, which will ultimately help to make them safer.

2. What to Report?

A side effect (also called an adverse reaction) is an unwanted symptom or effect caused by therapeutic goods (drugs, vaccines, biological, alternative medicines and medical devices). Patient/consumer cannot always be certain that what they are experiencing is caused by the therapeutic good, but by reporting suspected side effects they can help the DRAP in their investigations, which will lead to safer therapeutic goods. Therefore, patients/consumers should report all those unusual symptoms or effects (adverse event), suspected to be caused by the therapeutic goods.

The patient and consumers of therapeutic goods should provide the maximum information in the reporting form about the following:

- ✓ Information about the person/patient who has experience adverse event (age, gender, weight).
- ✓ The description of adverse event including how it happens, what the patient experienced and onset date of event.
- ✓ Information about the therapeutic goods (brand name, generic name, dose, strength, prescribed for, route of administration, start and stop date etc.)
- ✓ Information about any other drug or therapeutic good that the patient was taking;
- ✓ Information about any other illness or medical condition.

2. Where and How to Report?

Patients or consumer of therapeutic goods should at first, report the adverse events of the above nature to his/her healthcare professional (pharmacist, nurse or doctor) by providing complete information of the event. Patient should always consult his/her healthcare professional in case of untoward event and ask the healthcare professional to report the adverse event to concerned quarters. If the patient doesn't have access to the healthcare professionals, then he can directly report the adverse event to Provincial Pharmacovigilance Centre of his/her province either via telephone or online through official website of the Provincial Pharmacovigilance Centre. Further, patient/consumer of therapeutic goods could also report the adverse event to Pakistan National Pharmacovigilance Centre by visiting the

official website of DRAP. In some cases patient or consumer also report the adverse event to registration holder of therapeutic goods. But, the patient and consumer should keep one thing in mind that is to “report an adverse event through only channel only”, in order to avoid duplication of reports.

3. When to Report?

Patient should report serious adverse event as soon as possible to healthcare professionals, Provincial Pharmacovigilance Centre, Pakistan National Pharmacovigilance Centre or registration holder of therapeutic goods. Sometimes, the adverse event might be unexpected and might be posing harm to other patient. An earlier reporting of adverse event by patient will be helpful to minimize harm to other patients. Further, non-serious adverse event should also be reported at the earliest through the above channel.

(Annex-F)

REPORTING GUIDELINES FOR HEALTHCARE PROFESSIONALS (DOCTOR, DENTIST, PHARMACIST, NURSE AND PHYSIOTHERAPIST)

What to Report?

The healthcare professionals can submit the following type of reports:

- ✓ Known or unknown serious spontaneous adverse event or adverse drug reaction reports with therapeutic goods;
- ✓ Known or unknown non-serious spontaneous adverse event or adverse drug report with therapeutic goods;
- ✓ Adverse Event Following Immunization reports with Vaccines and immunization errors;
- ✓ Lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening; and
- ✓ Adverse events with medication errors;
- ✓ Adverse events with quality problems.
- ✓ Adverse events or adverse drug reaction reports associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

Where and How to Report?

Healthcare professionals, who are working in hospital and are not pharmacovigilance officers, should at first report the suspected adverse drug reaction/ event to pharmacovigilance officer/ Pharmacovigilance Focal Person of the hospital, who document it and take further action. Healthcare professionals should also manage the adverse event/reaction to prevent harm to the patient.

Healthcare professionals who are working in private clinics or does not have access to pharmacovigilance officers/Focal Person of Pharmacovigilance can report the suspected adverse drug reaction/event to Pakistan National Pharmacovigilance centre (PNPC) by visiting the official website of Drug Regulatory Authority of Pakistan (DRAP): <https://www.dra.gov.pk/docs/Suspected%20Adverse%20Reaction%20Reporting%20Form%20for%20Health%20Care%20Professionals.pdf> This can be downloaded, filled in, and send to PNPC through post. In addition, PNPC also have online reporting system for healthcare professionals, wherein healthcare professionals can report the suspected adverse drug reaction/event online. The report can also be email on the following official email address of PNPC: npc@dra.gov.pk. The healthcare professionals should perform causality assessment of the adverse event as per WHO-UMC method (Annex- D) or Naranjo Method (Annex-C), if they are trained in this.

Healthcare Professionals can also report the suspected adverse drug reaction/event to Provincial Pharmacovigilance Centre (PPC) and registration holders of therapeutic goods. But, the healthcare professionals should keep one thing in mind that is to “report an adverse

drug reaction/event through one channel only”, in order to avoid duplication of reports.

How to Fill in the Reporting Form?

Healthcare professionals while filling the suspected adverse drug reaction reporting form (Annex A) or online reporting form should follow the guidelines provided in the Chapter 4 and Topic 4.1 of these guidelines. Furthermore, maximum information should be provided in the reporting forms. Healthcare professionals should always try his/her best to fill in the reporting form both the mandatory information and essentially required information for better assessment of reports as discussed in topic 4.1.1 of Chapter 4.

Causality Assessment of Report?

Healthcare Professionals if trained should perform the initial causality assessment of individual case safety report either by WHO-UMC (Annex-D) or Naranjo Method (Annex-C), when submitting report to Pakistan National Pharmacovigilance, Provincial Pharmacovigilance or Registration Holders of Therapeutic goods. For detailed guidelines about WHO-UMC causality assessment method please refer to topic 6.4 of chapter 6.