# GUIDELINES ON NATIONAL PHARMACOVIGILANCE SYSTEM

**Document Number:** **PHSR/GL/NP/001**
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**Effective Date:**

These guidelines were uploaded on the official website of DRAP on the 16th of September, 2024 to seek comments and suggestions from stakeholders on the draft document. The 1st and 2nd editions of these guidelines were previously issued and now this 3rd edition has been drafted. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using the prescribed format. For further guidelines on how to submit comments visit the DRAP website or click here. Comments and suggestions can be forwarded via email to pv@dra.gov.pk or can be posted at the mailing address, Director, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan, Prime Minister's National Health Complex, Park Road, Islamabad.



**Drug Regulatory Authority of Pakistan**
Islamabad-Pakistan

# 1. HISTORY

This is the 3rd edition of this document.

The 1st edition of these guidelines was drafted as per the *draft* Pharmacovigilance Rules and had chapters and sections for the guidance of healthcare professionals, patients and registration holders. Subsequently, the National Pharmacovigilance Centre (NPC) issued separate guidelines for the above pharmacovigilance stakeholders and also Pharmacovigilance Rules, 2022 were officially notified vide S.R.O 540 (I)/2022 dated 22nd April 2022. Therefore, the NPC-issued 2nd edition of guidelines with the title "*Guidelines on the National Pharmacovigilance System*" which were prepared in line with Pharmacovigilance Rules, 2022. All those sections /chapters for the guidance of the above stakeholders were removed and the WHO PV indicators were incorporated in Chapter 11 in the 2nd edition of the guideline. This 3rd edition of these guidelines has been drafted in light of WHO recommendations in the form of Institutional Development Plans (IDP) made during its assessment of the National Regulatory System of the DRAP. As per WHO recommendation and DRAP's Authority decision, the PRAEC has now been given an advisory role in relation to signal management and risk assessment; whereas, the NPC has been mandated to perform signal management and risk assessment process and to make decisions in the context of risk minimization and recommendation of regulatory actions to concerned Boards and Committees of the DRAP.

# 2. APPLICATION – (Guidance for pharmacovigilance stakeholders)

This document is for the guidance and support of all pharmacovigilance stakeholders of Pakistan.

# 3. PURPOSE

The purpose of this guidance document is to provide a basic framework for the implementation of the pharmacovigilance programme in Pakistan and to ensure that stakeholders are better equipped to monitor the safety of therapeutic goods and to detect, assess, understand, prevent and investigate pharmacovigilance data. The basic purpose is to explain the pharmacovigilance system of Pakistan and let the stakeholders understand how it is structured at the National and provincial levels. The overall aim is:

3.1. To operationalize the pharmacovigilance programme of Pakistan;

3.2. To detect, validate, and assess new signals in the National Pharmacovigilance database;

3.3. To continuously monitor the benefit-risk ratio of therapeutic goods in Pakistan's market;

3.4. To encourage and guide pharmacovigilance stakeholders about the reporting of pharmacovigilance data; and

3.5. To guide the stakeholders about the identification and assessment of AEs, ADRs and AEFIs, subsequent signal detection and risk communication.

# Contents

# 4. INTRODUCTION

Although therapeutic goods such as drugs, vaccines and biologicals are extensively tested in human subjects during clinical trials, everything related to their safety & risks i.e. ADRs cannot be determined in this short period. Therefore, after registration when these new therapeutic goods are released into the market and a large population is exposed, some new and unexpected serious ADRs can occur. The limitations of the clinical trials are:

- The number of trial subjects is less than patients in real practice;
- Trials subjects are highly selective and vulnerable groups such as pregnant women, the elderly, children and patients with other diseases and concomitant drugs are mostly excluded in clinical trials; and
- The duration of clinical trials is of few years as compared to real practice.

Owing to these limitations and in the aftermath of the Thalidomide tragedy, a dire need for post-marketing safety monitoring was felt across the globe. Among the number of initiatives taken for safety monitoring at that time was to have a vibrant National pharmacovigilance centre in the country along with a legislative backup. In line with this international practice, the DRAP established the National Pharmacovigilance Centre (NPC), under its Division of Pharmacy Services 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 the country. With its endeavours, Pakistan became the 134$^{th}$ Full member of the World Health Organization Programme for International Drug Monitoring (WHO-PIDM) in 2018. The NPC has developed different reporting forms and guidelines that are available through the official website for stakeholders. With the promulgation of Pharmacovigilance Rules, 2022, it is now the legal obligation of pharmacovigilance stakeholders to establish their system and report pharmacovigilance data to NPC.

# 5. DEFINITION AND ACRONYMS

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| **Abuse of therapeutic good:** | means persistent or sporadic, intentional excessive use of therapeutic good which is accompanied by harmful physical or psychological effects; |
| **Active Surveillance:** | is a process that involves, enhanced or targeted monitoring for certain events or therapeutic goods and seeks to ascertain |

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| | completely the number of adverse events or adverse drug reactions through a continuous pre-planned process; |
| **ADR:** | **"***Adverse Drug Reaction*" means a response to a drug or therapeutic goods which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal relationship between a therapeutic good and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a therapeutic good and an occurrence is suspected. |
| **AE:** | **"***Adverse Event"* means any untoward medical occurrence in a patient or clinical investigation subject, on the administration of a drug or therapeutic good and which does not necessarily have a causal relationship with this treatment. |
| **AEFI:** | *"Adverse Event Following Immunizations*" means any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. |
| **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. |
| **DRAP:** | The Drug Regulatory Authority of Pakistan, established under the DRAP Act, 2012. |
| **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). |
| **Causality Assessment:** | means the evaluation of the likelihood that medicine or therapeutic good was the causative agent of an observed adverse reaction; |
| **ESRP:** | Expert Safety Review Panel. |

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| **HCP:** | "Healthcare professionals": means any member of the medical, dental, pharmacy, nursing professions, any allied health professional or any other person who in the course of his professional activities may prescribe, recommend, purchase, supply, sell or administer a therapeutic good including medical technologies as registered or enlisted by the Authority. |
| **ICSR** | **"**Individual Case Safety Report": a report describing a suspected adverse drug reaction related to the administration of one or more medicinal products or therapeutic goods to an individual patient. |
| **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. |
| **Medication Error:** | Means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer |
| **Misuse of a Therapeutic Good:** | means situations where the therapeutic good or drug is intentionally and inappropriately used not in accordance with the registered therapeutic good information; |
| **Near Miss:** | WHO defines a near miss as "an error that has the potential to cause an adverse event (patient harm) but fails to do so because of chance or because it is intercepted" ("An error caught before reaching the patient") |
| **NPC:** | National Pharmacovigilance Centre working under DRAP established under Rule 3 of Pharmacovigilance Rules, 2022. |
| **Occupational Exposure***:* | exposure to a therapeutic good as a result of one's professional or non-professional occupation at the workplace. It does not include exposure to one of the ingredients during the manufacturing process before the release as a finished product at a pharma company. |
| **Off-Label Use:** | Refers to the use of an approved medicine under the direction or supervision of a healthcare professional for an unapproved indication, age group, dosage, route or form of |

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| | administration. |
| **Overdose of Therapeutic good:** | means administration of a quantity of a therapeutic good given per administration or cumulatively which is above the maximum recommended dose according to the registered therapeutic good information |
| **Passive Surveillance:** | A process where healthcare professionals or patients send spontaneous reports describing an adverse drug reaction or event after one or more therapeutic goods are administered to the registration holders or regulatory authority; |
| **PASS:** | Post-Authorization Safety Studies. |
| **PAES:** | Post Authorization Efficacy Studies. |
| **PV:** | "Pharmacovigilance" means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other therapeutic good-related problems. |
| **PRAEC:** | Pharmacovigilance Risk Assessment Expert Committee constituted under rule 9 of the Pharmacovigilance Rules, 2022 for risk management associated with the use of therapeutic goods, i.e. signal detection, causality assessment, risk minimization, communication-related to the risk of adverse events and evaluation of periodic reports etc. |
| **PO:** | "Pharmacovigilance Officer": means an officer notified under Rule. 6 of the Pharmacovigilance Rules, 2022 for the execution of pharmacovigilance activities at different levels such as NPC, PPC, PHPs and hospitals. |
| **PPC:** | "Provincial pharmacovigilance centre": means the centre established by each provincial government and administrative territory for the execution of pharmacovigilance activities as per Rule 5 of the Pharmacovigilance Rules, 2022; |
| **PHPs:** | **"**Public Health Programmes": are the health programmes at the level of National, Provincial or Administrative Territory that are designed for the prevention and eradication of disease and prolonging health through organized efforts of the society. They perform pharmacovigilance activities as per Rule 7 of the Pharmacovigilance Rules, 2022; |
| **Serious ADRs or AEs:** | means an untoward medical occurrence that at any dose results in patient death, is life-threatening, requires inpatient |

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| | hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or is judged to be a medically important event or reaction; |
| **Signal** | means 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; |
| **Spontaneous Reporting:** | a system whereby case reports of adverse drug events are voluntarily submitted from health professionals and registration holders to the National regulatory authority; or<br>unsolicited communication by a healthcare professional or<br>consumer to a company, regulatory authority or other organization such as the World Health Organization, and poison control centre that describes one or more adverse drug reactions in a patient who was given one or more therapeutic goods and that does not derive from a study or any organized data collection scheme. |
| **Registration Holder:** | Means manufacturer or importer possessing registration or enlistment of therapeutic goods, as the case may be as per Pharmacovigilance Rules, 2022; |
| **Therapeutic Goods:** | Includes drugs or alternative medicine or medical devices or biologicals or other related products as may be notified by DRAP. Further explanation of each class of therapeutic goods is given in Schedule II of the DRAP Act, 2012. |
| **Therapeutic Good Safety Alerts:** | means safety information as an alert for a specific audience issued by NPC or PPC; |
| **Therapeutic Good Sale Point**: | means a point of sale of drugs or therapeutic goods, defined in individual Drug Rules of respective Provinces and administrative territories, such as a medical store, pharmacy or wholesale; and |
| **WHO-UMC:** | World Health Organization Uppsala Monitoring Centre. |

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# 6. CHAPTERS

# Chapter-I

# 1. STRUCTURE OF PHARMACOVIGILANCE PROGRAMME OF PAKISTAN.

## 1.1 Legal basis for pharmacovigilance activities in Pakistan.

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

To accomplish the task, in the exercise of the powers conferred by Section 23 of the Drug Regulatory Authority of Pakistan Act, 2012 (XXI of 2012), the DRAP with the approval of the Federal Government notified Pharmacovigilance Rules, 2022 vide S.R.O 540 (I)/2022 dated 22nd April, 2022. These rules define the legal obligation of stakeholders such as National and Provincial Pharmacovigilance Centres, Public Health Programmes, Hospitals and Registration Holders concerning the submission of pharmacovigilance data. Further details regarding the Pharmacovigilance Rules, 2022 are available on the DRAP website.

## 1.2 Vision

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

## 1.3 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.

## 1.4 Scope of the pharmacovigilance programme of Pakistan

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

- Known or unknown serious spontaneous suspected ADRs or AEs reports with therapeutic goods;

- Known or unknown non-serious spontaneous suspected ADRs or AEs reports with therapeutic goods;
- Serious and Non-serious AEFI reports with vaccines;
- Reports of lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening conditions;
- AEs with quality problems (substandard and falsified); and
- Reports that are associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

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

- Allopathic Medicines (Drugs/Medicines);
- Alternative Medicines (Ayurvedic, Chinese, Unani, Homeopathic and Biochemic systems 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 the Authority.

## 1.5 Short-term goals

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

- To constitute the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) at the National level and coordinate with Provincial Centres for the constitution of their Provincial Pharmacovigilance Committees;
- Encourage HCPs to report of AEs, ADRs and AEFIs; and
- Integrate Provincial Centres in the National PV Programme and link them to the National database.

## 1.6 Medium-term goals

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

## 1.7 Long-term goals

- To detect signals in the National pharmacovigilance database;
- Alert generation and initiation of regulatory decisions relevant to the safety of therapeutic goods.
- Take necessary measures for active reporting of ADRs and AEs by HCPs;
- Initiation of post-authorization safety studies;

- Initiation of Active Surveillance, Cohort Event Monitoring and Pharmacoepidemiological studies in Pakistan.
- Good Pharmacovigilance Practices (GVP) Inspection of registration holders.

## 1.8 Overview of the system

The Drug legislation in Pakistan has bipartisan shared responsibilities between Federal and Provincial Governments. The Drug Regulatory Authority of Pakistan (DRAP) working at the Federal level is mandated 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 to safe, efficacious and quality therapeutic goods to the public of Pakistan.

The National Pharmacovigilance Centre (NPC) was established by DRAP under the Division of Pharmacy Services at its headquarters in Islamabad, to monitor the safety of therapeutic goods across the country. This centre has been notified by the DRAP vide notification No. F. No. 9-6/2022-DD (PS) dated 10th June 2022. The NPC collects reports from Healthcare Professionals, Patients, Provincial Pharmacovigilance Centres, Public Health Programmes and Registration Holders. In addition, the NPC is also responsible for communicating with National and global stakeholders. NPC is responsible for detecting and management of signals; risk assessment including assessment of RMPs, PBRER and education material for healthcare professionals; recommending regulatory actions; integrating provinces, hospitals and public health programmes in the national PV system; issuing safety communication; publishing newsletters; and performing other functions as elaborated in Pharmacovigilance Rules, 2022.

Pharmacovigilance Risk Assessment Expert Committee [PRAEC] is the advisory committee working at the National level and is facilitating the NPC in its function. The PREAC is responsible for providing advice about risk management associated with the use of therapeutic goods i.e. signal detection & management, risk minimization and risk communication and for providing necessary advisory recommendations on the periodic reports, risk minimization measures and risk management plans which are already evaluated by NPC and submitted to PRAEC. The official website of the DRAP may be visited to learn more about the National Pharmacovigilance System and how DRAP monitors the safety of

therapeutic goods.

Provincial Pharmacovigilance Centres (PPCs) are established by the Provincial Health Departments of each province. These centres collect pharmacovigilance data from therapeutic goods' sale points, public and private hospitals, healthcare professionals and patients. Provincial Health Departments nominate a Focal Person/Incharge of PPC for coordination with NPC. Provincial Pharmacovigilance Committees constituted by each Provincial Health Department under PPC evaluate the pharmacovigilance data of the province. PPC also notify and monitors the working of pharmacovigilance officers working at PPC and public hospitals of the province. For detailed functions of PPC, please refer to Rule 5 of the Pharmacovigilance Rules, 2022.

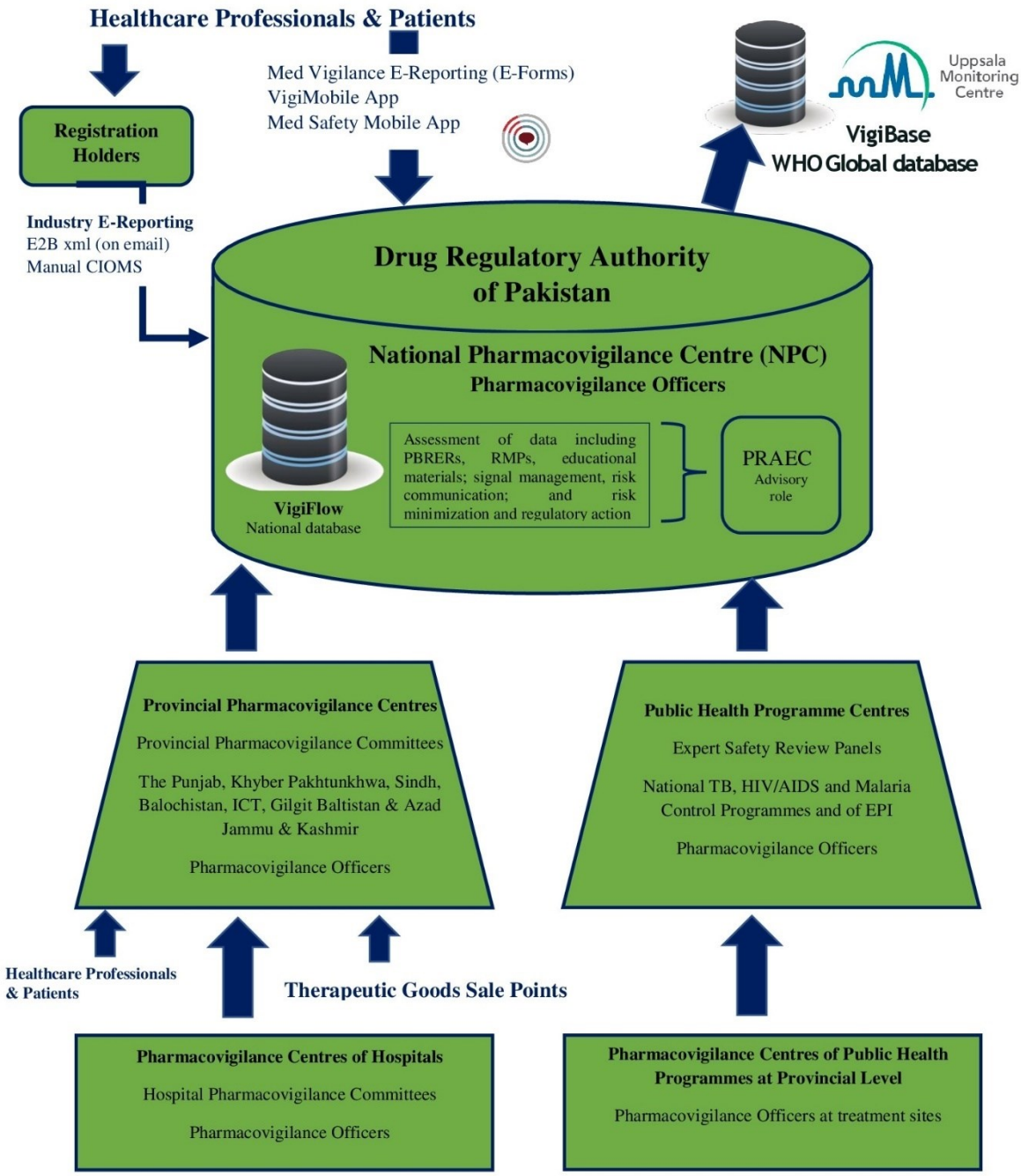
Pharmacovigilance centres are also established by Public Health Programmes (PHPs). Each PHP nominates a Focal Person for coordination with NPC and pharmacovigilance officers for the collection and assessment of data. PHPs will also constitute Expert Safety Review Panels (ESRP) for the evaluation of pharmacovigilance data. PHPs also conduct pharmacoepidemiological studies, cohort event monitoring and other active surveillance studies. The responsibilities of public health programmes are defined in Rule 7 of Pharmacovigilance Rules, 2022. Furthermore, the NPC-DRAP has also developed Guidelines on Pharmacovigilance for Public Health Programmes available on the DRAP website.

At each public and private sector, secondary and tertiary care hospital, pharmacovigilance centres will be established by Provincial Health Departments and the administration of private hospitals. Hospital administration nominates their Focal Persons for coordination with PPCs and regularly submits the pharmacovigilance data to PPC. Pharmacovigilance officers working in hospitals are responsible to collect and assess ADR/AE reports. Pharmacovigilance Committees are established in hospitals for the evaluation of pharmacovigilance data. The responsibilities of public and private hospitals are defined in Rule 8 of Pharmacovigilance Rules, 2022.

Registration holders establish their pharmacovigilance system, nominate a Qualified Person for Pharmacovigilance (QPPV), maintain the Pharmacovigilance System Master File (PSMF), collect and evaluate pharmacovigilance data, submit the data regularly to NPC, and perform other functions as per Rule 11 of the Pharmacovigilance Rules, 2022. Likewise,

comprehensive Guidelines on Good Pharmacovigilance Practices have also been prepared by the DRAP for registration holders.

## 1.9 Flow of reporting



## 1.10 Pharmacovigilance Risk Assessment Expert Committee (PRAEC).

The PRAEC Committee is notified by the Drug Regulatory Authority of Pakistan (DRAP) under Sub-rule (1) of Rule 9 of the Pharmacovigilance Rules, 2022 and vide notification no F. No 9-25/2019-DD (PS), dated 10th of June, 2022. The PRAEC works as an expert advisory committee at the National level and advises the NPC on risk management i.e. signal detection & management, risk minimization and risk communication related to therapeutic goods being used in the country. The NPC ensures that risks associated with the use of therapeutic goods are detected as early as possible, and through the advice of the PRAEC, the NPC takes necessary steps to minimize these risks and gives recommendations to the concerned Board or Committee for further regulatory actions. The composition of PRAEC as per sub-rule (3) of Rule 9 of Pharmacovigilance Rules, 2022 is as under:

(a) Chairman of the committee to be notified by DRAP from the members of PRAEC;

(b) Director, Division of Pharmacy Services, as Ex-Officio Co-Chair;

(c) Additional Director or Deputy Director, Division of Pharmacy Services, or Pharmacovigilance to be nominated by Authority as its Ex-Officio Secretary plus member;

(d) One professor of pharmacy practice to be nominated by DRAP (member);

(e) Expert in basic pharmacology having at least ten-year experience to be nominated by DRAP (member);

(f) Expert of clinical pharmacology having at least ten-year experience to be nominated by DRAP (member);

(g) Expert of clinical pharmacy or clinical pharmacist having at least ten-year experience in a hospital to be notified by DRAP (member);

(h) Expert of medicine or medical specialist having at least ten-year experience in a hospital to be nominated by DRAP (member);

(i) Expert of epidemiology or pharmacoepidemiology having at least ten-year experience to be nominated by DRAP (member);

(j) Expert of toxicology or forensic medicines having at least ten-year experience to be nominated by DRAP (member);

(k) Expert of pharmacovigilance at least ten-year experience in the conduct of pharmacovigilance activities to be nominated by DRAP (member);

(l) Expert of clinical trials or drug research having at least ten-year experience to be nominated by DRAP (member);

(m) Expert of biologicals having at least ten-year experience to be nominated by DRAP(member); and

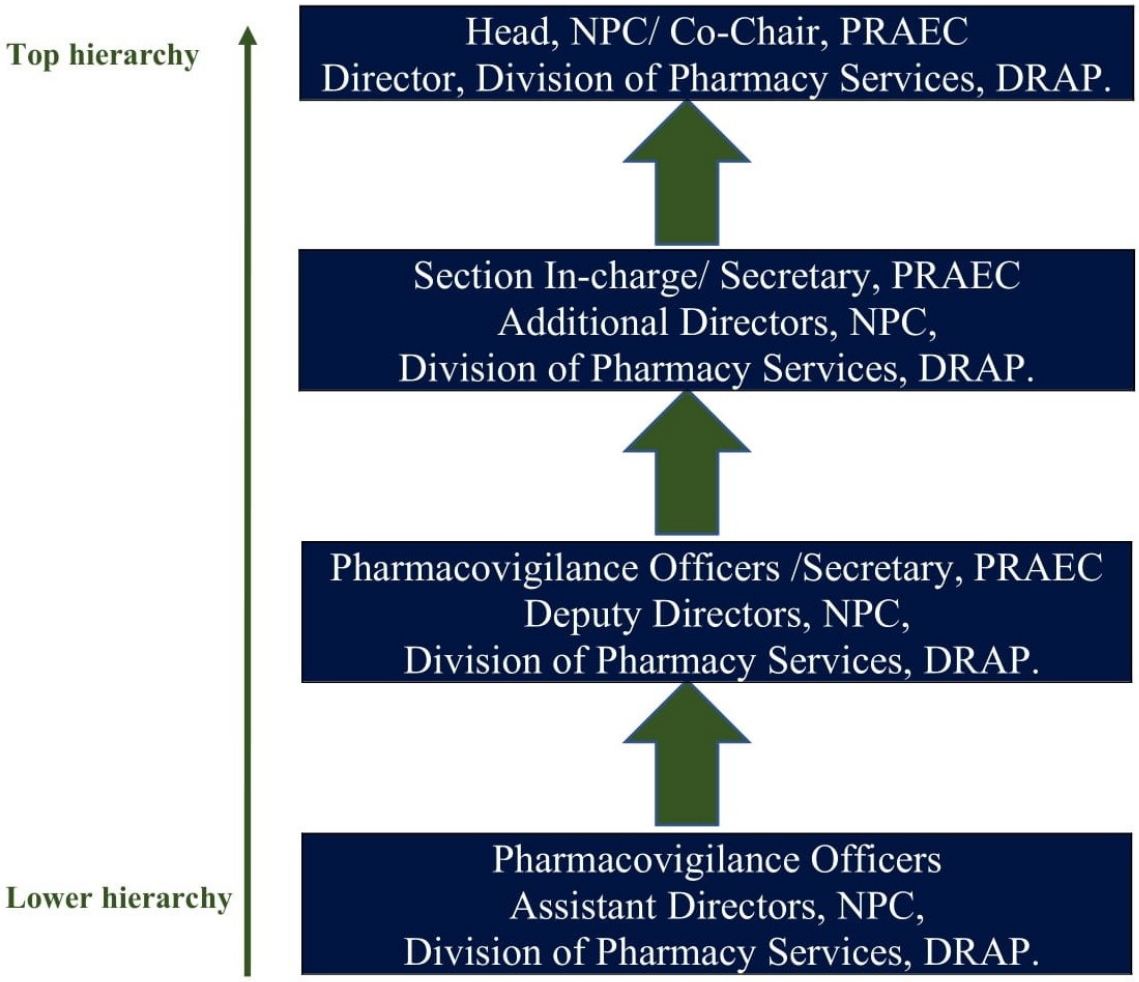
(n) Expert of biostatistics having at least ten-year experience to be nominated by DRAP (member).

As per Rule 10 of Pharmacovigilance Rules, 2022 and in line with the decision of DRAP's Authority the following are the functions of PRAEC, namely:

- Provide advice to NPC-DRAP on all aspects of risk management associated with the use of therapeutic goods, i.e. signal detection, assessment, risk minimisation and communication related to risks of adverse drug reactions;
- NPC detect and manages signals; whereas, the PRAEC can prioritise signals, perform further signal assessment and provide advice to NPC related to the signal management process.
- Provide necessary advisory recommendations on the assessment reports generated by NPC-DRAP for PBRERs, RMP and PASS, or appoint a rapporteur for the assessment or in-depth analysis;
- Provide advice to NPC-DRAP to recommend a regulatory or necessary remedial action to the concerned Board, Committee or Division after assessment of pharmacovigilance data;
- Provide necessary advice to NPC to consider and if deemed appropriate to impose PASS and PAES studies on registration holders through the registration board as a result of safety concerns;
- Provide expert advisory recommendations to NPC-DRAP on safety reports of reliance cases for implementation in Pakistan. NPC review safety reports/alerts published by reference regulatory authorities and if deemed appropriate submits these

cases to PRAEC for expert advice and the NPC accordingly implements these in Pakistan.

## 1.11 Organogram of National Pharmacovigilance Centre, DRAP



## 1.12 Job description of staff at National Pharmacovigilance Centre

| Designation of Post | Brief of Job Description. |
|---|---|
| Head, NPC/ Co-Chair, PRAEC<br>Director, Division of Pharmacy | • Responsible for the development and promotion of the pharmacovigilance system in Pakistan;<br>• Co-Chair the meeting of PRAEC.<br>• Supervise and execute the programme on PV training.<br>• Sign MOUs with PPCs, PHPs and other relevant organizations.<br>• Responsible for inter-provincial coordination on PV.<br>• Execution of risk minimization measures (regulatory actions) through other Divisions of DRAP.<br>• Present rules, guidelines and procedures before the Authority for subsequent approval from Policy Board and Federal Government. |
| Section In-charge/ Secretary, PRAEC<br>Additional Directors, NPC, | • Preparation of agenda/ minutes of PRAEC.<br>• Through consultation with Chair, convene a meeting of PRAEC.<br>• Head of the relevant section of NPC.<br>• Development of training plans for NPC, PPCs and PHPs.<br>• Communication with PV stakeholders and arrangement of meetings.<br>• Responsible to issues therapeutic goods safety alerts, newsletters and press releases of the respective section.<br>• Responsible for the awareness campaign<br>• Evaluate the quality and causality of entered ADRs.<br>• Chair the meeting of the Signal review group of the respective section of NPC. |
| Pharmacovigilance Officers /Secretary, PRAEC<br>Deputy Directors, NPC | • Preparation of agenda/ minutes of PRAEC<br>• Through consultation with the Chair, convene a meeting of PRAEC.<br>• Chair the meeting of the causality assessment group of the relevant section of NPC.<br>• Assist Additional Directors and Head NPC in their work<br>• Guide Assistant Directors on data entry, causality assessment and signal detection and management process.<br>• Search the Pakistan database for new signals along with Assistant Directors of the relevant section of NPC.<br>• Review the material of training, therapeutic goods safety alerts, newsletter and other communication.<br>• Help the Additional Director of the relevant section of NPC in the awareness campaign. |
| Pharmacovigilance Officers<br>Assistant Directors, NPC | • Collect, assess, enter and transfer pharmacovigilance data.<br>• Perform initial causality assessment or signal detection and management process or review the causality of pharmacovigilance data received from PPCs and PHPs.<br>• Member causality assessment and signal review groups of relevant sections of NPC.<br>• Prepare material for training, therapeutic goods safety alerts, newsletters and press releases.<br>• Assist Deputy Directors and Additional Directors of the relevant section of NPC.<br>• Communicate with PPCs and PHPs in the follow-up of PV reports. |

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# CHAPTER 2

# 2. STAKEHOLDERS OF PHARMACOVIGILANCE IN PAKISTAN.

## 2.1 Ministry of National Health Services Regulations and Coordination.

The Ministry of NHS, R&C is the ultimate administrative body of Health in Pakistan (in respect of coordination and regulations) and performs the following functions:

- 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.
- Oversee the working of the Drug Regulatory Authority of Pakistan.

## 2.2 Drug Regulatory Authority of Pakistan (DRAP).

- The DRAP has the mandate to ensure access to safe, efficacious and quality medicines for the people of Pakistan.
- Supervise the working of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services.
- Allocation of budget for the National Pharmacovigilance Centre.
- Hiring/Appointment of personnel for NPC.
- Implementation of the regulatory actions or any other risk minimization measures across Pakistan is as follows: implementing the decisions by other Divisions of DRAP; implementing the decisions by the registration holders, and coordination with Provincial Health Departments.
- Implementation of the policies, legislation, and rules approved by the Ministry of NHSR&C and the Federal Government 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 respect of therapeutic goods safety and other matters of drug legislation.

- Notify pharmacovigilance officers working at NPC.
- Capacity building and professional development of Pharmacovigilance officers at NPC.

## 2.3 National Pharmacovigilance Centre (NPC).

- Development of Pharmacovigilance System in Pakistan in coordination with National and international stakeholders:
    - Coordinate with the World Health Organization (WHO) and Uppsala Monitoring Centre (UMC);
    - Coordinate with Provincial Pharmacovigilance Centres (PPC), Registration Holders and Public Health Programmes (PHPs); and
    - Coordination with hospitals and academia.
- Development of adverse events reporting forms for all pharmacovigilance stakeholders.
- Monitor the database to determine whether there are new risks and whether those risks impact the risk-benefit ratio of drugs or therapeutic goods.
- Supervision of the National Pharmacovigilance database i.e. VigiFlow and integration of the pharmacovigilance centres of provinces, public health programmes and hospitals with NPC through the VigiFlow database.
- Review of Pharmacovigilance System Master File (PSMF) when required and carry out GVP inspection of registration holders.
- Perform or review the causality assessment of collected reports and undertake the complete signal management process, i.e. signal detection, management, prioritization, evaluation, confirmation and risk communication.
- Assessment of protocol and safety data of Post Authorization Safety Studies (PASS), Periodic Benefit-Risk Evaluation Reports (PBRERs), and Risk Management Plans (RMPs) submitted by registration holders.
- Perform assessment of educational material for healthcare professionals and patients as well as the contents of Direct Healthcare Professionals Communication (DHPCs) as a part of additional risk minimization measures.

- On the basis of the assessment of RMPs, PBRERs, study results, signal assessment, and benefit-risk assessment, if it is found that the risk of therapeutic goods outweighs its benefit, the NPC with the advice of PRAEC will recommend regulatory or necessary remedial action or any other safety-related action to concerned Board/ Committee/ Division of DRAP for implementation within Pakistan. These actions may include variation, suspension, revocation, market withdrawal, PASS studies; change in safety specification of therapeutic good or any other action which it considers appropriate.
- The NPC may consider and if deemed appropriate, following the advice of PRAEC implement within Pakistan, pharmacovigilance-relevant decisions of other reference regulatory authorities and regional bodies of the following nature as a part of the reliance mechanism:
    - Modification or removal of an approved indication of therapeutic good due to safety reasons;
    - Addition of contraindications;
    - Imposition of post-authorization safety or efficacy studies due to safety reasons;
    - Major changes in the statements of warning, precaution or adverse reactions in the product information;
    - Withdrawal or suspension of therapeutic goods in other countries due to safety reasons; and
    - Any other safety information or decision which it considers appropriate, for ensuring the safety of the public.
- Communication of risk minimization measures, regulatory actions and signals to concerned stakeholders in Pakistan in the form of safety alerts, healthcare professional advisories, press releases on the website or through other means of communication.
- Initiation and implementation of Post-Authorization Safety Studies (PASS) through registration holders.
- Training of Pharmacovigilance officers of NPC, PPCs and PHPs on proper reporting of ADRs and AEs through the VigiFlow database.
- Collection of ADRs/ AEs /AEFIs from PPCs, PHPs, Registration Holders, HCPs and Patients.

- Work as Secretariat for the PRAEC committee and convene its meetings.
- Encourage PPCs, PHPs, Registration holders, healthcare professionals and patients to report suspected adverse reactions and events to the NPC.
- Develop or amend pharmacovigilance rules and frame guidelines for pharmacovigilance stakeholders. Develop standard operating procedures on different processes at the NPC level.
- Share pharmacovigilance data of Pakistan internationally to the VigiBase (Global database) of WHO-UMC.
- Issue therapeutic goods safety alerts and Publish newsletters.
- Conduct awareness campaigns for HCPs and patients on ADR reporting.

## 2.4 Provincial Pharmacovigilance Centres & Provincial Governments.

PPCs are established by Health Departments of the respective Province as per Pharmacovigilance Rules, 2022, which at first nominate their Focal Persons of Pharmacovigilance for coordination with NPC and then notify/constitute the Provincial Pharmacovigilance Committees**.** The following are the functions of PPCs:

- Collection of reports from public and private hospitals through the VigiFlow database, and therapeutic goods' sale points such as (pharmacies, medical stores, retailers and distributors).
- Sign Memorandums of Understanding with hospitals and academia of the province.
- Perform the causality assessment of AE reports submitted to PPC and review the causality assessment of collected ADR reports
- Submission of pharmacovigilance data to NPC regularly as per defined timelines through the VigiFlow database.
- Support hospitals and sub-regional (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-regional (sub-provincial/divisional) pharmacovigilance centres in the provinces.
- Arrange awareness sessions/campaigns for sensitization of HCPs of the province.
- Implement regulatory actions and risk minimization measures of NPC in the province.
- Participation of POs of PPC in the meeting of PRAEC if required.
- Convene meetings of the Provincial Pharmacovigilance Committee.
- Participate in meetings, training, seminars, and symposiums arranged by NPC.

## 2.5 Public Health Programmes (PHPs).

- Pharmacovigilance centres are established by each PHP (i.e. Tuberculosis, HIV/AIDS, Malaria Control Programmes and Federal Expanded Programme Immunization (EPI) at the National level and integrate with the provincial chapter of the said public health programme as per Pharmacovigilance Rules, 2022.
- Effective coordination with NPC by nominating a Focal Person for this purpose.
- Collection of pharmacovigilance data from the provincial chapter of PHP and treatment sites through the VigiFlow database.
- Regular submission of pharmacovigilance data to NPC through the VigiFlow database.
- Notification of POs at National, Provincial and site levels of PHP.
- Constitution of an Expert Safety Review Panel (ESRP) at the National level, which shall perform functions 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 campaigns for patients.

- Signing of MOU with NPC with respect to collection and submission of pharmacovigilance data.

## 2.6 Registration Holders

- Establish pharmacovigilance systems for the fulfilment of their pharmacovigilance activities in accordance with Pharmacovigilance Rules, 2022.
- Nomination of a Qualified Person of Pharmacovigilance for communication with NPC who is responsible for the establishment and maintenance of the pharmacovigilance system as per rules.
- Maintenance of Pharmacovigilance System Master File and its submission to NPC.
- Submission of ADRs/AEs to NPC through the Industry E reporting system as per the timelines prescribed in Pharmacovigilance Rules, 2022.
- Conduct non-interventional Post-Authorization Safety Studies either voluntarily or if imposed by NPC.
- Submission of Periodic Benefit-Risk Evaluation Reports (PBRER) as per the timelines prescribed in Pharmacovigilance Rules, 2022.
- Submission of Risk Management Plans (NPC) to Registration Board and NPC.
- Issuance of Direct Healthcare Professional Communication.
- Implementation of regulatory actions and risk minimization measures.
- Inform NPC about the risk of their product detected during the self-assessment process.
- Submit adverse outcome reports to NPC in case of abuse, misuse, overdose, off-label use, medication errors, and occupational exposure to therapeutic goods.
- Submit reports of lack of efficacy of therapeutic goods to NPC.

## 2.7 Academia.

- Academia such as Pharmacy, Medical/Dental, Nursing councils and institutions contribute to the pharmacovigilance system through enhancing education and research.

- Inclusion of curriculum on pharmacovigilance in undergraduate and postgraduate levels of study for healthcare professionals.
- Training and awareness campaign on pharmacovigilance.
- Arrange symposiums and conferences on pharmacovigilance.
- Coordination with PPC and NPC.

## 2.8 Hospitals.

- Establishment of pharmacovigilance centres at the hospital level as per Pharmacovigilance Rules, 2022.
- Nomination of Focal Person for coordination with PPC.
- Constitution Pharmacovigilance Committees at the level of the hospital.
- Notification of POs at the hospital level in case of private sector hospitals or autonomous public hospitals.
- Initial causality assessment of AEs.
- Regular submission of pharmacovigilance data to PPC through the VigiFlow database.
- Signing of MOUs with PPC.
- Implement risk minimization measures of NPC and PPC in the hospital.

## 2.9 Therapeutic Goods' Sale Points (TGSP).

- TGSP includes distributors, wholesalers and retailers of therapeutic goods.
- Report the suspected ADR or AE to PPC.
- Counselling of patients to immediately consult HCP if they experience AE.

## 2.10 Healthcare Professionals.

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

- Perform the initial causality assessment of AEs.
- Report the suspected ADR or AE to PPC, registration holders or NPC. But, at a time a suspected ADR or AE shall be reported through one channel to avoid duplication of reports.
- Counselling of patients to immediately consult HCP if they experience AE.

## 2.11 Patients/ Consumers.

- Reporting of the adverse events immediately to their healthcare professionals, National Pharmacovigilance Centre, Provincial Pharmacovigilance Centre or registration holder. But, at a time an AE shall be reported through one channel to avoid duplication of reports. Support from national associations of consumers and patients may add to the general acceptance of pharmacovigilance in the country.

## 2.12 Media

Good relations with leading journalists may be helpful, e.g. for the 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 AEs are also reported in the media, which can be further followed up by National and provincial centres. The Head of NPC-DRAP or public relations officer nominated by DRAP is the only authorised person to engage with the media. Press releases in print media and news on electronic media are some examples of media coverage. The media should always consult DRAP for accuracy and verifiable risk of therapeutic goods.

# Chapter 3

# 3. BASIC CONCEPTS OF PHARMACOVIGILANCE

## 3.1 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

## 3.2 Classification of Adverse Drug Reactions.

ADRs are broadly classified into 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 glyceryl trinitrate.

*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, hepatitis with halothane and agranulocytosis with clozapine.

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

a. *Type C (Continuous):* – Reaction due to long-term use, e.g. adrenal suppression with corticosteroids.

b. *Type D (Delayed):* – e.g. tardive dyskinesia with neuroleptics and teratogenic or carcinogenic effects with drugs.

c. *Type E (End of use):* – e.g. withdrawal reactions with benzodiazepines.

d. *Type F (Failure of Therapy):* Treatment of Failure.

## 3.3 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 are given below:

| **Dose** | **Time** | **Susceptibility** |
|---|---|---|
| Toxic<br>Collateral<br>Hyper susceptibility | Independent<br>Dependent:<br>– rapid administration<br>– first dose<br>– early, intermediate, late<br>– delayed<br>– withdrawal | Age<br>Gender<br>Ethnic Group<br>Genetic<br>Disease |

| | | |
|---|---|---|
| *'*Toxic' means that reactions occur as a result of drug levels being too high;*<br>** 'collateral' means that reactions occur at drug levels which are in the usual therapeutic range;*<br>** 'hyper susceptibility' means that reactions may occur even at very low, sub-therapeutic doses.* | ** 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).*<br>** A withdrawal reaction means one that is specifically precipitated by stopping the drug.* | |

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, the 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.

## 3.4 Categorization of AEFIs

Reported adverse events can either be true adverse events – i.e. resulting from the vaccine or immunization process – or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.

| Cause-specific type of AEFI | Definition |
|---|---|
| Vaccine product-related reaction | An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. |
| Vaccine quality defect-related reaction | An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer. |
| Immunization error related reaction (formerly "programme error") | An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable. |
| Immunization anxiety-related reaction | An AEFI arising from anxiety about the immunization. |
| Coincidental event | An AEFI which is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists. |

Based specifically on 1) cause and 2) seriousness and frequency, vaccine reactions may be grouped into two broad categories:

1. Cause-specific vaccine reactions:
    - vaccine product-related reaction;
    - vaccine quality defect-related reaction;
2. Vaccine reactions by seriousness and frequency:
    - common or minor reactions;
    - rare or major
    - severe or serious

## 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 or lack of therapeutic effect. 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 occurrence of ADRs.

**Chapter 4**

# 4. GUIDELINES FOR REPORTING OF PHARMACOVIGILANCE DATA.

## 4.1 Who can report?

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

i. *Healthcare professionals* (physicians or doctors, dentists, pharmacists and nurses); and

ii. *Patients and consumers* of the therapeutic good or relatives of the patient.

Whereas, the following stakeholders of the pharmacovigilance programme of Pakistan also collect spontaneous reports from patients and healthcare professionals and accordingly submit these reports to NPC, DRAP:

i. *Registration holders;*

ii. *Provincial Pharmacovigilance Centres (PPCs);*

iii. *Public Health Programmes (PHPs);*

*Hospitals and therapeutic goods sale points (*distributors, wholesalers and retailers) report the suspected ADR to the respective PPC, which after assessment submits the report to NPC.

## 4.2 What to report?

*4.2.1 Types of Reports.*

The following types of reports are accepted at NPC:

- Known or unknown serious spontaneous suspected ADRs or AEs reports with therapeutic goods;
- Known or unknown non-serious spontaneous suspected ADRs or AEs reports with therapeutic goods;
- Serious and non-serious AEFIs report with vaccines;
- Reports of lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening

conditions;

- AEs with quality problems; and
- Reports that are associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

*4.2.2 Mandatory & Essentially Required Information.*

All the stakeholders such as patients, healthcare professionals, hospitals, public health programmes, provincial pharmacovigilance centres and registration holders should collect all the information required to be filled in the AE reporting forms. In case complete information is not available, then all the essentially required fields/ information should be filled in the reporting form. In case essentially required information is not available, then the reporting form must contain all the mandatory information to be considered as a report. Mandatory information is the minimum criteria for reporting, therefore, a form without mandatory information will not be accepted.

| **Mandatory Information** | **Essentially Required Information.** |
|---|---|
| **1. Patient information.**<br><br>**2. One or more suspected reaction (s).** The reaction terms or event summary must be given in case ADRs or ADE/medication errors has affected the patient<br><br>**3. One or more suspected drug(s).**<br><br>**4. Reporter information.** | 1. Patient initials, and age at the time of reaction or event.<br>2. Sex of the patient.<br>3. Reaction term(s) or incident summary<br>4. Time-to-onset of reaction (start date/time of suspected drug +start date/time of reaction)<br>5. Suspected drug (s) (dose, strength, dosage form)<br>6. Indication for use.<br>7. The seriousness of the reaction or event<br>8. The outcome of the reaction or event<br>9. De-challenge (in case of ADR)<br>10. Re-challenge (not always ethical to perform) (in case of ADR)<br>11. Reporter information (designation, contact details)<br>12. Case Narrative in free text (chronology of happening of ADRs or AEs) |

| | |
|---|---|
| | 13. Date of report. |

*4.2.3 Necessary Information in a Report*

All the pharmacovigilance stakeholders should provide the maximum information in the AE reporting form about the following:

- ✓ Information about the person/patient who has experienced an AE or AEFI (age, gender, weight, and name etc);
- ✓ The description of an AE or AEFI including how it happens, what the patient experiences, and the onset date of the event;
- ✓ Information about the therapeutic goods (brand name, generic name, batch number, dose, strength, indication, route of administration, start and stop date etc.);
- ✓ Information about any other drug or therapeutic good that the patient was taking at the same time;
- ✓ Information about any other illness or medical condition; and
- ✓ Information about past allergies if any.

## 4.3 Reporting Forms.

### *A. Suspected Adverse Drug Reaction Reporting Form (For Healthcare Professionals)*

The NPC, DRAP has designed Yellow Form in hard format **(Annex A)** for the collection of suspected ADRs or AEs reports from Healthcare professionals. There are fields of mandatory and essentially required information in this reporting form that need to be filled in properly for proper assessment of the report. This form is available on the DRAP website and can be mailed to NPC either through email address or mailing address. The necessary contact details of the National PV Centre are as under:

**National Pharmacovigilance Centre**
Division of Pharmacy Services
Drug Regulatory Authority of Pakistan
Prime Minister's National Health Complex
Park Road, Islamabad

Phone No: +92-9255910
Email Address: npc@dra.gov.pk
Website: www.dra.gov.pk

### *B. Med Vigilance E Reporting System (WHO E-Forms based): (For patient and healthcare professionals):*

AEs can also be reported to NPC, and DRAP through the Med Vigilance E Reporting System that is available on the official website. A telephone number of the reporter in the relevant field of the E-Reporting system should be provided in case staff from NPC, DRAP intends to follow up and get further information from HCP. The form is also available in Urdu language to make it more user-friendly for the patient and their relatives and to remove the language barrier in the reporting of ADRs.

Healthcare professionals, patients, and patients' relatives can report through this channel. Please see the adverse events reporting guidelines for patients and healthcare professionals for further details. Please see (**Annexure B)** for how to report and fill in the form.

### *C. VigiMobile App (For patients and healthcare professionals)*

This is a mobile application developed by the Uppsala Monitoring Centre (UMC) for the National Pharmacovigilance Centre of the DRAP. The application can be assessed through the QR code available on the DRAP website, wherein it can be downloaded for Android or iOS platforms. For guidelines on how to download the application visit the website.

Scan the below QR code to access the mobile application:

### *D. Med Safety Mobile Application (For patients and healthcare professionals)*

This is a mobile application developed by WEB-RADR, Medicine and Health Product Regulatory Agency (MHRA), United Kingdom and Uppsala Monitoring Centre (UMC) that was initially launched for reporting of AEs in low and middle-income countries. The Med Safety App is available for download from the App Store (For iOS devices) and Google Play Store (For Android devices). Guidelines for downloading and creating an account in the Med Safety Mobile App are annexed as **(Annexure C).** Once you have created your account please see the Med Safety Mobile Application use video to understand how to fill and report the AE.

### *E. Industry E-Reporting (For Registration holders)*

The DRAP in collaboration with the Uppsala Monitoring Centre has launched the industry e-reporting for submission of adverse drug reaction (ADR) reports by registration holders. Now registration holders will have to submit reports of ADRs/ICSRs through a manual data entry module or E2B upload module through this new tool of industry e-reporting. Industry e-reporting will allow the registration holders to carry out reporting, installation and operation of Pharmacovigilance, through the reporting of ADRs that occur nationwide with the medicine registered in their name, thus providing quality information in the reports. Access to this system is through secure logins, which will be provided to registration holders after submission of the application on pv@dra.gov.pk. Two user name accounts will be provided to each registration holder. For further details please go through "***Industry E reporting Manuel***". Registration holders have to submit the ICSRs as per the timelines defined in Pharmacovigilance Rules, 2022.

Registration holders of therapeutic goods can assess the Industry E reporting system through the following link:

https://industryereporting.who-umc.org/

### *F. CIOMS Form (For Registration holders)*

In 1986, CIOMS set up its first Working Group on pharmacovigilance, a *Working Group on International Reporting of Adverse Drug Reactions* to explore means of coordinating and standardizing international adverse drug reporting by pharmaceutical manufacturers to

regulatory authorities. The Working Group devised a method for reporting by manufacturers of suspected adverse drug reactions which included standardized definitions, procedures and format. The report contains the CIOMS reporting Form 1, which for the first time set the minimum standard for reporting.

Since the launch of Industry E-reporting, those registration holders who have no facilities to generate reports have to manually enter the data in the Industry E-reporting system. However, in unavoidable circumstances or in case of non-functioning of the Industry e-reporting system, such reports can be sent in hard format on CIOMS Form-I **(Annexure D)** to NPC, DRAP, Islamabad on the following mailing address.

**National Pharmacovigilance Centre**
Division of Pharmacy Services
Drug Regulatory Authority of Pakistan
Prime Minister's National Health Complex
Park Road, Islamabad
Phone No: +92-9255910
Email Address: npc@dra.gov.pk
Website: www.dra.gov.pk

## *G. E2B XML Reporting (For Registration holders)*

After the launch of the Industry e-reporting system, the only system to report E2B XML files to NPC is to upload those files in the Industry e-reporting system by the registration holders themselves. However, in unavoidable circumstances or in the case of non-functioning of the industry e-reporting system, the E2Bxml files (R2 or R3) should be sent to NPC's official email address: npc@dra.gov.pk as per the timelines provided in the Pharmacovigilance Rules, 2022.

## *H. Reporting through VigiFlow (By PPC, PHPs and hospitals).*

VigiFlow is the National database used by NPC, DRAP. Logins of VigiFlow are being provided to POs of Provincial Pharmacovigilance Centres, Public Health Programmes and Hospitals. VigiFlow is adopted as a uniform ADR reporting tool in the country. Therefore, provincial pharmacovigilance centres (PPC), Public Health Programmes and Hospitals would have to report the ADRs/AEs and AEFI through the VigiFlow database. When deployed in hospitals, the VigiFlow should only use for reporting ADRs not for any other purpose.

## 4.5 Where and how to report?

| S. No | Name of Stakeholder | Means of Reporting | Where to Report |
|---|---|---|---|
| 1 | Provincial Pharmacovigilance Centres | Uniformed ADRs reporting tool of VigiFlow | NPC, DRAP |
| 2 | Public Health Programmes | Uniformed ADRs reporting tool of VigiFlow | NPC, DRAP |
| 3 | Registration Holders | Through the Industry E Reporting system<br><br>In the case of the non-functioning of the system, then<br>▪ EB2 XML (Email reporting)<br>▪ CIOMS Forms (Mailing Address) | NPC, DRAP |
| 4 | Public Hospitals and Private Hospitals | ▪ Preferably through the uniformed ADRs reporting tool of VigiFlow. | Provincial Pharmacovigilance Centre |
| 6 | Therapeutic goods sale point | Means of reporting established by PPC. | Provincial Pharmacovigilance Centre |
| 7 | Healthcare Professionals | Med Vigilance E-Reporting System (E-Forms)<br>VigiMobile Application<br>Med Safety Application<br>Yellow Form<br>Telephone or Email<br><br>Means of reporting of PPC or Registration holder of therapeutic goods | NPC, DRAP<br><br><br><br><br>Provincial Centre or Registration Holders |
| 8 | Patients | Med Vigilance E-Reporting System (E-Forms)<br>VigiMobile Application<br>Med Safety Application<br>Yellow Form<br>Telephone or Email<br><br>Means of reporting of PPC or Registration holder of therapeutic goods | NPC, DRAP<br><br><br><br><br>Provincial Centre or Registration Holders |

## 4.6 When to report?

The patient as the case may be healthcare professionals should report a serious AE or AEFI as soon as possible to the NPC, PPC or registration holders. Sometimes, the AE might be unexpected and might be posing harm to other patients. Therefore, prompt reporting will be helpful to minimize harm to other patients. Further, the non-serious/mild AEs should also be reported at the earliest.

There are defined timelines of reporting in Pharmacovigilance Rules, 2022 for other

stakeholders such as provincial pharmacovigilance centres, public health programmes, hospitals and registration holders as that is summarized under.

| S. No | Name of Stakeholder | Non-Serious | Serious | Where to Report |
|---|---|---|---|---|
| 1 | Provincial Pharmacovigilance Centres | 30 Days | 15 days | NPC, DRAP |
| 2 | Public Health Programmes | 30 Days | 15 days | NPC, DRAP |
| 3 | Registration Holders | 90 Days | 15 days | NPC, DRAP |
| 4 | Public Hospitals & Private Hospitals | 30 Days | 15 days | Provincial Centre |
| 5 | Healthcare Professionals | As per convenience | As soon as possible | NPC, DRAP<br>Provincial Centre<br>Registration holders |
| 6 | Patients | As per convenience | As soon as possible | NPC, DRAP<br>Provincial Centre<br>Registration holders |

## 4.6 What Happens to Reports?

1. *Hospital:* A pharmacovigilance officer (PO) working in hospitals needs to collect all serious and non-serious AEs/ADRs from patients and other healthcare professionals. At first, the ADR/AE is documented by giving it an identification number in a register. The ADR/AE is checked for data quality of essentially required and mandatory information. If follow-up information is required, healthcare professionals and patients can be contacted. The PO performs the initial causality assessment of the report. The report is then presented before the pharmacovigilance committee of the hospital for assessment and action. When the causality of the report is reviewed by the pharmacovigilance committee it is sent to PPCs as per the reporting timelines provided in the Pharmacovigilance Rules, 2022. In case the hospital is a sub-regional centre and is integrated into the National PV system; then, the PO should enter the report into VigiFlow, by properly coding through terminologies such as MedDRA and WHO-Drug.

2. *Provincial Pharmacovigilance Centres (PPC):* POs at PPC should first document the ADR/AE report by assigning a unique identification number in the register. Subsequently, reports should be checked for mandatory and essentially required information. If information is missing, POs should contact the HCP, patient, therapeutic goods' sale point or PO/Focal Person in the hospital. Accordingly, the POs at PPCs perform the initial causality assessment and present the case before the Provincial Pharmacovigilance Committee, which reviews the causality assessment. In other words,

PPCs perform the complete assessment of individual reports that will be discussed in detail in the respective section. If PPC is integrated into the National PV database, the POs at PPC should accordingly enter the report into VigiFlow using terminologies such as MedDRA and WHO-Drug and transfer these reports as per reporting timelines provided in the Pharmacovigilance Rules, 2022. If a PPC does not have the logins of VigiFlow, the reports should be submitted manually in hard format with the consent of NPC, and DRAP.

3. *Public Health Programme (PHP):* POs of PHP working at the treatment sites collect the reports and send these to the provincial chapter of PHP, which after assessment sends 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 as it may desire. This panel performs the causality assessment of the collected reports and signal detection of programme-specific drugs. If PHP is integrated into the National PV database, the data is entered directly in VigiFlow using the most appropriate terminologies. If the PHP is not integrated the reports are manually shared with NPC-DRAP.

4. *National Pharmacovigilance Centre (NPC):* NPC collects ADR/AE/AEFI reports from patients, healthcare professionals, provincial pharmacovigilance centres, public health programmes, and registration holders. POs at NPC, at first check the report for mandatory and essentially required information. If the ADR/ AE/AEFI have missing mandatory information, the reporter is contacted. The POs also contact the reporter for more information in case of serious ADRs/AEs/AEFIs. The reports which are received through VigiFlow from PPCs, PHPs and via industry e-reporting systems through registration holders are also checked for data quality. Further, the reports which are received online from HCPs and patients are also properly coded and checked for data quality. The POs at NPC also enter the report into VigiFlow using terminologies if the report is received in hard format from the reporter. The assessment of the complete cases is carried out by the Pharmacovigilance officer of the NPC individually or by causality assessment groups which perform the complete causality assessment of new reports or review the causality assessment already performed at the hospital, PPC or PHP level. In other words, NPC performs a complete assessment of individual reports

that will be discussed ahead in detail. The database is checked for new signals by pharmacovigilance officers individually or by the signal review groups followed by proper validation, prioritising, assessment and confirmation of the signal for further action. The individual case safety reports in the National PV database are accordingly transferred to the VigiBase, the database of WHO-UMC. The NPC with the advice of the NPC may initiate the following action:

- ✓ New warning/ contraindication,
- ✓ Remove indication of therapeutic goods for specific diseases or age groups,
- ✓ Advice on how the therapeutic good should be used, or
- ✓ In some cases, even stop the use of therapeutic goods.
- ✓ Overall, the processing at NPC, DRAP is to monitor the safety of therapeutic goods in order to optimize the use of therapeutic goods with minimum harm to the patient.

## 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 staff of the centre and by using the services of expert 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 for 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: As per definition.

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 the identification, characterization, assessment, and prioritization of risks, followed by coordinated and economical application of resources to, minimize, monitor, control and prevent the probability and impact of unfortunate events.

3. *Drug Regulations:* After approval of a therapeutic good, all available domestic information is continuously monitored by the NPC-DRAP, PPCs and registration holders. The pharmacovigilance data of Pakistan can be useful for updating the prescribing information/package inserts, recalling or withdrawing a product, imposition of restrictions on use, or cancellation of registration of therapeutic goods.

4. *Risk Communication and Information:*

News bulletins/Newsletters or therapeutic goods safety alerts are important sources for the dissemination of information to healthcare professionals. In the case of an emergency, the NPC and registration holders may send direct healthcare professionals communication (DHPC) to inform the healthcare professional about the risks.

5. Education and Feedback:

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

CHAPTER 5

# 5. TYPES OF SURVEILLANCE IN PAKISTAN.

## 5.1 Passive Surveillance

Passive surveillance is a process where healthcare professionals or patients send spontaneous reports, describing an adverse drug reaction or event after one or more therapeutic goods are administered, to the registration holders or regulatory authority. 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 the entire population and monitors adverse effects in patients that occur in real-time practice. Although it is the 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.

*5.1.1 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 (NPC or PPC in the 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”.

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

Passive surveillance is the primary method of reporting, being 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.

## 5.2 Active Surveillance

Active Surveillance is a process that involves, enhanced or targeted monitoring for certain events or therapeutic goods and seeks to ascertain completely the number of adverse events or adverse drug reactions through a continuous pre-planned process. 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 Schemes (Sentinel sites) Prescription/ Drug Event Monitoring and Registries.

### *5.2.1 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.

### *5.2.2 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.

*5.2.3 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's data of interest, can collect a set 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.

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

*5.3.1 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, constitutes a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. These studies are best used to examine the prevalence of disease at a one-time point or to examine trends over time when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilised when exposures do not change over time.

*5.3.2 Case-Control Study*

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

*5.3.2 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.

## 5.4 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 PASS is the interventional study of Phase IV origin then provisions of Bio-Study Rules, 2017 shall apply. In some instances, pharmacodynamics and pharmacokinetic studies might be conducted to determine whether a particular dosing regimen can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicinal product in clinical practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and therapeutic drug monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from preapproval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include older persons, pregnant women, children or patients with renal or hepatic disorders. Children, older persons and persons with co-morbid conditions may metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials may be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

## 5.5 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 determine rates of adverse events. DUS has been used to describe the effect of regulatory actions and media attention on the use of medicinal products in everyday medical practice, to examine the relationship between recommended and actual clinical practice, to monitor medication errors and to determine whether a medicinal product has the potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. DUS are particularly useful as a first step in the design of post-authorisation safety studies, to obtain a sufficient understanding of the characteristics of the user population of the medicinal product under study and the determination of the most appropriate comparator as well as important potential confounders to consider. They are also useful to provide a first indication of the level of public health impact anticipated if there is a true causal association between the exposure of interest and an adverse event, for example given the size of the population exposed, the extent of off-label use, and so on.

## 5.6 Structure in Pakistan.

In Pakistan, the routine method used for data collection is spontaneous reporting wherein the healthcare professionals voluntarily report the ADRs or AEs or AEFIs to NPC, PPCs or PHPs. In some instances, the Clinical Pharmacy & Pharmacovigilance Officers (CPPOs) in hospitals may be advised to actively report the ADRs or AEs, especially with high-alert medications or other drugs.

Similarly, as per Rules 7 (4) and 7 (6) of Pharmacovigilance Rules, 2022 public health programmes have to conduct pharmacoepidemiological studies and cohort event monitoring studies in Pakistan with the drug used in that programme.

Likewise, as per Rule 11 (7) of Pharmacovigilance Rules, 2022, registration holders could either voluntarily initiate the Post-Authorisation Safety Study (PASS) or it may be imposed by the registration board or by NPC on the advice of PRAEC. The said rule is reproduced as under:

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

The Pharmacovigilance Risk Assessment Expert Committee (PRAEC) under Rule. 10 (1) (f) of the Pharmacovigilance Rules, 2022 may *also recommend to the Registration Board to impose obligations on the registration holder to conduct post-authorization safety and efficacy studies if it is found that during the evaluation of data, there is a safety concern with the use of the drug.*

Further details regarding Post-Authorization Studies conducted by Registration holders in Pakistan can be found in Module 7 of "Guidelines on Good Pharmacovigilance Practices for Registration Holders".

## 5.7 Criteria for initiation of active surveillance.

The criteria for the start of active surveillance varied across the country due prevalence and nature of the disease, the types of medicines registered and the severity of adverse events. The NPC-DRAP may consider the following two criteria i.e. for the initiation of active surveillance in Pakistan.

1. The following type or nature of medicine and vaccine may be subjected to active surveillance or additional monitoring–
    - Introduction of new vaccine or biological including monoclonal antibodies;
    - New active substance;
    - New drugs for the treatment of HIV, tuberculosis, malaria and hepatitis;
    - Orphan drugs for the treatment of rare diseases.
    - If active surveillance is a condition of registration; and
    - Medicine was authorized under exceptional circumstances or emergency conditions or EUA.
2. Sometimes, active surveillance is initiated due to adverse events or other conditions.
    - Post Authorization safety studies initiated by registration holders are recommended by NPC-DRAP
    - Adverse events of special interests (AESIs) of new vaccines;
    - Serious event with unknown occurrence;
    - Serious hepatic, renal, haematological and dermatological adverse events.
    - Rare events;

- New indication; and
- Events affecting specific populations such as children, pregnant and elderly.

## 5.8 Stakeholders involved in active surveillance in Pakistan.

The NPC-DRAP can undertake active surveillance through alliance or networking with several pharmacovigilance stakeholders in Pakistan.

- With a network of potential sentinel hospitals;
- Alliance with the medical universities having attached teaching hospitals;
- Through provincial Pharmacovigilance Centres by assigning the task to pharmacovigilance officers working in hospitals;
- Through Public Health Programmes at potential treatment sites for programme-specific vaccines and for new drugs of HIV, tuberculosis, malaria and hepatitis and
- Active surveillance initiated by registration holders voluntarily or as per the direction of NPC.

# CHAPTER 6

# 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 another way, it is a structured approach to determine the relationship between a reported event and a suspected drug.

The rationale for the causality assessment is the following: to define the relationship Drug-ADR; and help in the 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 measurements of relationship likelihood |
| Classify relationship likelihood | Distinguish valid from invalid cases |
| Mark individual case reports | Prove the connection between a drug and an 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); and
- 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 methods. It is 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**.** 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 the total score is ranked on four probability scales, the answer of the aggregate score is the result of causality assessment:

i. "*Definite" (Certain):* if the score is more than 9.

ii. *"Probable":* if the score is between 5 -8.

iii. *"Possible":* if the score is between 1-4.

iv. "*Doubtful" (Unlikely):* if is less than 1.

| S. No | Question | Yes | No | Don't Know | Score |
|---|---|---|---|---|---|
| 1. | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | |
| 2. | Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | |
| 3. | Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 | |
| 4. | Did the adverse event reappear when the drug was re-administered? | +2 | -1 | 0 | |
| 5. | Are there alternative causes that could on their own have caused the reaction? | -1 | +2 | 0 | |
| 6. | Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | |
| 7. | Was the drug detected in blood or other fluids in concentrations known to be toxic? | +1 | 0 | 0 | |
| 8. | Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 | |
| 9. | Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 | |
| 10. | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | |

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.*

## 6.4 WHO-UMC system for standardised case causality assessment.

The WHO-UMC system for standardised case causality assessment 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 a combined assessment considering 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 judgement may therefore differ. Other algorithms 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 a drug). Based on the above criteria the ADR can be classified into the following six categories.

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

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

*All points should be reasonably complied with

*6.4.1 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 the 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 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 Type 1 allergic reactions 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, increased 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, for example, hepatitis or tendonitis then that's an observable clinical condition. It's pathological in contrast, for the "probable" category i.e. reaction symptoms which 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 a rechallenge is carried out, the patient should have first recovered from the clinical event

by 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 chances of a false positive outcome. 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 a lack of recognition that an illness following the exposure to the drug previously was an adverse reaction until it happened again or lack of a proper record of the previous reaction.

*6.4.2 Probable/Likely.*

The assessment criteria for the "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 required

***Further Explanation of the term "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 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.

*6.4.3 Possible.*

The assessment criteria for the "possible" category are as under:

- Event or laboratory test abnormality, with a 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 the "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 a 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. The 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 the lack of information about the outcome when the suspect drug was stopped, which 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.

*6.4.4 Unlikely.*

The assessment criteria for the "Unlikely" category are 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 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.

*6.4.5Conditional/Unclassified.*

The assessment criteria for the "Conditional/Unclassified" category are as under:

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

***Further Explanation of the "Conditional/ Unclassified" category.***

"Unclassified" ADR reports usually contain very little information. Sadly, we receive several reports that have very little information in them. For example, we might have reports which 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.

*6.4.6 Unassessable/Unclassifiable.*

The assessment criteria for the "Unassessable/Unclassifiable" category are as under:

- Report suggesting an adverse reaction
- Cannot be judged because the 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.

A case series is a group of patients with similar exposure (drug) and similar outcomes (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 a 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. Logical analysis is applied which is a development from a single case assessment. However, it is important to first carry out a single case assessment of the reports in the case series.

A set of criteria was proposed by Sir Austen Bradford Hill 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 there is disproportionality.
2. *Temporal relationship*: the event should commence after the drug was started and fit with the pharmacology of the drug or host responses (Reasonable time to onset.)
3. *Consistency:* It means that reports are received from a range of reporters in the case of National databases or, in international databases from 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, if 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 the suspected reaction fit with existing knowledge. For example, we know that furosemide can cause loss of potassium but cannot retain it. So if someone has reported high blood potassium levels with furosemide, then there would be other causes of high potassium levels. 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 an event on dose decrease and the onset of the event on dose increase. It is good evidence of causality but may not be observable in some situations

7. *Specificity*: Specific AE is not the cause of ADR. Many adverse reactions have multiple causes, for example, headache, abdominal pain, and 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 intervals.

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

### *6.6.1 Healthcare Professionals*

If trained, should perform the initial causality assessment of individual reports either by WHO-UMC or Naranjo method, when submitting a report to NPC, PPCs or registration holders.

### *6.6.2 Hospital*

Pharmacovigilance officers, at the hospital, perform the initial causality assessment of AEs or AEFIs. The causality assessment of each report is reviewed by the pharmacovigilance

committee of the hospital using the WHO-UMC method. Subsequently, these reports are submitted to PPCs.

*6.6.3 Public Health Programme*

Perform the causality assessment of AE and AEFIs as per the WHO-UMC method. This is accordingly reviewed by the Expert Safety Review Panel (ESRP) and submitted to NPC.

*6.6.4 Provincial Pharmacovigilance Centre*

Pharmacovigilance officers perform the causality assessment of reports received directly from therapeutic goods' sale points, HCPs and patients. Whereas, the causality of reports received from hospitals is reviewed. Accordingly, it is reviewed by the provincial pharmacovigilance committee and submitted to NPC. PPCs also perform the causality assessment of the case series as per Bradford Hill Criteria.

*6.6.5 National Pharmacovigilance Centre:*

At the NPC level, the causality assessment is performed by pharmacovigilance officers either individually or in the form of groups. The causality assessment of complete cases received directly from HCPs and patients is performed; whereas, the causality assessment of the ADRs submitted by the provincial pharmacovigilance centres, public health programmes and registration holders is reviewed. Furthermore, the NPC has developed inclusion criteria based on priority levels in case if higher number of reports are received directly in the National Centre. The NPC also performs the causality assessment of the case series as per Bradford Hill criteria. Once done, the reports are then transferred to WHO-UMC VigiBase (Global database).

## 6.7 Assessment of Medication Errors/ Near Miss.

Quality improvement & patient safety programs within healthcare organizations must include mechanisms for reporting medication errors, examining and evaluating causes of errors, analyzing aggregate data to determine trends and making necessary changes within their healthcare delivery system to prevent errors from occurring.

Timely analysis of the medication error reports from clinical settings could identify opportunities for quality improvement and system changes. In general, there are two steps for error analysis,

- The first is to identify individual problems and deficiencies in an event that can lead to the error; and
- The second is to analyze the defective design of the system.

Institute for Safe Medication Practices (ISMP) emphasizes that the cause of a medication error is rarely the fault of a single person practising within the vast and complex medication-use process. Rather, medication errors are often the result of a breakdown of at least 1 of 10 key elements that affect medication use. These key elements are interrelated subprocesses of the 5 core steps in the medication-use process i.e.: medication prescribing, order processing, dispensing, administration, and monitoring.

When performing a root cause analysis, the following 10 key elements that affect the core medication use steps should be thoroughly evaluated to determine the cause of the error:

1. **Patient information** that is accessible and accurate (e.g. demographics, lab reports, history etc.).
2. **Drug information** that is accessible, accurate, and usable (e.g. information on how to safely order, dispense, administer a drug and monitor its effects).
3. **Communication** between providers that is consistent and not complicated (e.g. medication information communicated during hand-offs between shifts or when the patient is transferred or discharged).
4. **Drug labelling and packaging** that facilitates safety and the consistent use of appropriate nomenclature (e.g. products that are look-alike or sound-alike – LASA).
5. **Drug storage and stock** that facilitates appropriate distribution with standardized drug concentrations and administration times.
6. **Drug device acquisition:** methods that ensure proper use and monitoring (e.g. infusion pumps, syringe pumps etc used for administration of medicines).
7. **Work environments:** that provide an appropriate workload and limit unfavourable conditions such as poor lighting, noise, and interruptions.
8. **Staff competency** That is assessed and can be improved with opportunities for continuing education.
9. **Patient education:** That is accurate and provided consistently.
10. **Medication use processes** that are evaluated for quality and can be redesigned

to improve safety.

## 6.8 Tools for pharmacovigilance.

*6.8.1 Tools for Reporting & Collection*

1. ***Suspected Adverse Drug Reaction Reporting Form*:** Refer to Chapter 4, topic **4.3 A** along with "Annex A"

2. ***Med Vigilance E Reporting System- UMC E-Forms Based (for HCPs and Patients):*** Refer to Chapter 4, Topic **4.3 B** along with "Annexure B".

3. ***VigiMobile App*: *(For healthcare professionals and patients):*** *Refer to Chapter 4, Topic **4.3C***

4. ***Med Safety Application (For HCPs and patients):*** Refer to Chapter 4, Topic **4.3D** along with "Annexure C".

5. ***Industry E-Reporting System: (For Registration holders):*** Refer to Chapter 4, Topic **4.3E.**

6. ***CIOMS Form-I (for Registration holders):*** Refer to Chapter 4, Topic **4.3F**, "Annexure-D".

7. ***E2B XML reporting (for Registration holders):*** Refer to Chapter 4, topic **4.3G.**

8. ***Telephone No: 051-9255981*** *and email address: npc@dra.gov.pk*

*6.8.2 Tool for assessment & signal detection.*

1. ***Naranjo Algorithm for Causality Assessment*:** Refer to Chapter 6 and Topic 6.3.

2. ***WHO-UMC System for Standardised Case Causality Assessment*:** Refer to Chapter 6 and Topic 6.4.

3. ***Bradford Hill Criteria for Causality Assessment of Case Series:*** Refer to Chapter 6 and topic 6.5

4. ***VigiLyze for Signal Detection*:** Refer to Chapter 10 and Topic 10.2.4.

*6.8.3 Tool for data storage and coding.*

1. ***National Database in the Form of VigiFlow*:** Refer to Chapter 10 and Topic 10.2.3

2. ***Medical Dictionary for Regulatory Activities.*** Refer to Chapter 10 and Topic 10.3

3. ***WHO-Drug*:** Refer to Chapter 10 and Topic 10.2.1

# CHAPTER 7

# 7. SIGNAL MANAGEMENT.

## 7.1 Definition of Signal

World Health Organization define a signal as "*reported information on a possible causal relationship between an adverse event and a drug or a therapeutic good, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action"*

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

"*Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action".*

## 7.2 Responsibilities of NPC, DRAP.

As per clause (iv) of sub-rule (1) of Rule 4 of Pharmacovigilance Rules, 2022 the NPC shall monitor the National database to determine whether there are new risks and whether those risks impact the risk-benefit balance of drugs or therapeutic goods and also periodically evaluate the database for new signals and submit these signals to PRAEC under clause (viii) of sub-rule (1) of Rule 4 of Pharmacovigilance Rules, 2022 for advice. Likewise, as per clause (b) of sub-rule 3 of Rule 6 of Pharmacovigilance Rules, 2022, the Pharmacovigilance Officers at NPC shall perform the signal detection and subsequent signal management process either in groups or individually. The pharmacovigilance officer undertakes the complete signal management process at the National level, i.e. signal detection, management, prioritization, evaluation, confirmation and risk communication. The signal is then submitted to PRAEC for necessary advice which may prioritize or further assess if required.

NPC also take necessary action on the confirmed signal in light of the advice of PRAEC and subsequently recommends the necessary regulatory or risk minimization action to concerned Boards/ Committees/ Divisions of DRAP for implementation within Pakistan with the advice of the NPC.

## 7.3 Signal Management Process

A set of activities performed, 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, to determine whether there are new risks associated with an active substance or a therapeutic good or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

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

## 7.4 Signal Management Process

Signals detected through any sources should be handled according to NPC's signal management process, considering the general principles outlined below. The below-mentioned steps are undertaken jointly or individually by the pharmacovigilance officers or signal review groups of the NPC. The signal management process covers all steps from detecting signals to recommending action(s) as follows:

*7.4.1 Signal Detection*

The process of looking for and/or identifying signals using data from any source. Signal detection may involve a review of ICSRs, statistical analyses, or a combination of both, depending on the size of the data set. When it is not relevant or feasible to assess each case (e.g. signals detected from published studies, healthcare record data), an assessment of aggregated data should be considered.

Signal detection can be of two types: *hypothesis-driven signal detection* (qualitative method) wherein an assessor proposes either the new causal relationship between drug

and event or a new aspect of a known relationship; and *Data mining-data-driven signal* detection (quantitative method), wherein a signal is either automatically or manually found in a large database using statistical tools. Signals 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 the 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, the computation of the information component (IC) is based on prior and posterior probabilities. According to WHO-UMC, the IC value 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. Likewise, reporting odds ratio (ROR) and proportional reporting ratio (PRR) are methods of disproportionality and are available in the VigiLyze database. Each method used for signal detection has its advantages and disadvantages, and no one method can be considered the gold standard.

*7.4.2 Signal Validation:*

The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. This evaluation should take into account

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

When a new signal is detected, first it is validated in order to verify that the available data supports the new causal relationship. It is then followed by a complete assessment of the signal. In case of spontaneous adverse drug reaction reports it is 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, gender, current and past medical condition, genetics, pregnancy, lifestyle factors, allergy, previous major illness);
- History of the registration of drugs/classes across the globe;
- Case series data in case of case series (demographic, pattern, age, re-challenge, de-challenge);
- Determining the strength of association, contributing factors and performing preventability method;
- Analysis of data from Risk Management Plans and PBRER along with Information on causal relationships from literature/ studies;

- Root cause analysis through Ishikawa Diagram, and assessment of similar data in global databases and other countries' databases; and performing disproportionality analysis.
- Information from clinical trials;
- Actions taken if any by other regulatory authorities.

*7.4.3 Signal Prioritization*

The process, continuously performed throughout signal management, aims to identify those signals suggesting risks with potential important patients or public health impact or which may significantly affect the risk-benefit balance of the therapeutic good and thus require urgent attention and management without delay. In some circumstances, signals that could cause media attention and/or public concerns (e.g. adverse events following mass immunisation) may deserve special attention. The timeframe for further management of the signal will depend on the prioritisation. The prioritization is performed by PRAEC.

*7.4.4 Signal Assessment*

The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or drugs or therapeutic good or whether known risks have changed. This review may include nonclinical and clinical data and should be as comprehensive as possible regarding the sources of information. A complete signal management process is performed at the NPC level including assessment. However, if further assessment is required the process is undertaken by the PRAEC of DRAP.

*7.4.5 Recommendation for Action*

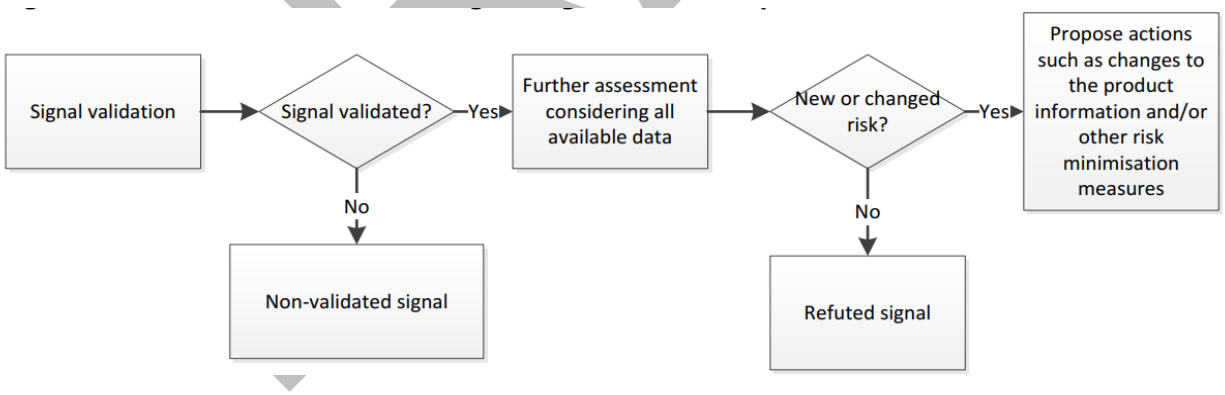
The effect of the newly identified risks is evaluated after properly performing the benefit-risk assessment of the therapeutic goods and subsequent risk minimization actions are initiated by NPC with the advice of PRAEC. The recommendations of NPC in the form of regulatory actions or risk minimization action are communicated to the concerned Board, Committee or Division of the DRAP or other pharmacovigilance stakeholders in Pakistan.

*7.4.6 Exchange of Information:*

NPC-DRAP, PPCs and registration holders accordingly communicate among themselves and with healthcare professionals, media patients etc. about the newly detected signals and the decisions by NPC in the matter.

## 7.5 Signal Management at NPC.

The Pharmacovigilance Officers or Signal Review Group constituted at the NPC performs the complete signal management process from the step of signal detection to the step of recommendation of regulatory or remedial action with the advice of PRAEC. During the process, the POs may search the database through VigiLyze for any rise in IC value (data mining driven signals or quantitative method), or if any new information of possible causal relationship has been found (hypothesis-driven signal or qualitative method). The signal is then validated by finding information in the available documents, potential causal relationships or a new aspect of known association. If a signal poses a serious threat to public health it is prioritised. The validated signals are further evaluated considering all available evidence including nonclinical and clinical data. After assessment, the signals are either confirmed or refuted. Subsequently, the signals are presented in the forthcoming meeting of PRAEC, which after deliberation and assessment (if required) may advise the NPC about the initiation of regulatory actions or risk minimization measures.



CHAPTER 8

# 8. SAFETY COMMUNICATIONS & RISK MINIMIZATION MEASURES

## 8.1 Safety communication

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

## 8.2 Content of safety communication.

Contents include important new information; reason for initiating safety communication; any recommendations to healthcare professionals and patients; information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL); additional information about the use of the therapeutic good; a list of literature references; and a reminder about reporting ADRs as per guidelines.

Good communication is the one that is issued timely; targets the right audience; uses appropriate channels; provides essential and useful information; uses appropriate language, and is truthful. Therefore, it contributes to risk minimization; helps HCPs to make wise decisions in their choice of therapeutics; and fosters trust in Regulatory Authorities, Provincial Centres and Registration holders.

## 8.3 Responsibilities of NPC, DRAP.

As per clause (xi), sub-rule (1) of Rule 4 of Pharmacovigilance Rules, 2022, the function of NPC is to ensure that the public is given important information on pharmacovigilance concerns and risks relating to the use of therapeutic goods in a timely manner through one of

the following modes i.e. therapeutic goods safety alerts, healthcare advisory or newsletters on a website and through other means of publicly available information as necessary.

Likewise, as per the relevant clauses of sub-rule 3 of Rule 6 of the Pharmacovigilance Rules, 2022, the responsibilities of pharmacovigilance officers at NPC include processing of therapeutic goods safety alerts, communication and coordination with pharmacovigilance stakeholders and communication of risk minimization measures.

Clause (b), sub-rule (1) of Rule 10 of Pharmacovigilance Rules, 2022 states that on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, PRAEC may advise NPC to inform pharmacovigilance stakeholders through available means, where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the indication of therapeutic goods etc. is necessary.

Communication with WHO-UMC and WHO headquarters will be managed by NPC-DRAP. The NPC-DRAP is responsible for publishing/ communicating any findings from the National database to the media; whereas, other stakeholders are required to get prior approval from NPC-DRAP to publish or communicate any data or information originating from the Pharmacovigilance programme of Pakistan.

## 8.4 Target audiences

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

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

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

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

## 8.5 Means of safety communication (Risk Communication Plan of NPC)

Following are some of the means adopted for safety communication as a part of the Risk Communication plan:

*8.5.1 Direct healthcare professional's communication (DHPC):*

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

*8.5.2 Documents in lay language:*

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

*8.5.3 Press communication:*

Press communication includes press releases and press briefings which are primarily

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

*8.5.4 Website:*

A website is a key tool for members of the public (including patients and healthcare professionals) and other stakeholders actively searching the internet for specific information on therapeutic goods. NPC-DRAP as well as registration holders 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. DRAP has allocated a dedicated portion of its website for safety that contains necessary information related to safety alerts, reporting and the basics of the pharmacovigilance system.

*8.5.5 Social media and other online communications*

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

*8.5.6 Therapeutic good safety alert*

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

*8.5.7 Newsletter:*

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

*8.5.8 Inter and Intra country communication:*

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

*8.5.9 Advisories:*

NPC, DRAP and other Divisions of the Drug Regulatory Authority of Pakistan also prepare advisories for different stakeholders about the safety, quality and availability of therapeutic goods, which after approval are disseminated through different means to pharmacovigilance stakeholders.

*8.5.10 Responding to enquiries from the Public:*

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

## 8.6 Risk minimization measures

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

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

The NPC recommend and implements risk minimisation measures to mitigate identified risks and enhance the safe use of drugs or vaccines as per the advice of PRAEC.

## 8.7 Routine and additional risk minimization measures.

Risk minimisation measures may consist of *routine risk minimisation* or *additional risk minimisation measures*.

Routine risk minimisation applies to all drugs and involves the use of the following tools

i. The summary of product characteristics/ prescribing information;

ii. The labelling (e.g. on inner and outer cartons);

iii. The package leaflet;

iv. The pack size(s);

v. The legal status of the product.

- Restricted medical prescription
- Special medical prescription

Safety concerns of a medicinal product are in normal conditions adequately addressed by

routine risk minimisation measures. In some exceptional cases, however, routine risk minimisation measures will not be sufficient for some risks and therefore additional risk minimisation measures will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product. When additional risk minimisation activities are needed, safety concerns are to be prioritised in terms of frequency, seriousness, severity, impact on public health and preventability. Likewise, careful consideration is then to be given to whether the goal/aim can be reached with routine minimisation activities, and, if not considered sufficient, which additional minimisation measure(s) is (are) will be the most appropriate. Additional risk minimisation activities/measures should only be introduced when they are deemed to be essential for the safe and effective use of the medicinal product and should be developed and provided by suitably qualified people.

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

i. Educational programmes
   - For healthcare professionals
   - For patients;
   - Patient alert cards;

ii. Controlled access programmes; and

iii. Other risk minimisation measures
   - Controlled distribution system
   - Pregnancy prevention programme
   - Direct Healthcare Professional Communication (DHPC)

Further details regarding routine and additional risk minimization measures are available in DRAP Guidelines on Good Pharmacovigilance Practices for Registration Holders.

# CHAPTER-9

# 9. TRAINING, CAPACITY BUILDING AND AWARENESS CAMPAIGN.

## 9.1 Responsibilities as per Pharmacovigilance Rules, 2022.

*9.1.1 The Function of NPC as per Pharmacovigilance Rules, 2022.*

As per clause (ix) of sub-rule (1) of Rule 4 of the said rules, the NPC should take appropriate measures to encourage PPCs, PHPs, registration holders, patients and healthcare professionals to report ADRs and AEs to the NPC.

As per clause (x) of sub-rule (1) of Rule 4 of the said rules, the NPC should facilitate patient and healthcare professional reporting through the provision of alternative reporting formats in addition to the hard format of reporting forms.

Likewise, as per clause (xiii) of sub-rule (1) of Rule 4 of the said rules, the NPC should arrange training sessions for POs of PPCs and PHPs for proper reporting of ADRs and AEs through the National database.

Similarly, as per clause (xv) of sub-rule (1) of Rule 4 of the said rules, the NPC should take necessary measures for training or capacity building of the POs of NPC regarding data collection, causality assessment, signal detection and risk management etc.

*9.1.2 The Function of provincial and hospital centres as per rules.*

As per clause (h) of sub-rule (4) of Rule 5 of the Pharmacovigilance Rules, 2022, the provincial pharmacovigilance centres (PPCs) should arrange awareness sessions, campaigns or take other necessary measures to sensitize healthcare professionals and patients to promote spontaneous reporting culture in the province and administrative territory.

As per clause (i) of sub-rule (4) of Rule 5 of the said rules, the PPCs should arrange pharmacovigilance training for public sector hospitals of the province and coordinate for their proper functioning.

Similarly, as per sub-rule (3) of Rule 8 of Pharmacovigilance Rules, 2022, the Pharmacovigilance Committee of the hospital shall develop spontaneous reporting trends and culture in the hospitals by sensitizing health care professionals, medical students and patients.

## 9.2 Training and Capacity Building.

National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, at first, conducts necessary pieces of training for pharmacovigilance officers working in NPC on data collection, causality assessment, signal detection and risk management. NPC also identifies other key areas where training is required at the National level. To this end, DRAP either invites international trainers for the purpose of training in Pakistan or sends their pharmacovigilance officers abroad to participate in international training/courses. In this regard, the NPC develops a pharmacovigilance training plan and updates it at least once a year and keeps a record of staff training. During the recent focus on the virtual era of communication, many of the training sessions for pharmacovigilance officers of NPC were arranged virtually.

The pharmacovigilance officers of the NPC once trained provide further training to stakeholders such as provincial pharmacovigilance centres (PPCs), public health programmes (PHPs), healthcare professionals and registration holders. The training provided to provincial pharmacovigilance centres and public health programmes is focused on the collection, validation and data entry of adverse events/ reactions in the VigiFlow database. In addition, NPC also coordinates with PPCs and PHPs for the establishment of their pharmacovigilance centres. To this end, DRAP arranges 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, and data entry etc. Sometimes, the NPC-DRAP also arranges training sessions for registration holders on specific guidelines/directives etc, wherein necessary training is provided on pharmacovigilance system establishment in line with Good Pharmacovigilance Practices guidelines.

The NPC-DRAP also arranges different workshops, seminars, symposiums, conferences and meetings at the National level, wherein Pharmacovigilance Officers of the NPC, PPCs, and PHPs along with other stakeholders such as registration holders, healthcare professionals and people from academia are invited for sharing of knowledge and learning from other experiences.

PPCs also arrange training sessions for Pharmacovigilance Officers, hospitals and healthcare professionals of the provinces on the identification, assessment and reporting of ADR and AEs. Officers of NPC also participate in these training which are provided at the provincial level. In addition, PPCs also utilize 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 related to VigiFlow data entry and data collection is provided by NPC-DRAP. Pharmacovigilance officers of DRAP also participate in training sessions arranged by PHPs in Pakistan.

Registration holders also properly train their qualified persons at the time of appointment on different pharmacovigilance activities. In addition, healthcare professionals should also be trained as a part of additional risk minimization activities. An awareness campaign for healthcare professionals and patients should also be launched by registration holders.

## 9.3 Awareness Campaign:

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

On World Patient Safety Day, the 17th of September each year, awareness campaigns for healthcare professionals and the public are launched by NPC and PPCs. Different means of the awareness campaign for healthcare professionals and patients are adopted. Academia, public health programmes, hospitals and registration holders also play their part in awareness campaigns on World Patient Safety Day.

The main international campaign that is held annually through social media is MedSafety Week in collaboration with the Uppsala Monitoring Centre. National Pharmacovigilance Centres, regulatory bodies and relevant stakeholders participate through their national centres in this campaign through social media to raise awareness and encourage reporting of side effects and adverse events.

Routine awareness among healthcare professionals can be raised through meetings, symposiums, and face-to-face training. Pamphlets and posters that encourage reporting are also to be circulated in the hospitals to sensitize healthcare professionals. Those healthcare professionals who report more frequently are 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. The NPC and PPCs should also run awareness campaigns for healthcare professionals through print and electronic media, in the form of press-notes in newspapers highlighting the importance of reporting or in the form of short documentaries/videos in electronic media.

Healthcare professionals in hospitals can play a crucial role to increase awareness among patients. Doctors, Pharmacists, and Nurses should properly counsel their patients about the risks of medicines and should encourage patients to consult them in case they experience any untoward event. NPC and PPCs should launch social mobilization and public awareness campaigns both in print and electronic media. Circulation of the pamphlets at times of public gathering is another effective way to increase awareness among the public. In addition, awareness among the general public can also be raised through posters, billboards or educational campaigns. Coordination can also be made with the civil society of Pakistan to arrange marathons, walks or rallies to raise awareness among the general public on World Patient Safety Day.

# CHAPTER 10

# 10. COLLABORATION WITH INTERNATIONAL STAKEHOLDERS.

## 10.1 World Health Organization

The World Health Organization (WHO) is the custodian of the World Health Organization Programme for International Drug Monitoring (WHO-PIDM) which was started in 1968 in the aftermath of the thalidomide tragedy. Membership in this programme is only provided to WHO member countries. Uppsala Monitoring Centre (UMC), Sweden is responsible for providing operational support to WHO-PIDM, whereas, WHO retains full responsibility for 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, the Safety and Vigilance Section is responsible for increasing knowledge of real-life adverse events and coordinates actions taken against adverse events, mitigating risks and protecting against substandard/falsified products. Work areas of Safety and Vigilance are medicine safety, vaccine safety and substandard and falsified medicines. WHO arranges an annual meeting of representatives of National pharmacovigilance centres, issues drug safety alerts among the National centres, and convenes the meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP). WHO also issues pharmaceutical newsletters, wherein new information on the safety and efficacy of medicines, new signals detected and regulatory actions taken by countries are shared and published. WHO has also issued guidelines on different aspects of pharmacovigilance. In Pakistan, NPC-DRAP is responsible for coordinating with WHO on the matter of Pharmacovigilance. There are different collaborating centres of WHO, that are also contributing to pharmacovigilance. Uppsala Monitoring Centre (UMC), Sweden is a WHO collaborating centre that is responsible to the lead operations, acting as a technical partner, database management, analysis, communication, research and training. WHO Collaborating Centre (WHO-CC) in Oslo, Norway is responsible for ATC/ DDD training, whereas, WHO-CC Morocco supports medication errors, training, country support (Francophone, Arabic), and convergence of pharmacovigilance systems. The last one is WHO-CC Lareb, in the 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 the 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. The 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). Its main areas of work are scientific development (*thinking*), provision of technology and support tools (*tools*), and teaching, training and advocacy (*teaching*). It is the custodian of tools such as VigiBase (global database), WHO-Drug, VigiFlow (National database), and VigiLyze. A National centre needs to contact WHO-UMC to get access to VigiBase. Further, UMC also provides VigiFlow, VigiLyze and WHO-Drug subscriptions to National Centres after an agreement between the two parties. The UMC also detects signals in VigiBase, which are at first shared with National centres and subsequently are published in the WHO pharmaceutical newsletter. UMC conducts annual pharmacovigilance training courses at Uppsala, Sweden and also conducts some pharmacovigilance courses in collaboration with pharmacovigilance partners in other parts of the world. In addition, UMC also provides specific training courses on the request of National Centres. UMC also have distance learning training programmes where free online training courses are provided. The National Centre of the country is responsible for coordinating 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 enables the grouping of reported drugs with the same active substance(s); same active moiety(ies); and same Anatomical Therapeutic Pharmacological Chemical (ATC) classification. WHO-Drug is used by Regulatory Authorities, Pharmaceutical Companies, Clinical Research Organizations, PV centres and the 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. The 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 an agreement with WHO-UMC 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 (individual case safety reports) submitted by member countries since 1968. The VigiBase data resource is the largest and most comprehensive in the world and it has been developed and maintained by the UMC on behalf of WHO since 1978. At present, 157 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 computerised 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 2022, VigiBase has over 35 million anonymised reports of suspected adverse effects of medicines (individual case safety reports) suffered by patients.

*10.2.3 VigiFlow*

A web-based ICSR data management system that is available to the National pharmacovigilance centres of the member countries of the WHO Programme for International Drug Monitoring. VigiFlow is compliant with the international ICH E2B standard and is maintained by Uppsala Monitoring Centre in Uppsala, Sweden. Since it is a 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 as 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. It is also equipped with e-reporting wherein healthcare professionals and patients can directly report to the National Centre. The data entered has a complete record in the form of audit and traceability. At the National Pharmacovigilance Centre, the entered ADRs are saved and after assessment are transferred to VigiBase via one click. 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 the new VigiFlow i.e. National, regional/provincial and sub-regional (hospital or divisional level). Furthermore, ADRs can also be

assigned by National centres to regional centres.

*10.2.4 VigiLyze.*

VigiLyze is a powerful search and analysis tool that provides access to more than 30 million ICSRs in VigiBase, submitted by over 152 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 a 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 views i.e. qualitative view and a quantitative view. In a qualitative view, the ICSRs can be viewed in tabular and chart form, filtered by country, region, gender, age etc., and these ICSRs can be exported to an excel sheet and further searched by applying different filters. Whereas, the Quantitative view is equipped with data mining tools such as Information Component (IC) and IC 0.25, that measure the disproportionality of the Drug-ADR combination in VigiBase. It helps in signal detection by applying powerful filters that enable 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 but rather a clinically-validated international medical terminology used by regulatory authorities and the 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); which are further sub-divided into 337 High-Level Group Term (HLGT); 1738 High-Level Term (HLT); 25,412 Preferred Term (PT); and 85,885

Lowest Level Term (LLT). In addition, there are 104 Standardized MedDRA Queries (SMQs) constructed at the level of Preferred Terms 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 MedDRA website.

# CHAPTER 11

# 11. PHARMACOVIGILANCE INDICATORS FOR ASSESSMENT OF PHARMACOVIGILANCE SYSTEM.

## 11.1 Pharmacovigilance Indicators

Pharmacovigilance indicators are measures of inputs, processes, outputs, outcomes, and impacts of development projects, programmes or policies related to health systems and services. They provide information for measuring how well a pharmacovigilance programme is achieving its objectives. These indicators measure the existence and performance of key pharmacovigilance structures and processes and are able to identify the strengths and weaknesses, as well as reveal the achievements, growth or lack of growth of the pharmacovigilance systems. They also measure the degree of attainment of set strategic objectives. The main objective of the pharmacovigilance indicators is to provide measures that will enable the assessment of the status of pharmacovigilance, the activities and their impact, globally at all levels of the healthcare system, with a view to ensuring patient safety.

The indicators are expected to give a panoramic view of the pharmacovigilance landscape. Some of the indices may be measured annually or more frequently. However, for indices requiring epidemiological studies, surveys, and/or research which is likely to be cost-intensive (both financial cost and personnel time), measurements may be less frequent, in some instances every 5 years. This is especially true for indicators that measure the outcome or impact of various pharmacovigilance activities, which often require considerable resources and expertise.

## 11.2 Classification (Types) of Pharmacovigilance Indicators.

The pharmacovigilance indicators are classified into the following three groups:

*11.2.1 Structural indicators:* The structural indicators assess the existence of key pharmacovigilance structures, systems and mechanisms in the setting being studied. The availability of basic infrastructure is required to enable pharmacovigilance operations. These indicators assess the elements that give visibility to pharmacovigilance. They also assess the existence of a policy and regulatory framework which enables pharmacovigilance to operate. These indicators are essentially qualitative.

*11.2.2 Process indicators*: These indicators assess the extent of pharmacovigilance activities. They focus on the constellation of activities which describe the mechanism of pharmacovigilance – the collection, collation, analysis and evaluation of ADR reports. They also consider other activities which influence those listed above. These are measures that assess directly or indirectly the extent to which the system is operating.

*11.2.3 Outcome or impact indicators:* These indicators measure the effects (results and changes) of pharmacovigilance activities. They measure the extent of realization of the pharmacovigilance objectives which, in essence, constitute ensuring patient safety.

## 11.3 Categories of Pharmacovigilance Indicators

*11.3.1 Core indicators (C)* are those considered to be highly relevant, important and useful in characterizing pharmacovigilance. There are 27 core pharmacovigilance indicators: 10 structural, 9 processes and 8 outcome or impact indicators.

*11.3.2 Complementary indicators (T)* are those additional measurements considered to be relevant and useful. They serve to further characterize the pharmacovigilance situation in the stated setting but need not be used in all instances. There are 36 complementary indicators: 11 structural, 13 processes and 12 outcome or impact.

*11.3.3 Pharmacovigilance indicators for public health programmes*: There are nine pharmacovigilance indicators for public health programmes. Further detail is available in DRAP's guidelines on pharmacovigilance for public health programmes from the official website.

## 11.4. Core pharmacovigilance indicators

*11.4.1 Core Structural Indicators.*

The 10 core structural indicators (CSTs) are as follows:

**CST1**. Existence of a pharmacovigilance centre, department or unit with a standard accommodation

**CST2.** Existence of a statutory provision (national policy, legislation) for pharmacovigilance

**CST3**. Existence of a medicines regulatory authority or agency

**CST4.** Existence of any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre

**CST5**. The pharmacovigilance centre has human resources to carry out its functions properly

**CST6**. Existence of a standard ADR reporting form in the setting

***Subset indicators:*** The standard reporting form provides for reporting:

**CST6a:** suspected medication errors;

**CST6b:** suspected counterfeit/substandard medicines;

**CST6c:** therapeutic ineffectiveness;

**CST6d:** suspected misuse, abuse of and/or dependence on medicines;

**CST6e:** ADRs by members of the general public

**CST7.** A process is in place for collection, recording and analysis of ADR reports

**CST8.** Incorporation of pharmacovigilance into the national curriculum of the various health-care professions (includes *subset indicators*:

**CST8a**: for medical doctors;

**CST8b:** for dentists;

**CST8c:** for pharmacists;

**CST8d:** for nurses or midwives;

**CST8e:** for others − *to be specified*)

**CST9.** Existence of a newsletter, information bulletin or website for dissemination of pharmacovigilance information

**CST10**. Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety.

*11.4.2 Core process indicators.*

The nine process indicators are as follows:

**CP1.** Total number of ADR reports received in the previous calendar year (also expressed as number of ADRs per 100 000 persons in the population)

**CP2.** Current total number of reports in the national, regional or local database

**CP3.** Percentage of total annual reports acknowledged and/or issued feedback

**CP4**. Percentage of total reports subjected to causality assessment in the previous calendar year

**CP5.** Percentage of total annual reports satisfactorily completed and submitted to the National Pharmacovigilance Centre in the previous calendar year

***Subset indicator* CP5a**: of the reports satisfactorily completed and submitted to the National Pharmacovigilance Centre, percentage of reports committed to the WHO database

**CP6.** Percentage of total reports attributed to therapeutic ineffectiveness received in the previous calendar year

**CP7**. Percentage of reports on medication errors reported in the previous year

**CP8.** Percentage of registered pharmaceutical companies having a functional pharmacovigilance system

**CP9**. Number of active surveillance activities initiated, ongoing or completed during the past five calendar years.

*11.4.3 Core outcome or impact indicators.*

The eight outcome or impact indicators are as follows:

**CO1.** Number of signals detected in the past 5 years by the pharmacovigilance centre

**CO2**. Number of regulatory actions taken in the preceding year as a consequence of national pharmacovigilance activities includes

**CO2a:** number of product label changes (variation);

**CO2b:** number of safety warnings on medicines to: (i) health professionals, (ii) the general public;

**CO2c:** number of withdrawals of medicines;

**CO2d:** number of other restrictions on the use of medicines

**CO3.** Number of medicine-related hospital admissions per 1000 admissions

**CO4.** Number of medicine-related deaths per 1000 persons served by the hospital per year

**CO5.** Number of medicine-related deaths per 100,000 persons in the population

**CO6.** Average cost (US$ or PKRs) of treatment of medicine-related illness

**CO7.** Average duration (days) of medicine-related extension of hospital stay

**CO8.** Average cost (US$ or PKRs) of medicine-related hospitalization

## 11.5. Complementary Pharmacovigilance Indicators

### *11.5.1 Complementary Structural Indicators*

The 11 complementary structural indicators are as follows:

**ST1.** Existence of a dedicated computer for pharmacovigilance activities

**ST2.** Existence of a source of data on the consumption and prescription of medicines

**ST3.** Existence of functioning and accessible communication facilities in the pharmacovigilance centre

**ST4.** Existence of a library or other reference source for drug safety information

**ST5.** Existence of a computerized case-report management system

**ST6.** Existence of a programme (including a laboratory) for monitoring the quality of pharmaceutical products

***Subset indicator* ST6a:** The programme (including a laboratory) for monitoring the quality of pharmaceutical products collaborates with the pharmacovigilance programme

**ST7.** Existence of an essential medicines list which is in use

**ST8**. Systematic consideration of pharmacovigilance data when developing the main standard treatment guidelines

**ST9.** The pharmacovigilance centre organizes training courses

**ST9a:** for health professionals;

**ST9b:** for the general public

**ST10**. Availability of web-based pharmacovigilance training tools

**ST10a:** for health professionals;

**ST10b:** for the general public

**ST11**. Existence of requirements mandating market authorization holders to submit periodic safety update reports

1 *11.5.2 Complementary process indicators*

The 13 complementary process indicators are as follows:

**P1.** Percentage of healthcare facilities with a functional pharmacovigilance unit (i.e. submitting ≥ 10 reports to the pharmacovigilance centre) in the previous year

**P2**. Percentage of total reports sent in the previous year by the different stakeholders includes

**P2a:** percentage of total reports sent by medical doctors;

**P2b:** by dentists;

**P2c:** by pharmacists;

**P2d:** by nurses or midwives;

**P2e:** by the general public;

**P2f:** by manufacturers

**P3.** Total number of reports received per million population per year

**P4.** Average number of reports per number of health-care providers per year includes

**P4a:** by medical doctors;

**P4b:** by dentists;

**P4c:** by pharmacists;

**P4d:** by nurses or midwives

**P5.** Percentage of health-care providers aware of and knowledgeable about ADRs per facility

**P6**. Percentage of patients leaving a health facility aware of ADRs in general

**P7.** Number of face-to-face training sessions in pharmacovigilance organized in the previous year

**P7a:** for health professionals;

**P7b:** for the general public

**P8.** Number of individuals who received face-to-face training in pharmacovigilance in the previous year

**P8a:** number of health professionals trained in the previous year;

**P8b:** number of individuals from the general public trained in the previous year

**P9.** Total number of national reports for a specific product per volume of sales of that product in the country (product specific) from the industry

**P10.** Number of registered products with a pharmacovigilance plan and/or a risk management strategy among the marketing authorization holders in the country

***Subset indicator*** **P10a:** Percentage of registered products with a pharmacovigilance plan and/or a risk management strategy from the market authorization holders in the country

**P11.** Percentage of market authorization holders who submit periodic safety update reports to the regulatory authority as stipulated in the country

**P12**. Number of products voluntarily withdrawn by market authorization holders because of safety concerns in the previous year

***Subset indicator*** **P12a**: Number of summaries of product characteristics (SPCs) updated by market authorization holders because of safety concerns in the previous year

**P13.** Number of reports from each registered pharmaceutical company received by the pharmacovigilance centre

in the previous year

### *11.5.3 Complementary outcome or impact indicators*

The 12 outcome or impact indicators are as follows:

01. Percentage of preventable ADRs reported in the previous year out of the total number of ADRs reported
02. Number of medicines-related congenital malformations per 100 000 births
03. Number of medicines found to be possibly associated with congenital malformations in the past 5 years
04. Percentage of medicines in the pharmaceutical market that are counterfeit/substandard
05. Number of patients affected by a medication error in hospital per 1000 admissions in the previous year
06. Average work or schooldays lost due to drug-related problems
07. Cost savings (US $ or PKRs) attributed to pharmacovigilance activities
08. Health budget impact (annual and over time) attributed to pharmacovigilance activity

***Rational use of medicines***

09. Average number of medicines per prescription
10. Percentage of prescriptions with medicines exceeding the manufacturer's recommended dose
11. Percentage of prescription forms prescribing medicines with potential for interaction
12. Percentage of patients receiving information on the use of their

# REFERENCES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3. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool.
4. WHO pharmacovigilance indicators: a practical manual for the assessment of pharmacovigilance systems.
5. The Safety Monitoring of Medicinal Products Guidelines for Setting Up and Running a Pharmacovigilance Centre.
6. E2B, E2C, E2D and E2E guidelines of ICH>
7. Good Pharmacovigilance Practices Guidelines of European Medicines Agency.
8. Take & Tell Brochure of the Uppsala Monitoring Centre, Sweden.
9. European Medicine Agency adverse reaction reporting guidelines for patients.
10. DRAP guidelines on good pharmacovigilance practices for registration holders.
11. Guidelines on pharmacovigilance for public health programmes.
12. Adverse events reporting guidelines for patients, caretakers and consumers.
13. Adverse event reporting guidelines for healthcare professionals.


**********

# ANNEXURE A

## SUSPECTED ADVERSE DRUG REACTION REPORTING FOR HEALTHCARE PROFESSIONALS

### SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

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

*For Healthcare Professionals*

**National Pharmacovigilance Centre (NPC)**
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: +92519107413**

*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): _____

3. **Describe the reaction(s):** *(use additional pages if necessary):*

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

5. **Relevant tests/Laboratory data with dates:** *(use additional pages if necessary):*

6. **Do you consider the reaction(s) to be serious?** Yes/No
**If yes, please tick all that apply of the following:**
☐ Patient died due to reaction:
☐ Life Threatening:
☐ Involved or prolonged inpatient hospitalization:
☐ Involved persistent or significant disability or incapacity:
☐ Congenital anomaly/Birth Defects:
Other Serious (Medically Important Condition): please give details:
_____

7. **Reaction abated after use stopped or dose reduced?**
☐ Yes ☐ No ☐ Doesn't apply

8. **Reaction reappeared after reintroduction?**
☐ Yes ☐ No ☐ Doesn't apply

9. **Outcomes:**
☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered
Other _____

10. **You consider the problem related to which of the following:**
☐ Quality Problem ☐ Medication Error ☐ Adverse Event/Reaction
If other, please specify _____

**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 with **THERAPEUTIC GOODS**
- Suspected Adverse Drug Reactions with **NEW THERAPEUTIC GOODS**
- Suspected Adverse Drug Reactions for **ALL VACCINES**
- **LACK OF EFFICACY** in the case of vaccines, contraceptives, antibiotics, and lifesaving medicines.
- Adverse outcome due to suspected **QUALITY PROBLEM** in therapeutic good.
- Adverse outcomes as a result of an overdose, abuse, misuse, off-label use or medication errors.

✓ **THERAPEUTIC GOODS** include the following: Drugs, Vaccine, Biological or alternative medicine or medical devices or biologicals or other related product as may be notified by DRAP

✓ Fatal reactions, 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/vaccine/alternative medicine with each reaction as per the 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 the Public Interest, Please Report ADRs to DRAP even if you are unsure.**

For More Information/Queries, please contact:

*National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan, Prime Minister's National Health Complex, Park Road Islamabad.*
*Website: www.dra.gov.pk* **Email:** *npc@dra.gov.pk*
*Phone No: 051-9255981*

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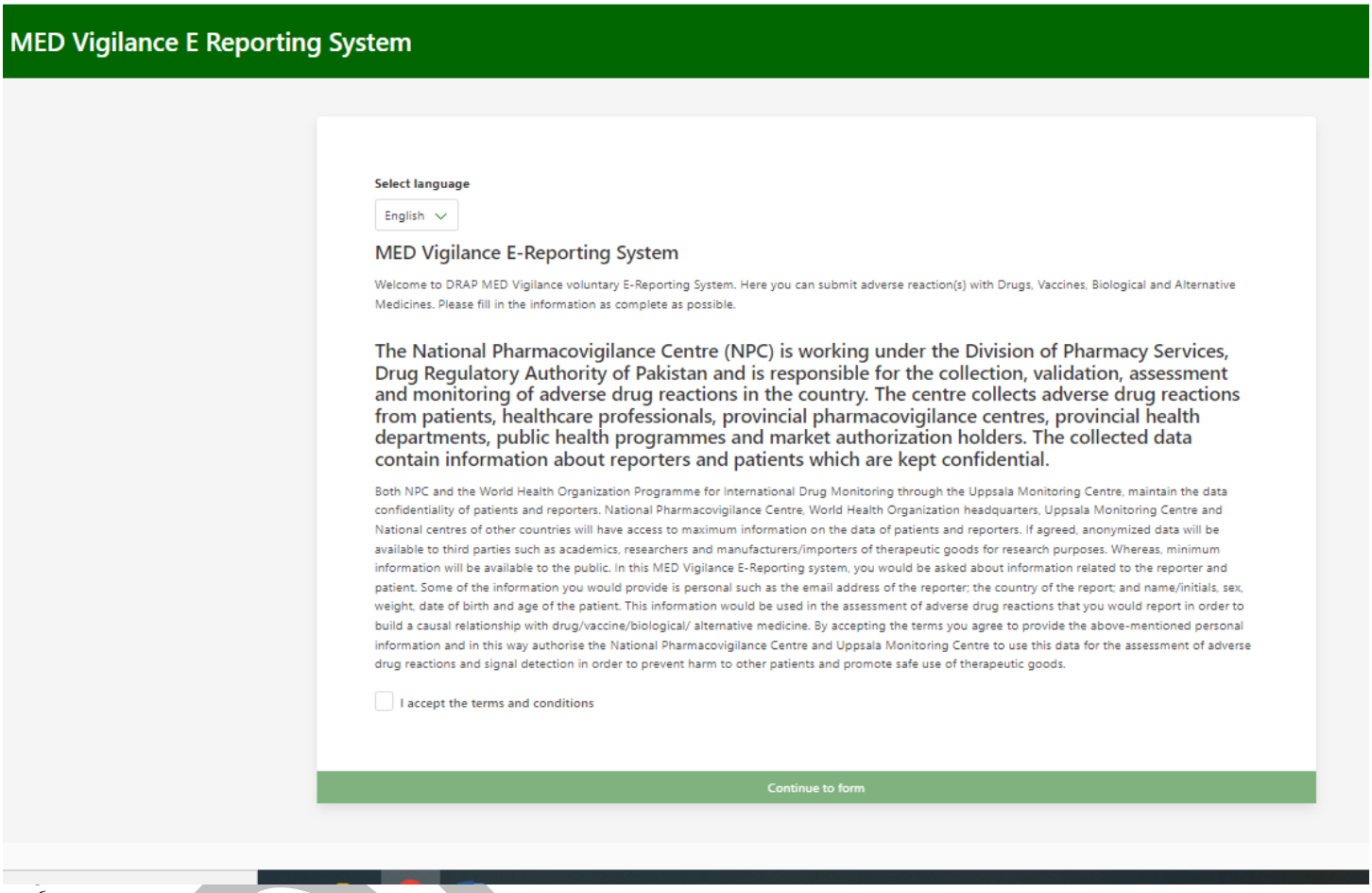
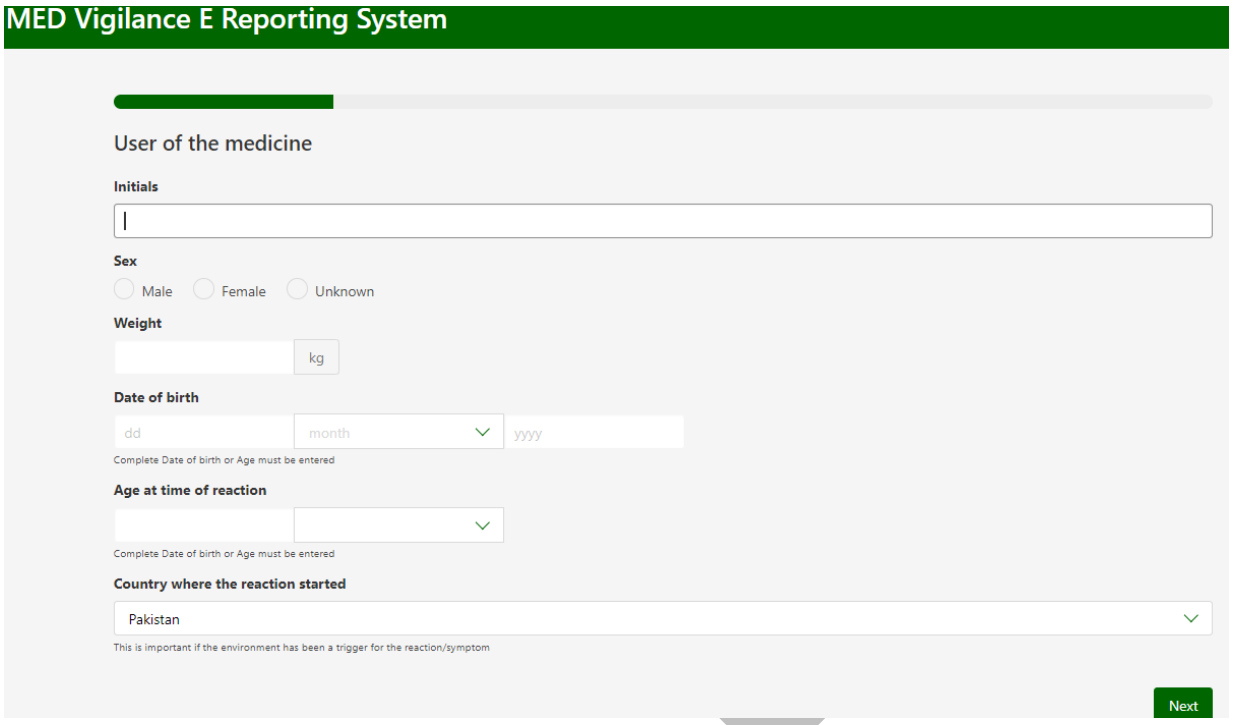
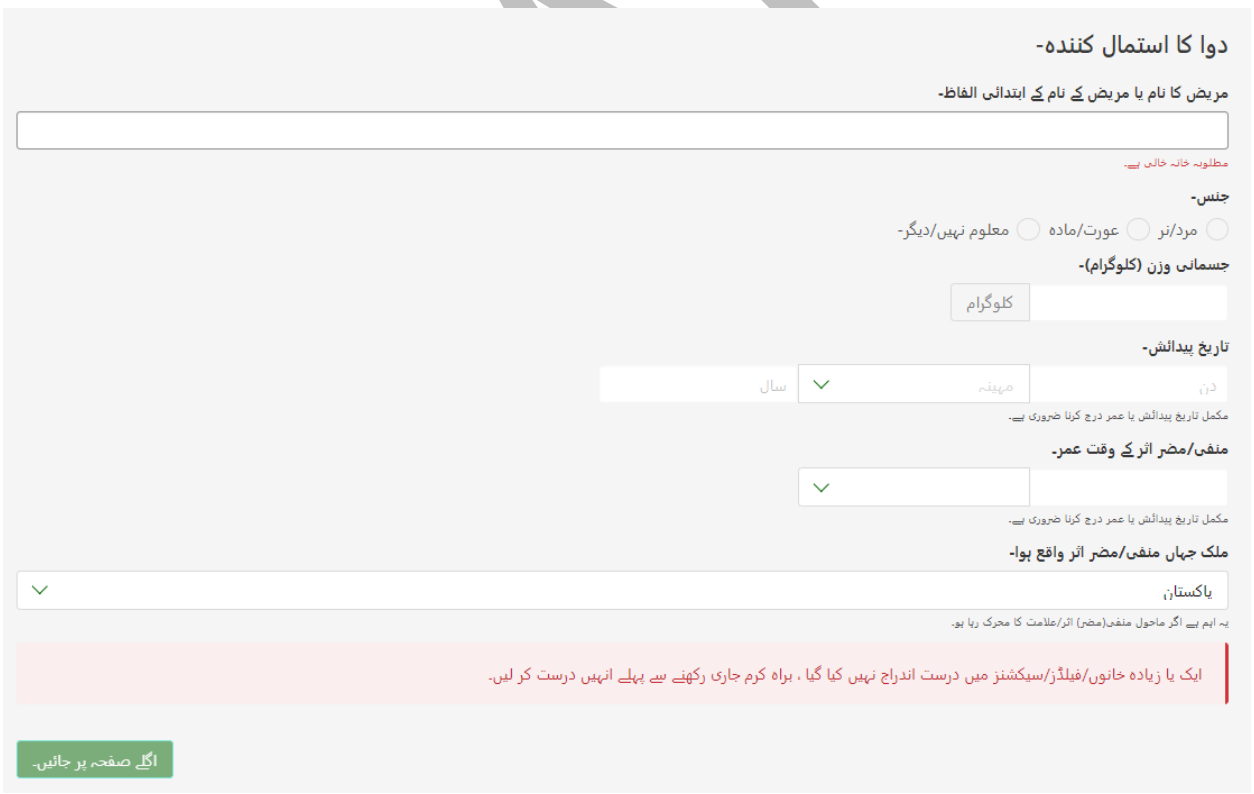
# ANNEXURE B

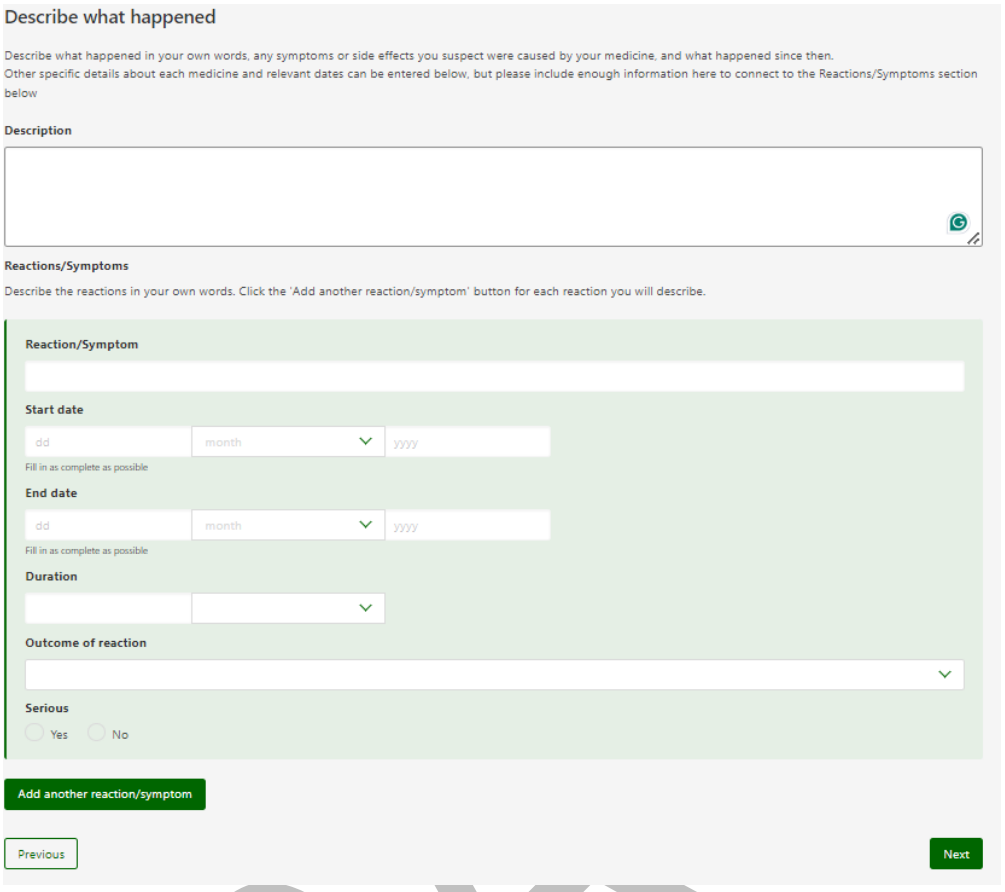
***Med Vigilance E Reporting System (WHO E-Forms based) (For patient and healthcare professionals)***




MED Vigilance E Reporting System
User of the medicine
Initials
Sex
Male
Female
Unknown
Weight
kg
Date of birth
dd
month
yyyy
Complete Date of birth or Age must be entered
Age at time of reaction
Complete Date of birth or Age must be entered
Country where the reaction started
Pakistan
This is important if the environment has been a trigger for the reaction/symptom
Next


دوا کا استعمال کنندہ-
مریض کا نام یا مریض کے نام کے ابتدائی الفاظ-
مطلوبہ خانہ خالی ہے۔
جنس-
مرد/نر
عورت/مادہ
معلوم نہیں/دیگر-
جسمانی وزن (کلوگرام)-
کلوگرام
تاریخ پیدائش-
دن
مہینہ
سال
مکمل تاریخ پیدائش یا عمر درج کرنا ضروری ہے۔
منفی/مضر اثر کے وقت عمر۔
مکمل تاریخ پیدائش یا عمر درج کرنا ضروری ہے۔
ملک جہاں منفی/مضر اثر واقع ہوا-
پاکستان
یہ اہم ہے اگر ماحول منفی(مضر) اثر/علامت کا محرک رہا ہو۔
ایک یا زیادہ خانوں/فیلڈز/سیکشنز میں درست اندراج نہیں کیا گیا ، براہ کرم جاری رکھنے سے پہلے انہیں درست کر لیں۔
اگلے صفحہ پر جائیں۔

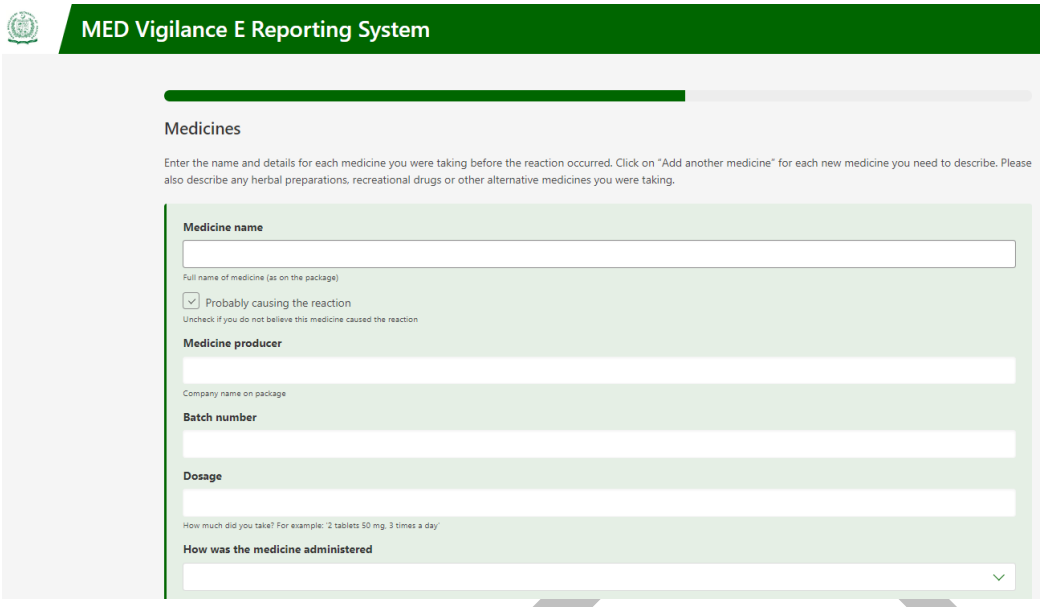
1


Describe what happened
Describe what happened in your own words, any symptoms or side effects you suspect were caused by your medicine, and what happened since then.
Other specific details about each medicine and relevant dates can be entered below, but please include enough information here to connect to the Reactions/Symptoms section below
Description
Reactions/Symptoms
Describe the reactions in your own words. Click the 'Add another reaction/symptom' button for each reaction you will describe.
Reaction/Symptom
Start date
dd
month
yyyy
Fill in as complete as possible
End date
dd
month
yyyy
Fill in as complete as possible
Duration
Outcome of reaction
Serious
Yes
No
Add another reaction/symptom
Previous
Next

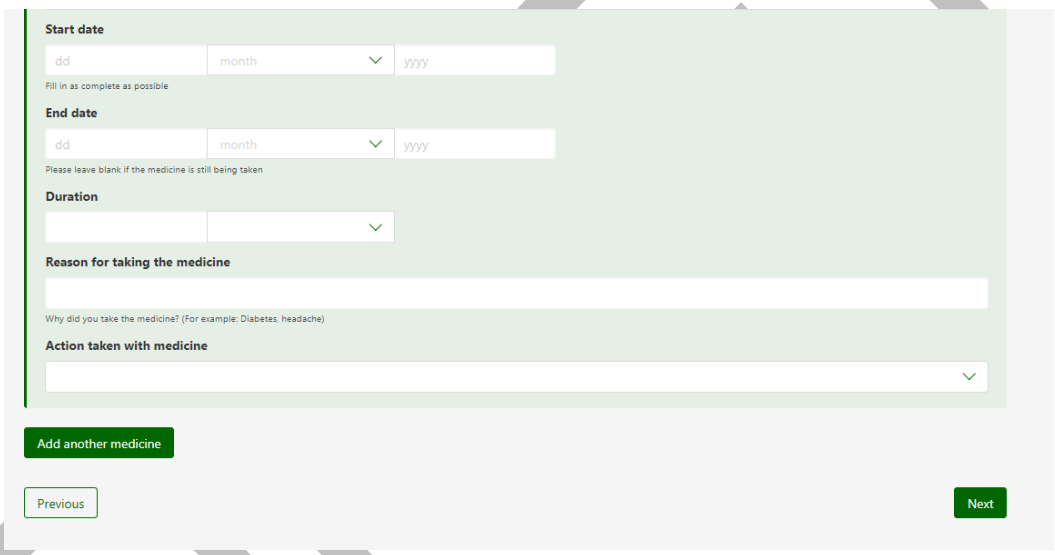
2


تفصیل سے بیان کریں کہ کیا اور کیسے ہوا۔
اپنے الفاظ میں تفصیل سے بیان کریں کہ کیا ہوا، کوئی بھی علامات یا ضمنی، منفی، مضر اثرات جن کا آپ کو شبہ ہے کہ آپ کی دوا کی وجہ سے ہوئے ہیں، اور اس کے بعد کیا ہوا۔
ہر دوا اور متعلقہ تاریخ کے بارے میں دیگر مخصوص تفصیلات ذیل میں درج کی جا سکتی ہیں۔ لیکن براہ کرم یہاں کافی معلومات شامل کریں جو منفی اثرات/علامات کے نیچے دیے گئے سیکشنوں میں مددگار ثابت ہو سکتی ہیں۔
کیس/ واقعہ کی تفصیل۔
مطلوبہ خانہ خالی ہے۔
منفی(مضر) اثرات/علامات۔
منفی(مضر) اثرات کو اپنے الفاظ میں بیان کریں۔ ہر ایک منفی(مضر) اثر کے لیے جو آپ بیان کرنے جا رہے ہیں 'ایک اور منفی(مضر) اثر/علامت شامل کریں' کے بٹن پر کلک کریں۔
منفی(مضر) اثر، جیسا کہ ابتدائی رپورٹر([اطلاع کُنْندَہ) نے رپورٹ کیا تھا۔
منفی(مضر) اثر شروع ہونے کی تاریخ۔
دن
مہینہ
سال
اس سیکشن/ خانے کو ہر ممکن حد تک مکمل کریں۔
منفی(مضر) اثر ختم ہونے کی تاریخ۔
دن
مہینہ
سال
اس سیکشن/ خانے کو ہر ممکن حد تک مکمل کریں۔
دورانیہ۔
منفی(مضر) اثر کا نتیجہ۔
کیا منفی/مضر اثر سنگین تھا؟
ہاں۔
نہیں۔
ایک اور منفی(مضر) اثر/علامت شامل کریں۔
ایک یا زیادہ خانوں/فیلڈز/سیکشنز میں درست اندراج نہیں کیا گیا ، براہ کرم جاری رکھنے سے پہلے انہیں درست کر لیں۔

1


MED Vigilance E Reporting System
Medicines
Enter the name and details for each medicine you were taking before the reaction occurred. Click on "Add another medicine" for each new medicine you need to describe. Please also describe any herbal preparations, recreational drugs or other alternative medicines you were taking.
Medicine name
Full name of medicine (as on the package)
Probably causing the reaction
Uncheck if you do not believe this medicine caused the reaction
Medicine producer
Company name on package
Batch number
Dosage
How much did you take? For example: '2 tablets 50 mg, 3 times a day'
How was the medicine administered

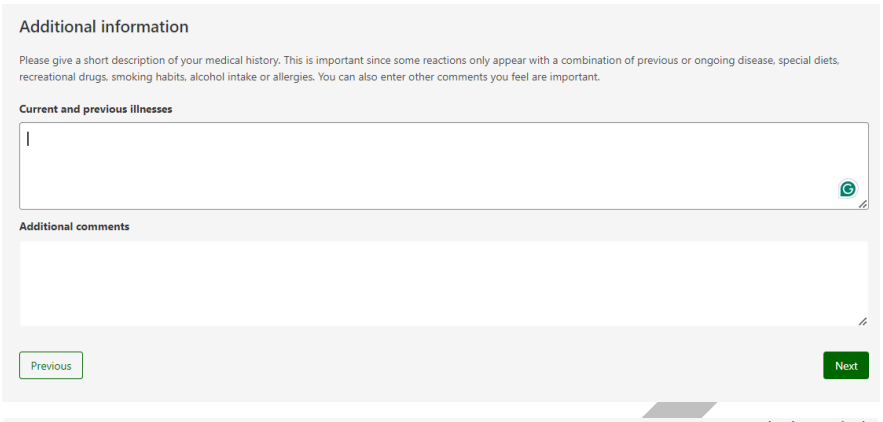
2


Start date
dd
month
yyyy
Fill in as complete as possible
End date
dd
month
yyyy
Please leave blank if the medicine is still being taken
Duration
Reason for taking the medicine
Why did you take the medicine? (For example: Diabetes, headache)
Action taken with medicine
Add another medicine
Previous
Next

3


ادویات-
دوا کا نام جیسا کہ ابتدائی رپورٹر(اطلاع کنندہ) نے بتایا تھا۔
دوا کا پورا نام (جیسا کہ دوا کے ڈبے پر ہے)
منفی(مضر) اثرات میں دوا کا کردار(رول)۔
دوا ساز کمپنی جس کے نام پر ادویات کی رجسٹریشن ہے۔
دوا کے ڈبے پر کمپنی کا نام۔
بیچ نمبر-
خوراک-
دوا کیسے دی گئی(راہِ مصرف دوا/ایڈمنسٹریشن)؟

1


Additional information
Please give a short description of your medical history. This is important since some reactions only appear with a combination of previous or ongoing disease, special diets, recreational drugs, smoking habits, alcohol intake or allergies. You can also enter other comments you feel are important.
Current and previous illnesses
Additional comments
Previous
Next

2


اضافی معلومات-
براہ کرم اپنی متعلقہ میڈیکل/طبی ریکارڈ/تاریخ کی مختصر تفصیل دیں۔ یہ اہم ہے کیونکہ کچھ منفی اثرات پچھلی یا موجودہ بیماری، خصوصی خوراک، تفریحی ادویات، تمباکو نوشی کی عادت، شراب کے استعمال یا الرجی کی وجہ سے ظاہر ہوتے ہیں۔ آپ اس کے علاوہ بھی تبصرہ/کمنٹس درج کر سکتے ہیں جو آپ اہم محسوس کرتے ہیں۔
متعلقہ میڈیکل ریکارڈ/طبی تاریخ-
رپورٹر(اطلاع کُنندہ) کا کوئی تبصرہ/کمنٹس-
اگلے صفحہ پر جائیں۔
پچھلے صفحہ پر جائیں۔

3


Contact details
Profession
Given name
Family name
Health facility
Email
Telephone
Previous
Submit report

4


رابطے کی تفصیلات-
رپورٹر(اطلاع کُنندہ) کی تعلیمی قابلیت-
دیا ہوا نام یا نام کا پہلا حصہ-
خاندان/ذات کا نام یا نام کا دوسرا حصہ-
ادارہ-
ای میل اڈریس-
ٹیلی فون نمبر-

# ANNEXURE C

## Med Safety Mobile App Pakistan

# ANNEXURE D

## CIOMS FORM I

CIOMS FORM

| SUSPECT ADVERSE REACTION REPORT | |
|---|---|

### I. REACTION INFORMATION

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

### II. SUSPECT DRUG(S) INFORMATION

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

### III. CONCOMITANT DRUG(S) AND HISTORY

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

### IV. MANUFACTURER INFORMATION

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

**National Pharmacovigilance Centre**
**Pharmacy Services Division**
**DRUG REGULATORY AUTHORITY OF PAKISTAN**
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Website: www.dra.gov.pk