ETHIOPIAN FOOD AND DRUG AUTHORITY

PHARMACOVIGILANCE AND CLINICAL TRIAL LEAD EXECUTIVE OFFICE

National Pharmacovigilance Guideline

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Document History

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001	New version	July, 2001
002	Revised to include preparation of easy to fill reporting form with prepaid postage and availing it for all healthcare professionals at each health institutions for voluntarly and spontaneous reporting. Moreover, it was developed with the intention to make the reporting of ADR consistent, regular and complete. It also gives information on what,when,how to report and to whom to report.	September, 2008
003	Amended to include the roles and responsibilities of stakeholders towards the maintenance of a national drug safety.	2014

004	Revised to outlines the comprehensive requirements for Good Pharmacovigilance Practices (GVP) and aims to standardize and harmonize pharmacovigilance activities. Prepared in alignment with the new Pharmacovigilance Directive No. 932/2022 and incorporating international best practices in pharmacovigilance and also provides detailed information on the roles and responsibilities of various stakeholders in pharmacovigilance. It includes the necessary contents of safety-related documents that Marketing Authorization Holders (MAHs) must prepare, as well as guidance on conducting pharmacovigilance inspections.	July, 2024

Asnakech Alemu, Signature,

Table of Contents

Abbreviations and acronyms

AE	Adverse Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization.
DLP	Data Lock Point
DTC	Drug and Therapeutic Committee
DTP	Drug Therapy Problems
EFDA	Ethiopian Food and Drug Authority
EPI	Expanded Program on Immunization
GBT	Global Benchmarking Tool
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice
ICSR	Individual Case Safety Report
IPAT	Indicator-based Pharmacovigilance Assessment Tool
IEC	Information Education and Communication
MAH	Marketing Authorization Holders
ME	Medication Error
PASS	Post Authorization Safety Studies
PBRER	Periodic Benefit Risk Evaluation Report
PQD	Product Quality Defect
PHP	Public Health Programme
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RHB	Regional Health Bureau
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund

WHO	World Health Organization
WoHO	Woreda Health Office
ZHD	Zonal Health Department

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Foreword

Responding to the health care needs of the public is one of the priorities of our national health care system. Medicines are one of the essential components in the health care system. Ensuring the safety, efficacy, and quality of medicines provided to the public is mandatory as numerous medicines are being released into the market every day with incomplete information on their safety levels. Moreover, limited information from clinical trials on the safety of medicines creates a concern for the public. This concern calls for a comprehensive Pharmacovigilance (PV) system that will act proactively to protect the public from preventable medicine-related harms.

The Ethiopian Food and Drug Authority (EFDA) is mandated by proclamation No. 1112/2019 under part two, Article 4 and 38 and regulation No. 299/2013: on Article 31; as well as through the pharmacovigilance directive No. 932/2022, to monitor the safety, efficacy and quality medicines.

To execute this responsibility, the authority requires a robust pharmacovigilance system that will enable the engagement of various sectors and stakeholders in pharmacovigilance-related activities. An up-to-date and practical pharmacovigilance guideline is needed to standardize and harmonize the pharmacovigilance activities throughout the country at different levels.

With the above context, I would like to present this 4th edition pharmacovigilance guideline. This updated and revised version addresses important stakeholders with a detailed elaboration of their involvement in the medicine safety monitoring system. Furthermore, international Good Pharmacovigilance Practices (GVP) including pharmacovigilance inspection guidance is incorporated.

I would like to take this opportunity to thank all those who contributed to developing and printing this National Pharmacovigilance Guideline. I also call upon interested parties to continue their support by forwarding their comments and suggestions to the Pharmacovigilance and Clinical Trial Lead Executive Office, EFDA, P.O.Box 5681 Addis Ababa, Ethiopia. Tel.251-115524122, e-mail: pharmacovigilance@efda.gov.et.

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Glossary of terms

Adverse Event (AE) means any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction (ADR) - means a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease,or the modification of physiological function."

Consumer- means anyone who uses, has used or may use any health or health-related service. It is not limited to those currently using a service. The terms "patients" and "users" generally apply only to those currently undergoing some form of treatment.

Crisis- a situation where after assessment of the incidents associated risks, routine measures are not considered sufficient and therefore urgent and coordinated actions within the country is required to manage and control the situation.

Data Lock Point – means a date designated as the cut-off for data to be included in the periodic safety update reports (PSUR), based on the international birth date (IBD)

Drug interaction- means a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect not produced on its own. Typically, interaction between drugs comes to mind (drug-drug interaction). However, interactions may also exist between drugs & foods (drug-food interactions), as well as drugs & herbs (drug-herb interactions.

Healthcare facilities- are places that provide health care that are involved in health promotion, disease prevention, treatment and rehabilitation, and laboratory services.

Healthcare Professional- means any person who is a member of the medical, dental, pharmacy, laboratory, or nursing professionals or any other person who, in the course of his or her professionalactivities, may prescribe, purchase, supply, recommend, or administer a medicinal product.

Identified Risk – means an undesirable clinical outcome for which there is sufficient scientific evidence that it is caused by the medical product.

Important identified risk and important potential risk –means an identified risk or potential risk that could have an impact on the risk-benefit balance of the medical product.

Incident- means a situation where an event occurs, or new information arises irrespective of whether this is in the public domain or not in relation to medicinal products used in the country and which could have a serious impact on public health.

Individual Case Safety Report- means a report providing the most complete information related to an individual adverse event case at a certain point in time.

Marketing authorization holder (MAH) – means an individual or a corporate entity/company responsible for placing a pharmaceutical product in the market either through manufacturing, importation,donation, or distribution in Ethiopia. This individual or company is responsible for all aspectsof the product, including safety, efficacy, and quality compliance with the conditions of the marketing authorization.

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

Medicine-means any substance or mixture of substances used in the diagnosis, treatment, mitigation, or prevention of human disease, disorder, abnormal physical or mental state, or the symptoms thereof; used in the restoring, correcting, or beneficial modification of organic or mental functions in human; or articles other than food, intended to affect the structure or any function of the body of human and it includes articles intended for use as a component of any of the above specified articles.

Periodic Safety Update Report (PSUR) – means an update of the world-wide safety experience of medicine obtained at defined times post-marketing authorization.

Periodic Benefit-Risk Evaluation Report (PBRER) – means an update of the worldwide marketing experience of medicine at defined times with a focus on the formal evaluation of benefits inspecial populations at defined times during the post-registration period.

Pharmacovigilance- means the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.

Pharmacovigilance System Master File (PSMF)- means a detailed description of the

Pharmacovigilance system used by the marketing authorization holder concerning one or more authorized medicinal products.

Product Quality Defect (PQD) - means attributes of a medicinal product or component that may affectthe quality, safety, and /or efficacy of the product, and/or which is not in-line with the approved market authorization. This includes suspected contamination, questionable stability, substandard,defective components, poor packaging, and labeling.

Potential Risk- means an undesirable clinical outcome for which there is scientific evidence to suspect the possibility of a causal relationship with the medical product.

Qualified Person for Pharmacovigilance (QPPV) - means a healthcare professional, usually an employee of a pharmaceutical manufacture or importer, who is personallyresponsible for the safety of the human pharmaceutical products marketed by that company.

Risk Management Plan (RMP) – means a detailed description of the risk management system and includes information on a medicine's safety profile; how its risks will be prevented or minimized in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine and measuring the effectiveness of risk-minimization measures.

Risk Management System -means a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to a medical product, including the assessment of the effectiveness of those activities and interventions

Risk Minimization Measure – means interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur.

Serious Adverse Event (SAE) -means any untoward medical occurrence that at any dose:

- results in death,
- Is life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction.
- requires inpatient hospitalization or results in prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect,
- is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Signal – means reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

Significant Safety Issue- means a new safety issue or validated signal considered by MAH in relation to medicines that require urgent attention of the EFDA. This may be because of the seriousness and potentially major impact on the benefit-risk balance of the medicine and/or on patient or public health, which could warrant prompt regulatory action and/or communication to patients and healthcare professionals.

Unexpected Adverse Reaction – means an adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization or expected from characteristics of the drug.

List of Figures:

Rationale for revision

This edition of the guideline comprehensively outlines the requirements for Good Pharmacovigilance Practices (GVP) and aims to standardize and harmonize pharmacovigilance activities. Prepared in alignment with the new Pharmacovigilance Directive No. 932/2022 and incorporating international best practices in pharmacovigilance, this edition also provides detailed information on the roles and responsibilities of various stakeholders in pharmacovigilance. It includes the necessary contents of safety-related documents that Marketing Authorization Holders (MAHs) must prepare, as well as guidance on conducting pharmacovigilance inspections

Scope of the guideline

This guideline applies to all pharmaceutical products (conventional medicine, traditional medicine, complementary and alternative medicine, and biological products) placed in the Ethiopian market. Moreover, this guideline also encompasses the monitoring of adverse events, medication errors, and product quality defects, such as counterfeit, falsified, and substandard products.

Purpose of the guideline

The purpose of this guidelines is to:

- Provide guidance on detecting, management, reporting, investigation and causality assessment, prevention, and feedback provision on Adverse Drug Events.
- Outlines the key stakeholders in medicines safety monitoring and clearly defines roles and responsibilities.
- Provide clear guidance for Marketing Authorization Holders on post marketing safety requirements and continuous monitoring of the safety profile of their medicines.
- Provide guidance on effective medicines safety and risk communication.

Chapter One

1. Introduction

1.1. Background

The use of medicine is an important aspect of many health programs that are designed to improve the health of a target population. A remarkable amount of the health budget is allocated for availing medicines in most countries, ranging from 6% to 45%. Maintaining the quality, safety, and efficacy of medicines is important not only because of their capacity to treat and prevent disease and to support health programs but also because it builds public confidence and trust in the healthcare system.

Medicines will undergo thorough pre-clinical and clinical studies to prove their quality, safety, and efficacy before market authorization is granted. However, the product has only been tested on a restricted number and type of patients for a limited length of time and used under strict protocols. In addition; pregnant mothers, children, the elderly, and patients with certain diseases or on certain medicines have often been excluded from these studies. These conditions make it impossible to detect rare Adverse Drug Reactions (ADRs), long-term effects, drug interactions, and particular patient risk groups or risk factors. Moreover, marketed medicines are not used according to strict protocols, as in the pre-marketing studies. In addition, problems can emerge from real-life medication use related to inadequate labeling, packaging, product information, product quality defects, and self-medication.

Post-marketing safety monitoring is therefore very important to detect medicine-related problems that were not possible to identify during the pre-marketing phases. Even if the medicine has been marketed previously in other countries or internationally, national post-marketing safety monitoring is necessary because of variations in genetic makeup and environmental context.

The medicine use process is dependent on patients' and healthcare professionals' vigilance in real-life settings to detect potential problems that need to be communicated to EFDA for preventative actions to be taken. Wherever medicines are being used, there should be a readiness to monitor and report unwanted and unexpected medicine-related problems.All medicines carry some risk of harm, and it is important to monitor their effects, bothintended and unwanted so that good evidence is available upon which to base an assessment of risk versus effectiveness or risk versus benefit. Furthermore, particularly with new medicines,early identification of unexpected adverse reactions and their risk factors is essential, so that the medicines can be used in an informed manner with the least chance of harm. Information gathered during pharmacovigilance may also assist in selecting

the most appropriate medicine for future use.

The specific aims of pharmacovigilance are to:

- Improve patient care and safety about the use of medicines and all medical interventions,
- Improve public health and safety about the use of medicines,
- Contribute to the assessment of the benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational and more effective use, and
- Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.

The scope of pharmacovigilance in monitoring safety has grown remarkably in recent times and is now considered to include the following domains (Figure 1):

- Adverse drug reactions/ events
- Medication errors
- Counterfeit or substandard medicines
- lack of efficacy of medicines
- Misuse and/or abuse of medicines
- Interaction between medicines.

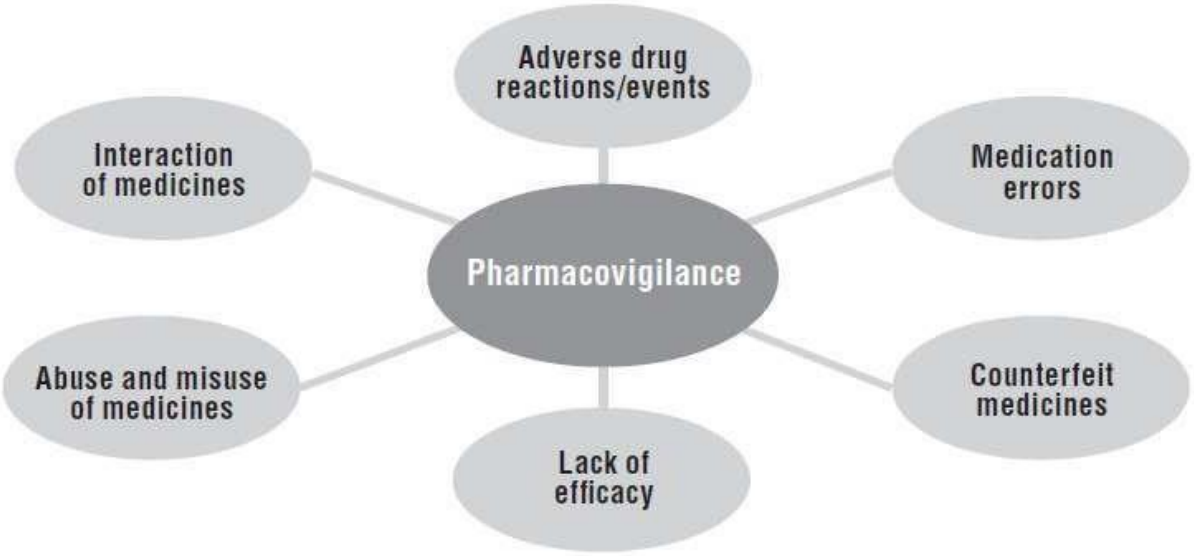


Figure 1. Scope of pharmacovigilance

The types of safety issues monitored through pharmacovigilance include

1. **Adverse Drug Reaction (ADR):**

- ADR is noxious, unintended, and occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
- An ADR contrary to an adverse event is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.
- ADRs can be classified into different types based on different criteria as indicated below.

a. Classification of ADRs by type

Types	Features	Examples	Management
A: Dose-related (Augmented)	Common Related to the pharmacologic action of the drug– exaggerated pharmacologic response Predictable Low mortality	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, serotonin syndrome with SSRIs, digoxin toxicity	Reduce dose or withhold drug Consider effects of concomitant therapy
B.Non–dose related (Bizarre)	Uncommon Not related to the pharmacologic action of the drug Unpredictable High mortality	Immunologic reactions: anaphylaxis to penicillin Idiosyncratic reactions: malignant hyperthermia with	Withhold and avoid in future
C. Dose Related and Time Related (Chronic)	Uncommon Related to the cumulative dose	Hypothalamic-pituitary- adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with	Reduce dose or withhold; withdrawal may have to be prolonged
D. Time Related (Delayed)	Uncommon Usually, dose-related Occurs or becomes apparent sometime after the use of the drug	Carcinogenesis Tardive dyskinesia Teratogenesis Leukopenia with lomustine	Often intractable

E. Withdrawal (End of use)	Uncommon Occurs soon after withdrawal Of the drug	Withdrawal syndrome With opiates or benzodiazepines (e.g., insomnia, anxiety)	Reintroduce the drug and withdraw slowly
F. Failure of therapy	Common Dose related. Often caused by drug	Inadquate dosage or oral contraceptives, particularly when used with specific enzyme inducers	Increase dosage Consider the effects of concomitant therapy

Classification of ADRs by severity

Assessment of ADRs is largely subjective. These reactions can be classified as mild, moderate, and severe based on severity. Mild ADRs are self-limiting and able to resolve over time without treatment. Moderate ADRs are those that require treatment or increased length of stay by at least one day. Severe ADRs are those that are life-threatening or cause permanent harm or death.

2. Medication errors

Medication errors may occur during any stage of the medicine use process such as prescribing, transcribing, preparation, administration, and dispensing as well as during use by patients. This is a pervasive problem that occurs with all persons who handle medications. The causes of errors are numerous and include lack of knowledge, fatigued employees, careless work attitudes, and poor procedures for drug distribution. Errors will occur no matter how ideal a health care setting may be. Therefore, healthcare professionals must provide a mechanism to monitor, assess, and prevent medication errors. It is also important that healthcare professionals report any identified medication errors to the regulatory authority.

It is estimated that one in 10 hospitalized patients in industrialized countries are harmed because of patient safety issues. The number is estimated to be higher in developing countries. Part of these patient safety problems can be caused by medication errors. Inadequate practice, products, procedures, or systems can result in patient harm. A majority of these events can be prevented.

There are many causes of medication errors, but the majority are attributed to the following three factors:

I.Human factors

- Heavy staff workload and fatigue
- Inexperience, lack of training, poor handwriting, and oral orders
- Negligence

II.Workplace factors

- Poor lighting, noise, interruptions

III. **Pharmaceutical factors**

a. Excessive prescribing

b. Confusing medicine nomenclature, packaging, or labeling

c. Frequency and complexity of calculations needed to prescribe, dispense, and administer medicine.

d. Lack of effective policies and procedures.

3. Product Quality Defect

Product quality problems may occur at any stage of the medicine supply chain process starting from manufacturing up to the use of the medicine by the patient. Healthcare professionals should ensure that the medicines that are available in their respective health facilities are of good quality and obtained through legal procedures or registered by EFDA.

With new safety concerns such as the illegal sale of medicines, irrational and potentially unsafe medicinal products, drug donation practices, and the widespread manufacture and sale of counterfeit and substandard medicines, being vigilant for product quality problems and reporting them to EFDA when they occur is very important.

Suspected contamination, questionable stability, defective components, poor packaging or labeling, and unexpected therapeutic ineffectiveness could be indicative of product quality defects. Medicines that have lost their potency after being stored at high temperatures would fall into this category.

1.2. The National Pharmacovigilance System

There are differences among countries in the occurrence of ADRs and other drug-related problems, and this is because of differences in diseases and prescribing practices, genetics, diet, traditions of the people, drug manufacturing processes, drug distribution, and use, and the use of traditional and

complementary drugs that may pose specific toxicological problems when used alone or in combination with other drugs, and therefore every country needs to establish and run a well-functioning pharmacovigilance system.

Accordingly, Ethiopia established the national pharmacovigilance system in 2002 and became the 88th full member of the WHO Programme for International Drug Monitoring in 2008. As part of the effort made for the global drug safety monitoring program, Ethiopia shares the Case Safety Report (ICSR) with the global community through WHO/UMC Vigibase.

The overall Adverse events monitoring is coordinated by the national pharmacovigilancecenter placed under the Ethiopian Food and Drug Authority. The pharmacovigilance center has been performing various activities since its establishment. Among these

- Establishing pharmacovigilance centers in selected university hospitals
- Development and distribution of different pharmacovigilance tools, guidelines,
- Development of pharmacovigilance directive
- Conducting active surveillances
- Introduction of electronic reporting tools (Medsafety mobile apps and web-based reporting tools)
- Establishing and strengthening of pharmacovigilance advisory committee.
- Establishing pharmacovigilance stakeholders' forum.
- Development of various standard operating procedures
- Providing capacity-building activities for healthcare professionals

The key role of the pharmacovigilance center is the safety monitoring of all medical products availablein the Ethiopian market. Its core activity is the collection and evaluation of AE reports submittedby healthcare professionals, consumers, and pharmaceutical companies in the country. The goal isto contribute to the rational and safe use of medicines and to continuously monitor the risks and benefits of all medicines available at every level of healthcare.

In the collection of AE reports, the flow of communication starts from patients with AEs and moves directly to the healthcare professionals at health institutions/public health programs and also to market authorization holders which finally lasts at the EFDA. This flow is a two-way process where feedbacks are provided to the AE reporters after a report is received.

AE reporting routes in the National Pharmacovigilance system are diagrammatically presented as follows:

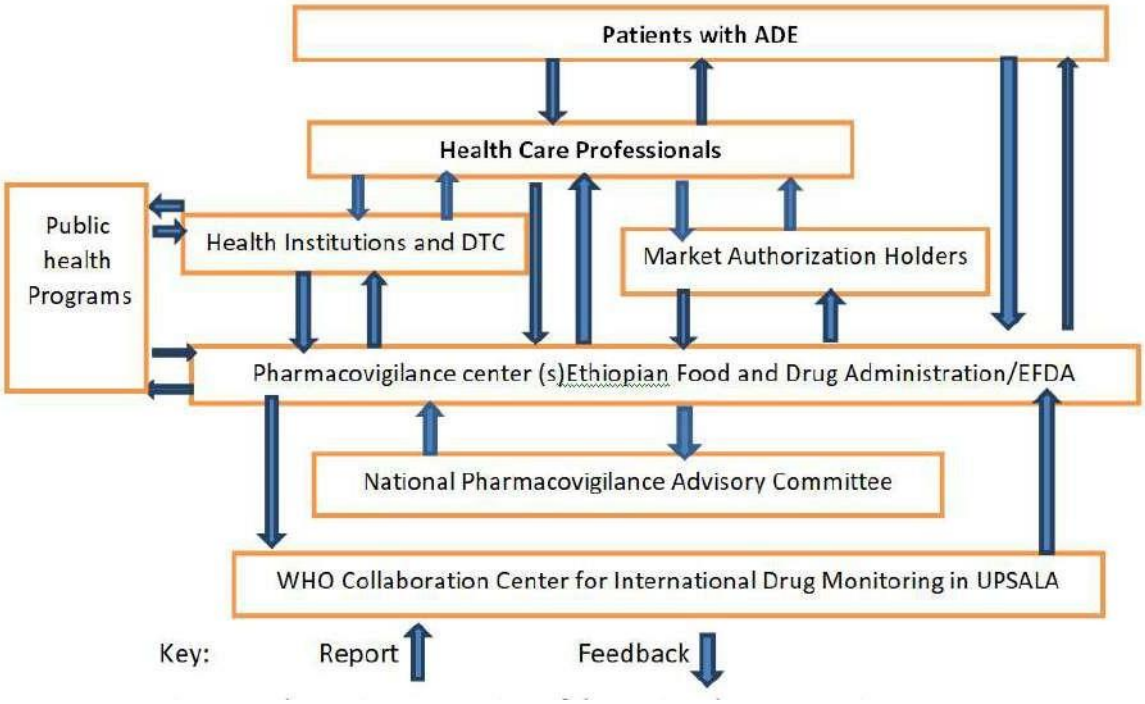


Figure 2: The National AE reporting flow and feedback mechanism

Chapter Two

2. Adverse Events Reporting system

Reporting adverse events to the national pharmacovigilance center is very important to ensure that medicines used in the healthcare system are safe, effective, and of good quality. An up-to-date safety profile of the medicine is crucial to perform a proper benefit-risk assessment and regulatory decision. The current safety profile of medicine can be generated when health care professionals detect, monitor, and report adverse events to the regulatory authority that occur in routine clinical practice.

2.1 Who should report adverse events?

All Health care professionals including physicians, dentists, health officers, nurses, pharmacy professionals, and community health workers should report AEs to the national PV center. Reporting an adverse event does not pose any legal liability or consequence to the reporter.

Market authorization holders are primarily responsible for monitoring the safety, efficacy, and quality of their products. They are obligated to report adverse events that occur in Ethiopia to the national pharmacovigilance center.

2.2 What to report?

All adverse events, including adverse drug reactions, product quality defects, and medication errors should be reported. In addition, any Adverse Event Following Immunization (AEFI) should be reported according tothe guidelines for AEFI Surveillance in Ethiopia by Healthcare Professionals engaged in a national expanded program for immunization /EPI/.

i. **ADRs which include:**

- All suspected reactions to medicines
- Unknown or unexpected reactions
- Serious adverse drug reactions
- Unexpected therapeutic effects
- Cluster of events
- Potential signal
- All suspected drug interactions, including interactions with other medicines, herbals,

chemicals, and food

- Treatment failures

ii. Product quality defects

It is very important to report product quality defects such as adulteration, contamination, packaging defects, substandard and falsified medical products, or tampering. The ultimate objective of reporting PQD is to enable EFDA to take appropriate regulatory measures including recall of the defective product, label change, banning of the product, suspension/cancelation of market authorization, closure of manufacturing facility, etc…, depending on the nature of the PQDs.

iii. **Medication errors**

Regardless of the results of ADR, any medication error such as prescribing error, dispensing error, administration error, overdose use of medicine, misuse of medicines, or abuse of medicine should be reported to EFDA.

2.3 When to report?

Any suspected ADRs, medication errors, or quality defects should be reported as soon as possible after all relevant information is compiled. Delays in reporting will make reports inaccurate and unreliable. Reporting while the patient is still in the health institution will give chance to the reporter to clear any ambiguity by re-questioning or examining the patient.

Healthcare professionals are encouraged to report suspected AEs even when they are not certain that the medicine is responsible for causing the reaction. The minimum information required for a valid case (i.e. information about the patient, suspected medicine, the adverse events, and information about the reporter) should always be included in the report.

After being identified by healthcare professionals, serious adverse events should be notified within 24 hours and reported to the national Pharmacovigilance center within 48 hours and non-serious adverse events should be reported within 7 working days.

The reporting detail for MAHs is described in chapter four of this guideline.

2.4 How to report suspected AEs

The national PV system has established different types of reporting tools to receive AEs from health care professionals, consumers, and other stakeholders. During the reporting of AEs by any one of

the tools, healthcare professionals or consumers should ensure that the minimum required information (patient details, event details, medicine details, and reporter details) is completed. The current available AE reporting tools are described below:

- **Paper-based AEs reporting form (yellow form):** after filling in all the necessary information in the reporting form, health care professionals are expected to send the filled form either to the national or regional PV centers. This reporting form is available on the authority website. In addition, it can be obtained at the health facilities pharmacy unit or DIC. The completed AE reporting form can be scanned and emailed to the center.
- **Electronic reporting tools:** the electronic reporting tools introduced and made available for reporting of AEs by healthcare professionals are web-based reporting tools and mobile app reporting tools.
  - ✓ **Web-based reporting tool:** the web-based reporting tool is available on the authority's official website (www.efda.gov.et).
  - ✓ **MedSafety Mobile app reporting tool:** Using a mobile application Medsafety that can be downloaded from the Google Play Store for Android phones or the APP store for IOS users, create an account using an email address and then enter through the "new report" button and filling the information onthe adverse event that is going to be reported
- **Reporting via email:** the filled AEs reporting form can be directly sent to the national pharmacovigilance center with a dedicated email address. (email: pharmacovigilance@efda gov. et)
- **8482 (toll-free line)**: 8482 is the EFDA toll-free number dedicated to notifying, providing, and/or requiring any regulatory-related issues. Through this toll-free number healthcare professionals or consumers can notify any AEs-related issues, and dedicated and trained experts can receive the information. While notifying AEs of related issues using this toll-free number, HCPs or consumers should make ready all the necessary information so that they can respond adequately to the authority's request.

2.5 To whom to report?

The final destination of all safety reports or AE is the national pharmacovigilance center of the EFDA. AE reports can be directly sent to the national pharmacovigilance center or through the sub-national level of the health care system. The sub-national levels that receive and transmit the

AE reports include EFDA branch offices, regional regulatory bodies, regional health bureaus, and regional (university hospital) pharmacovigilance centers.

2.6 Confidentiality of adverse event reports

The Ethiopia Food and Drug Authority maintains the confidentiality of all information related to the suspected medicine, AEs, patients, reporters, and MAHs. The information is used to generate evidence for the safe use of medicine and to protect the public from medicine-related problems.

2.7 What happens to the report?

Activities carried out at the national pharmacovigilance center after receiving the report include:

2.7.1 Validation and Verification

Up on the receipts of the report, EFDA will carefully review the report for the quality and completeness of thefilled information obtained in the report form. The reporter might also be contacted for informationin case of missing pertinent data by using the address he/she has provided.

2.7.2 Providing an Acknowledgement Letter to the Reporter

When the report has been received by the national Pharmacovigilance center, an acknowledgment letter and information education and communication materials prepared by the Pharmacovigilance Center will be sent to the reporter. If the report is sent through electronic reporting tools such as MedSafety mobile apps, an auto-generated acknowledgment letter will be sent to the reporter.

2.7.3 Follow-up Information

Any follow-up information for an event that has already been reported can be sent on a new AEform to the national pharmacovigilance center. Follow-up reports must be identified and linked to the original report to avoid duplications of reports in the pharmacovigilance database.

2.7.4 Data Entry to the Data Base

The pharmacovigilance center will store and manage all reported AEs in a dedicated database that will ensure their proper storage and confidentiality.

2.7.5 Investigation

All serious adverse event reports, any known or unknown cluster of events adverse events of community concern, and other eligible cases will be investigated by the authority and/or regional regulatory bodies as appropriate to establish a diagnosis and identify the cause of the adverse event.

For product quality defect reports, furtherinvestigation will be carried out. The investigation process may include site visits, taking samples, and laboratory analysis as required.

2.7.6 Causality Assessment for Eligible Investigated Cases

Serious adverse events and other eligible cases that are investigated will be classified for causal relationship by the national pharmacovigilance advisory committee. Whereas, non-serious adverse events will be assessed by the pharmacovigilance experts for their relatedness. The causality assessment or classification process follows primarily the WHO-UMC classification scale.

2.7.7 Analysis of the Report

The AEs report will be analyzed from the database regularly by the pharmacovigilance center. The summary reports containing relevant data variables will be prepared and communicated to the relevant stakeholders.

As part of the data analysis, the pharmacovigilance center will assess and review for detection of potential signals. A signal can initially be detected in a single incoming report. The literature, the WHO Signal document, the WHO Pharmaceutical Newsletter, and other international regulatory bodies will be regularly screened. Each detected potential signal will undergo further evaluation by the team. The final validation of signals will be done by the national pharmacovigilance advisory committee and recommendations will be forwarded for the required regulatory decision.

2.7.8 Regulatory Action

Based on the result of the different evaluations carried out and if necessary, using the quality control laboratory investigation results, and the recommendation obtained from the Pharmacovigilance advisory committee, regulatory measures or recommendations may be taken on the specific medicine or programs.

The regulatory actions might include a warning letter, revision of patient information leaflet (PIL), issuing dear healthcare professional letters(DHCPLs) and medicines safety alerts, product recall, product restrictions (up-scheduling, limited packaging, limited prescribers), suspension or cancellation of market authorization, etc.

2.7.9 Communication and Feedback

The final decision and/ or regulatory measures, summary reports, safety information, causality classification outcomes, and other relevant pharmacovigilance information will be communicated

to all concerned and relevant stakeholders who are involved in the national pharmacovigilance system. As part of the communication activates, the pharmacovigilance center will use different platforms, including the regular quarterly pharmacovigilance newsletter.

2.7.10.Incident and Crisis Management

The national Pharmacovigilance center is responsible to coordinate and design a framework for early detection, prompt assessment, and effective communication to mitigate potential risks and ensure swift resolution of incidents such as unexpected adverse reactions, quality defects, or supply disruptions. It provides comprehensive guidance on incident and crisis management to ensure the safety and efficacy of medicinal products.

The response to an incident will be addressed by an Incident Response committee that will be established by EFDA which will be composed of experts of various fields and relevant stakeholders. The committee ensures that all relevant information is gathered, analyzed, and shared promptly to make informed decisions and take appropriate actions. This collaborative approach enhances EFDA's ability to respond efficiently to incidents, minimizing the impact on public health.

Effective communication is a critical component of the EFDA's incident and crisis management strategy. The EFDA emphasizes the importance of clear, accurate, and timely communication with all stakeholders, including healthcare professionals, patients, and the public. This includes issuing safety warnings, updates, and guidance on managing the incident. EFDA also works closely with international partners to ensure a coordinated response to incidents that may have global implications. Through this robust framework, EFDA aims to maintain public trust and ensure the continued safety of medicinal products in the market.

Chapter Three

3. Roles and Responsibilities Pharmacovigilance Stakeholders

The well-functioning pharmacovigilance system works with the engagement and support of each healthcareprovider, the regulatory bodies, MAHs, PHPs, the public, and other stakeholders. Hence, each of these has an important role and responsibilities in the national pharmacovigilance system as indicated below.

3.1. Patient/Consumer

Patients who have experienced an adverse event to a drug or know thatan adverse event has occurred should report to the nearest health care facility, to a regional regulatory body, or EFDA using the toll-free number 8482. For further information refer to Guideline for consumer's reporting of side effects of medicines.

3.2. Healthcare professionals

All healthcare professionals in the country have a very important role in highlighting problems occurring when a marketed medicinal product is used. They need to notify and report to EFDA about suspected adverse drug reactions, medication errors, and product quality problems for the authority to act in preventing or minimizing the occurrence of medicine-related injury for other patients in the future. These activities include-

- Patient education on AEs including counselling to promote adherence and rational medicine use.
- Being vigilant and detecting adverse events.
- Diagnosis/detection and appropriate clinical management and treatment of patients presenting with adverse events.
- Monitor the quality of medicinal products to be dispensed or administered to patients.
- Identify medication errors and product quality defects.
- Adjust the dose or replace or stop the treatment for the ADR-suspected patient in consultation with the prescriber (clinician).
- Complete the yellow (AE reporting) form and/or other electronic reporting tools for all AEs and submit them to the national pharmacovigilance center (regional pharmacovigilance centers)

- Document the management of suspected ADR on the patient's history file.
- Analysis of the ADRs and/or events data for decision-making at the facility level.
- Ensure Pharmacovigilance activities are performed within the facility Drug and Therapeutic Committees

3.3. Healthcare Facilities

All healthcare facilities are responsible to:

- Establish and run a pharmacovigilance system as part of their routine practice and report Adverse events to the authority or regional regulatory.
- Incorporate pharmacovigilance activities in the annual plan of the health facility and allocate a dedicated budget.
    - Appoint a pharmacovigilance focal person who will coordinate adverse event monitoring and reporting activities at the health facility. The focal person will be mainly responsible for :
        a. Ensuring that all healthcare professionals are involved in detecting, assessing, managing, reporting, and preventing potential adverse events and have the appropriate knowledge and skill regarding adverse event monitoring.
        b. Ensuring that adverse event report forms and other reporting mechanisms are readily available and are known in all clinical areas and that healthcare professionals are familiar with how to use them.
        c. Be a leader in investigating adverse events that occurred in the facility.
        d. Analyze adverse event data, compile reports, and present them to the responsiblebody.
- Develop standard operating procedure/SOP/ on detection, management, and reporting of AEs to regional or national pharmacovigilance centers.
- Coordinate in-service training on medicine safety and the national and global pharmacovigilance system for healthcare professionals in collaboration with the national pharmacovigilance center and other partners.
- Maintain and document all records related to reported adverse events, share information when requested, and collaborate on any pharmacovigilance activities with authority.

- Implement the regulatory measures taken by the authority.
- Follow and implement the Pharmacovigilance requirements stated in the Ethiopian Hospital Reform Implementation Guideline (EHRIG) and Ethiopian Health center Reform Implementation Guideline (EHCRIG).

3.4. Regional pharmacovigilance centers

Considering the geography and population size of the country, it will be very difficult to monitor and ensure a complete pharmacovigilance system exists with a centralized pharmacovigilance model. Therefore, EFDA is trying to establish regional pharmacovigilance centers and decentralize PV activities at university hospitals, tertiary hospitals, and general hospitals.

The regional PV centers should create awareness and provide training on pharmacovigilance for health care professionals, collect AE reports, submit the reports by using Vigiflow, and document the reports.In addition, they should conduct a causality assessment of AEs.

3.5. Professional Associations

Professional associations need to play a major role in pharmacovigilance through adapting and disseminating pharmacovigilance information to their respective members. They should work on Providing pre-and in-service training as well as sensitization of their respective members on the AE monitoring system. Professional associations should also advocate, collaborate, and be engaged in pharmacovigilance research activities and projects.

3.6. Public Health Programs

Public health programs should work in collaboration with PV centers, and conduct monitoring of medicine safety activities in their respective public health programs. The Ministry of Health should include the pharmacovigilance system and activities in its documents and ensure proper integration of the pharmacovigilance system in documents and practices of lower levels. They need to ensure effective integration of the pharmacovigilance system in their respective organizational structures, (RHB, ZHD, WoHO, health facilities), policy documents, guidelines, training materials, annual plans, and practices.

The public health programs should allocate an appropriate budget for pharmacovigilance-related activities. Coordinate and provide pharmacovigilance training to healthcare professionals and ensure reporting of regular and quality AE data from each health facility to EFDA.

3.7. Market Authorization Holders (MAHs)

Manufacturers are uniquely placed for monitoring the safety of medicines, from the start of drug development and thereafter throughout the lifetime of the drug. Below are major activities tobe performed by pharmaceutical industries /MAHs/:

- Pharmaceutical companies should establish a pharmacovigilance system and employ a trained Qualified Person for Pharmacovigilance (QPPV) so that they can recognize, capture, and report safety information appropriately to EFDA.
- Develop and maintain the Pharmacovigilance System Master File (PSMF) according to the guidelines on Good Pharmacovigilance Practices (GVP).
- Collect, compile, and submit AE reports to the national PV center.
- Produce and submit Periodic Safety Update Reports (PSURs)/ Periodic Benefit Risk Evaluation Reports (PBRERs) to the national PV center.
- Conduct specific studies on safety and effectiveness under specific conditions and as necessary cover the cost.

3.8. Pharmacovigilance Advisory Committee (PAC)

The pharmacovigilance advisory committee members are composed of different health professions with specialized fields. The current composition includes Internists, Neurologist, Forensic Pathologist, Epidemiologist, Obstetrics andGynecologist, Pediatrician, Immunologist, Dermatologist, Pharmacologist, Pharmaco- epidemiologist, Cardiologist, Clinical Pharmacist and other expertise will be involved in causality classification depending on the nature of the case. The responsibilities of the committee contain but are not limited to the following activities,

- Review individual serious and unusual AE and other safety reports referred to by theEFDA to assess a potential causal link between the event and the medicine.
- Review the potential identified signal by the authority and validate the signal.
- Advise the national program managers and Regulatory Authority about AE-related issues when requested by those institutions.
- Make final decision on causality assessment of inconclusive investigations and ensuring quality control of pharmacovigilance system.

- Provides professional advice on the dissemination of drug information to the general public.
- Provides recommendations on measures to be taken on drugs with safety and efficacy problems.
- Provide recommendations for further investigation, education, corrective action, and communication.
- Give other drug-related advice as needed.

3.9. The National Pharmacovigilance center

The overall coordination of pharmacovigilance in the country lies at the national pharmacovigilance center at EFDA. Most of the roles and responsibilities of the national PV center are listed below.

- Develop and provide AE collection tools, methods, and procedures for regional pharmacovigilance centers, MAHs, healthcare professionals, consumers, and other relevant PV stakeholders.
- Collection of AE reports from healthcare professionals and other stakeholders.
- Perform active surveillance on selected medicines.
- Enter AE reports to national and international pharmacovigilance databases,
- Disseminate new ADR information from the global community to healthcare professionals and other stakeholders.
- Collaborative work with public health programs to maintain the safety of their medicines.
- Analyze and assess signals on reported AEs in collaboration with the National Pharmacovigilance Advisory Committee.
- Assess the benefit-risk balance of medicinal products in the market periodically and take interventions as appropriate.
- Make regulatory decisions based on the results of AE analysis.
- Alert prescribers, manufacturers, and the public to new risks of adverse reactions.
- Communicate with healthcare professionals, patients, and the public about the benefits, harm,effectiveness, and risks of medicines based on the available current safety profile.
- Give feedback and acknowledgments to AE reporters.

- Conduct gap identification assessments of healthcare professionals and coordinate the capacity building training, including in-service and pre-service pharmacovigilance training.
- Coordinate pharmacovigilance/medicine safety/ harmonization and review meetings for different stake holders.

3.10. Academia and research institutions

The authority should work in collaboration with health teaching institutions and other related institutions in the monitoring of medicine safety or pharmacovigilance through teaching, training, research, policy development, ethics committees, and the clinical service they provide. Some of the roles and responsibilities of academia and research institutions are listed below.

- Research pharmacovigilance/medicinal product safety/ issues to generateevidence for policy-making and priority setting.
- Facilitate and provide pre-service and postgraduate PV training in the field.
- Inclusion of basic pharmacovigilance topics in the pre-service curriculum.
- Expansion of scientific knowledge in drug safety and create pharmacovigilance awareness.
- Recognize AE monitoring as an essential quality assurance activity mainly in their clinical practices.
- Establish a system to extract information on Drug Therapy Problems (DTP) during the provision of clinical pharmacy courses and to pull the reports to the national pharmacovigilance center.
- Collaborate with the pharmacovigilance center and Drug Information Centers (DIC) in research activities.

3.11. World Health Organization (Uppsala monitoring center/UMC/)

The WHO ADR monitoring center at UMC provides technical support and guidance to national pharmacovigilance centers. It maintains the global ADR database (Vigibase) where ADR data from all member countries are collected and stored. WHO Analyses the reports from the ADR database to identify early warning signals of serious adverse reactions. In general, undertakes research into the mechanisms of action to aid the development of safer and more efficient medicines.

3.12. Developmental Partners

Various developmental partners provide technical and financial support for pharmacovigilance activities. In conducting these activities, they should plan in collaboration with the national and regional pharmacovigilance centers. In doing so, they support the sharing of global good practices in pharmacovigilance and mobilization of resources.

3.13. Other Stakeholders (media, advocacy group, consumer association, lawyer)

Other stakeholders (media, advocacy groups, consumer associations, lawyers, etc) in pharmacovigilance playa strong role in the monitoring of medicine safety. These stakeholders advocate the importance of medicine safety monitoring to the public and create awareness of pharmacovigilance policy and activities through appropriate platforms.

They should also communicate preventive measures and regulatory actions on medicine safety to the public using appropriate channels. In disseminating medicine safety information, they should refrain from using unverified medicine safety-related information and cooperate with EFDA to provide balanced and evidence-based medicine safety information during crisis.

Chapter Four

4. Marketing Authorization Holders (MAHs)

According to article 14 sub article 1-5 of the Ethiopian Pharmacovigilance Directive 932/2015, every market authorization holder should have responsibilities to set up a pharmacovigilance system for their medical products, to assign a Qualified Person for Pharmacovigilance (QPPV), to respect and implement regulatory measures taken by the authority, and to establish a risk management plan for its medicines to monitor the safety and quality of the medicine under its authorization status and report adverse events to prevent and minimizethe AE's from harming the public.

4.1. Pharmacovigilance and appointment of the QPPV

The MAHs are required to operate a pharmacovigilance system to detect, assess, and report adverse events associated with their medicinal products. The pharmacovigilance system should be regularly monitored to ensure compliance with regulatory obligations. All adverse events must be reported by national and international legislation and relevant guidance to EFDA. The MAH is responsible for appointing and having at its disposalpermanently and continuously, a qualified person for pharmacovigilance (QPPV) who is responsible for the maintenance of the MAH's pharmacovigilance system.

The MAH should:

- Ensure that the QPPV has received appropriate training.
- Ensure that the QPPV has sufficient authority to:
  - Implement pharmacovigilance activities.
  - Provide inputs into the Risk Management Plan when necessary.
  - Provide inputs into the preparation of regulatory documents to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to Patients and Healthcare Professionals)
- Ensure that there are appropriate processes, resources, communication mechanisms, and access to all sources of relevant information in place for the fulfillment of the QPPV's responsibilities and tasks.
- Notify the authority of the absence of the QPPV not later than 14 days after the position

becomes vacant.

- Have a signed employment agreement with the QPPV. The QPPV should be a full-time permanent employee.
- Submit the following information to the Authority relating to the QPPV.
  - Curriculum vitae including key information on the role of the qualified person.
  - Contact details include but are not limited to the name, telephone, fax and e-mail, postal, and official working address.
  - A description of the responsibilities guaranteeing that the QPPV has sufficient authority over the pharmacovigilance system to promote, maintain, and improve compliance.
  - Details of back-up arrangements to apply in the absence of the QPPV.
- Ensure that the qualifications of the QPPV are detailed as follows.
  - The person designated as QPPV should be a healthcare professional with a minimum of a bachelor's degree in health sciences and at least two years of experience in pharmacovigilance-related activities. However, the authority highly recommends that pharmacists and medical doctors with appropriate PV-related training be assigned as QPPV.
  - The QPPV should receive formal training in pharmacovigilance recognized by the authority.
  - The QPPV should not be freelance but needs to be an employee of the MAH or a local representative who can be reached 24/7.
  - The assigned QPPV should be proficient in English and preferably understand at least one local language of Ethiopia.
- Ensure that the responsibilities of the QPPV are executed appropriately.
- The MAHs should appoint the QPPVs responsible for all products registered and marketed in Ethiopia.
- The Qualified Person Responsible for Pharmacovigilance should be resident in Ethiopia.

4.2. Responsibility of the QPPV

The QPPV should have the following responsibilities.

- Act as a single point of contact for the authority on all matters relating to pharmacovigilance and safety of marketed products including pharmacovigilance inspections.
- Establish and maintain a system that ensures that information about all suspected adverse events, which are reported to the marketing authorization holder by any means, are collected, collated, processed, evaluated, and forwarded to the authority in line with the timelines stipulated by EFDA.
- Prepare the following documents for submission to the authority.
    - ✓ Periodic Safety Update Reports (PSURs) /Periodic
    - ✓ Periodic Benefit-Risk Evaluation Reports (PBRER), when necessary
    - ✓ Company-sponsored pre- and post-registration study reports
    - ✓ Risk Management Plans.
    - ✓ Ongoing pharmacovigilance evaluation during the post-registration period.
    - ✓ Ensure that any request from the authority for additional information deemed necessary for the evaluation of the risk-benefit ratio of a marketed product is provided to the authority promptly and fully.
    - ✓ Oversee the safety profiles of the company's marketed products and any emerging safety concerns.

4.3. Reporting safety information on medicines

Any Market Authorization Holder should report periodic safety update reports, Periodic Benefit Risk Evaluation Reports, and Individual case safety reports in line with the national Pharmacovigilance Directive 932/2015. Concerning the reporting of safety information to the regulatory authority, the following timelines should be followed.

a) Any serious adverse events should be notified within 48 hours and,must be reported as soon as possible but no later than 15 calendar days of initial receipt of the information.

b) Non-serious Adverse events must be reported within 90 days after awareness of the event.

c) The market authorization holder should also inform the authority of any significant safety

issue(from other than single case reports) or action taken by a foreign agency that affects the safety or useof products marketed, donated, imported, and/or for compassionate use including the bases for such action within 3 working days of first knowledge by the market authorization holder.

d) Information on withdrawal of the registration status in any country because of safety issues must be noted to the authority within 48 hours of the first knowledge by the market authorization holder.

e) For reporting of ICSRs, the MAHs can use either CIOMS or ICH (E2B) forms. The completed form should be submitted to the authority in hard copy or through email. Other Safety information reports (Example: PSURs/PBRERs, RMPs) should be prepared as per international standards and be submitted using the Authority's e-mail. The MAH can submit either PSUR or/and PBERER depending on the company's procedures.

4.4. Periodic safety update reports/ Periodic Benefit-Risk Evaluation report

The main objective of PBRERs/PSURs is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.

The submission timeline for PBRERs/PSURs will be based on the international birth date (IBD) of the medicine. For new medicines that are registered and marketed in the country, BRERs/PSURs should be submitted to the authority every 6 months for the first two years after market approval, annually for three years, and thereafter every three years. If no Adverse events have been received by the market authorization holder, it is obliged to submit a "Null" report, i.e., a report stating that it has not received any adverse event reports on its medicinalproduct as part of PBRERs/PSURs. However, when a medicine is marketed in a foreign country but new to the Ethiopian market, the authority may require the previous PBRERs/PSURs as needed.

The following timelines apply for the submission of PBRERs/PSURs:

a) Within 70 calendar days of the Data Lock Point (Day 0) for PBRERs/PSURs covering intervals of 6 to 12 months.

b) Within 90 calendar days of the DLP (Day 0) for PBRERs/PSURs covering intervals over 12

months.

c) Ad hoc PBRERs/PSURs should be submitted upon request within 90 calendar days of the DLP unless otherwise specified.

The PBRERs/PSURs should emphasize the following contents:

a) Scientific evaluation of the benefit-risk profile

b) Recommend action(s) to optimize the benefit-risk profile.

c) Summaries of relevant scientific/clinical data including literature searches.

d) Summarizing relevant new safety information that could have an impact on the benefit- risk profile of the medical product.

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

f) All data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

g) Collection of adverse events (AEs) information (i.e. local serious AEs, local non- serious AEs, foreign serious AEs, foreign non-serious AEs, case reports published on international or local literature including academic conferences);

h) In addition, an executive summary of any changes that may have occurred from the last submission. Classify whether these changes are major or minor. The reaction terms used in the report should be by the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The MAH should continuously evaluate whether any revision of the reference product information/Reference Safety Information (RSI) is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI/ made during the interval should be described in the executive summary.

4.5. Risk Management Plans (RMPs)

The aim of a Risk Management Plan (RMP) is to document the risk management system (RMS) considered necessary to identify, characterize, and minimize a medical product's important identified risk.

The products which are subject to RMP and the time when the plan is applied are described below:

- In the time of approval review of new drugs (include new additional indication and dosage, revised/additional dosage and administration, new combination drug, additional dosage form: the same shall apply hereinafter), and when Safety Specification is newly submitted during the re-examination period.
- When Safety Specification is newly submitted in the post-marketing phase of generic drugs and drugs for which the re-examination was completed.
- At the time of approval of the generic, in the case that its reference drug has already been obligated to develop an additional risk minimization activity.

The RMP document contains:

1. The identification or characterization of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and alsoon which safety concerns need to be managed proactively or further studied (the ‘safety specification’);
2. The planning of pharmacovigilance activities to characterize and quantify clinically relevant risks, and to identify new adverse reactions (the ‘pharmacovigilance plan’);
3. The planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the ‘risk minimization plan’)
4. The risk management system should be proportionate to the identified risks the potential risks of the medicinal product, and the need for post-authorization safety data.

The structure and details regarding the pharmacovigilance plan should be as prescribed in the current version of the ICH E2E Pharmacovigilance planning guideline. The structure of the pharmacovigilance plan can be varied depending on the product in question and the issues identified in the safety specification. The structure should contain the following:

- Summary of Ongoing safety issues

- Routine pharmacovigilance practice
- Action plan for safety issues
- Summary of actions to be completed, including milestones.

The MAH should have RMPs for their medicinal products throughout their lifecycle. The RMPs should be proportionate to the identified risks the potential risks of the medical products and the need for post-authorization safety data.

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

The safety concerns included in the RMP document may be removed based on the following circumstances.

i. For important potential risks:

- When accumulating scientific and clinical data does not support the initial supposition, or the impact on the individual is less than anticipated.
- When there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk.

ii. For important identified risks:

- In certain circumstances, where the risk is fully characterized and appropriately managed (e.g. For products marketed for a long time for which there are no outstanding additional pharmacovigilance activities and/or the risk minimization activities have become fully integratedinto standard clinical practice such as inclusion into treatment protocols or clinical guidelines.

iii. For missing information:

- The missing information might not be appropriate anymore once new data become available, orwhen there is no reasonable expectation that further feasible pharmacovigilance activities could further characterize the safety profile.

Format of Risk management plan

The MAH should prepare and submit the RMP to the authority. This document is expected to be submitted as one single document including all sections andannexes, as relevant. RMP should contain the below minimum information.

a) Safety Specifications: identification or characterization of the safety profile of the medicines with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');

b) Pharmacovigilance plan: planning of pharmacovigilance activities to characterize and quantifyclinically relevant risks, and to identify new adverse reactions.

c) Risk minimization plan: planning and implementation of risk minimization interventions, including the evaluation of the effectiveness of these activities.

4.6. Pharmacovigilance System Master File (PSMF)

The PSMF is prepared to provide an overview of the pharmacovigilance system, which may be requested and assessed by the EFDA during MAH or post-market authorization. It should also contribute to the appropriate planning and conduct of self-audit by the MAH and inspections or other verification of compliance by EFDA.

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

a) Gain assurance that a pharmacovigilance system has been implemented by the EFDA and international requirements.

b) Confirm aspects of compliance with the system.

c) Obtain information about deficiencies in the system, or non-compliance with the requirements.

d) Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

The PSMF should include documents to describe the pharmacovigilance system; the content of the PSMF should reflect the globally available safety information for medicinal products authorized in the country. The PSMF to be presented should fulfill the minimum international requirements. MAHs should always maintain the pharmacovigilance system master file (PSMF)

and make it available upon request by the EFDA.

4.7. Case reports from published scientific literature.

The MAH should review both local and international journals regularly. Whenever published suspected AEs related to their medical products occur in and outside Ethiopia for registered products, the MAH should submit the full article to the EFDA within not more than 30 calendar days of the publication. The published report should be completed for each identifiable patient with an identifiable adverse drug reaction and submitted to the EFDA.

4.8. Post-Authorization Safety Studies (PASS)

A post-authorization safety study (PASS) is any study relating to an authorized medical product conducted to identify, characterize, or quantify a safety hazard, confirm the safety profile of the medicinal product, or measure the effectiveness of risk management measures.

The Pharmacovigilance methods to address specific situations can vary, depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information and whether signal detection, evaluation, or safety demonstration is the main objective of further study. The PV methods include passive and active surveillance. The sponsors/MAHs should use the mostup-to-date methods that are relevant and applicable.

The authority may require MAHs to conduct post-authorization studies on safety and efficacy at the time of the granting of the marketing authorization or later. The need for a PASS could be identified by the EFDA during a post-authorization procedure, for example, an extension or a variation to a marketing authorization, a renewal procedure, or a PSUR procedure. The authority will notify with an official letter indicating the objectives and timeframe for the submission and conduct of PASS. The request may also include recommendations on key elements of the study (e.g., study design, setting, exposure(s), outcome(s), and study population).

A study should be classified as PASS when the main aim for initiating the study includes any but not limited to the following objectives:

a. To quantify potential or identified risks

b. To evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g., pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);

c. To evaluate the risks of a medical product after long-term use;

d. To provide evidence about the absence of risks;

e. To assess patterns of drug utilization that add knowledge regarding the safety of the medicinalproduct or the effectiveness of a risk management measure (e.g., collection of information on indication, off-label use, dosage, co-medication, or medication errors in clinical practice that mayinfluence safety, as well as studies that provide an estimate of the public health impact of any safety concern);

f. To measure the effectiveness of risk management measures.

The authority may order the MAH to conduct PASS due to the following concerns;

a) As an obligation by Risk Management Plans stipulated in this guideline because they are keys to the risk-benefit profile of the product.

b) As a specific obligation in the framework of a marketing authorization granted under exceptional circumstances.

c) Required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimization activities. Such studies included in the pharmacovigilance plan are also legally enforceable.

The Market Authorization Holder should submit the PASS protocol for review and approval. The study protocol should be developed by individuals with appropriate scientific backgrounds and experience. If the necessity for amendment arises, the PASS protocol should be amended and approved bythe Authority as needed throughout the study.

PASS should be initiated, managed, or financed by a marketing authorization holder voluntarilyor under imposed obligations by the EFDA and progress reports on PASS studies should be submitted. In cases where PASS needs to be outsourced, the research contract between the marketing authorization holder and investigators should ensure that the study meets its regulatory obligations.

Any new information that may affect the risk-benefit balance of the product should be communicated as an emerging safety issue to EFDA. The reporting should be as per the reporting requirements described in chapter two of this guideline.

The MAH initiating, managing, or financing a PASS should communicate to EFDA, the final

manuscript of the article within two weeks before submission for publication to allow EFDA to review in advance the results and interpretations to be published.

4.9. Clinical trials

The authority uses safety information obtained through clinical trial studies conducted in Ethiopia. Such safety reports will be treated as per the national regulations and requirements for clinical trials.

Chapter Five

5. Pharmacovigilance Inspections and Self-audits

Articles 21(1) of the Pharmacovigilance directive 932/2022 gives EFDA the responsibility to perform pharmacovigilance inspections and regulate market authorization holders with respect to their monitoring of safety, quality and efficacy of their medicines.

The authority conducts pharmacovigilance inspections of the companies whose products have been granted marketing authorization in Ethiopia to ensure that MAHs comply with their pharmacovigilance obligations.

The objectives of the PV inspections include:

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

5.1. Types Inspection

There are four types of post authorization pharmacovigilance inspections that would be conductedby EFDA.

5.1.1. Routine inspections

Routine pharmacovigilance inspections should be scheduled in advance as part of inspection programmes. The frequency of routine inspections may also be performed on case-to-case basis depending on other considerations like risk analysis criteria. The MAH or manufacturer should be notified of the planned inspection in 14 calendar days in advance. This is to ensure adequate preparation and availability of relevant individuals at the sites to be inspected. Occasionally, EFDA may give a short notice when the inspection is conducted in a short timeframe due to urgent safety reasons. A MAH that is expected to have pharmacovigilance obligations should be inspected at least once in three years depending on the type of inspection to be performed.

5.1.2. Pharmacovigilance System and product-related inspections

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

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

5.1.3. Investigative or "for cause" inspections

Investigative or "for cause" inspections will be conducted when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. This inspection should focus on specific pharmacovigilance processes or include an examination of identified compliance issuesand their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. These inspections may arise when for example; one or more of the triggerslisted below are identified:

a) Risk-benefit balance of the product:

i. Change in the risk-benefit balance where further examination through an inspection is considered appropriate;

ii. Delays or failure to identify or communicate a risk or a change in the risk benefit balance;

iii. Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the EFDA, as needed;

iv. Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the EFDA.

v. Suspension or product withdrawal with no advance notice to the Authority

b) Delays or omissions in reporting and poor quality or incomplete reports;

c) Failure to provide the requested information or data within the deadline specified by the Authority and poor quality or inadequate provision of data to fulfill requests for information.

d) Delays or failure to carry out specific obligations relating to the monitoring of product safety and the fulfillment of risk management plan (RMP) commitments.

e) Delays in the implementation or inappropriate implementation of corrective and preventive actions.

f) Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP)

g) Inspection information received from other medicine regulatory authorities, which may highlight issues of non-compliance, others:

h) Concerns following review of the pharmacovigilance system master file;

i) Other sources of information or complaints.

5.1.4. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritize re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also beappropriate when it is known from a previous inspection that the inspected MAH had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

5.1.5. Remote inspections

These are pharmacovigilance inspections performed by inspectors remotely from the premises of theMAH. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the country but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak ortravel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical

aspects of the remote inspection should be considered following liaison with the marketing authorization holder.

Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection hasrevealed issues which require on-site inspection or if the objectives of the inspection could not bemet by remote inspection.

5.2. Inspection planning

The Authority plans the inspection and informs the MAH with a preliminary notification about thescheduled inspection. Relevant documents will be requested to facilitate the inspection at least seven calendar days to the scheduled inspection date.

5.3. Conduct of inspection

The pharmacovigilance inspection will be conducted at the local representative or the MAH's location. The local representative or the MAH has the right to choose which members of staff participates in these meetings but should include the QPPV.

5.4. Reporting and Follow-Up

Deficiencies found during the Pharmacovigilance inspections are grade as follows:

- Critical: A deficiency in pharmacovigilance systems, practices or processes that adversely affectsthe rights, safety or well-being of patients or that poses a potential risk to public health.
- Major: A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health
- Minor: A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

In general, preliminary findings will be communicated at the closing meeting. An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report. The report is sent to the local representative or MAH, usually within 15 calendar days of the site visit or the date of the provision of the last document requested.

5.5. Regulatory Measures

After the report is finalized, the authority will inform the MAH regarding the non-compliance and advised on how this can be corrected. In addition, the authority may also conduct inspection to determine the extent of non-compliance and re-inspection to ensure compliance is achieved. Based on the results obtained, the authority may apply regulatory actions and sanctions as per article 22 of the pharmacovigilance directive 932/2022.

5.6. Self-Audit

The MAH are expected to perform audits of their pharmacovigilance systems including risk-basedaudits of their quality systems. The MAH should develop audit criteria that reflect their pharmacovigilance and quality systems and maintain records, statements, or other information, which are relevant to the audit criteria and can be verified by the authority during pharmacovigilance inspections. MAH should conduct self-audit at least once yearly.

Chapter Six

6. Safety Communication

As stated in article 21 of the pharmacovigilance directive 932/2022, the authority is responsible to provide information on adverse events and signals to the public and other stakeholders on a timely basis. The aim of safety communication is to provide timely evidence-based information on the safety, quality, and efficacy of medicine at each level of the healthcare structure to promote rational medicine use and support risk minimization practices, and to make a decision for the regulatory authority.

Safety communication also ensures providing timely and accurate information about the potential risk-benefit and any changes in the safety profile of a medicine. A reliable flow of relevant information allows people to stay informed about the benefits and risks of medicines, the importance of reporting AEs, and minimize unnecessary dialogue between patients and healthcare professionals.

6.1. Target audience

Based on the nature and importance of the safety information, EFDA should communicate to relevant stakeholders listed below.

- The patient, client
- General public
- Healthcare professionals
- Professional associations
- Consumer associations
- Healthcare facilities
- Regional Health bureaus/Regional regulatory bodies
- Ministry of health
- Teaching institutions
- Research institution

- Medicine manufacturer, importer, distributor, exporter, retail outlet
- Development partners, donors
- International organizations such as WHO, UNICEF
- The Media
- Other Governmental organizations

In addition to external stakeholders, safety information can be communicated within the authority among different executive offices and EFDA branches offices.

6.2. Communication channels

Selection appropriate channels and language is crucial for safety information communication. The communication channels and language will be decided based on the information to be transmitted, the objective of communication and the target audience. Additional we need to consider the preference of the target audience while selecting communication channels.

The channels of safety communication include but not limited-

- Mainstream Media
- Website
- Newsletters
- Official letter
- Emails
- SMS messages
- Social Media
- Media Campaigns
- Formal correspondences (Dear Health Care Professional letters,)
- Interpersonal Communication

6.3. Safety communication by the marketing authorization holder

Prior to making a public announcement related to new medicine safety information, the MAH is

required to inform the authority and get approval before disseminating the information. The MAH is responsible for ensuring that the safety information to be communicated to the public is not misleading.

The detailed procedure of safety communication should be carried out according to the authority communication strategy.

Chapter Seven

7. Monitoring and Evaluation

Monitoring and evaluation is a critical component of the pharmacovigilance system. Continuous monitoring and periodic evaluation of activities by appropriate tools needs to be carried out to know whether activities are implemented according to the plan or need some amendment so that the result will be communicated to all responsible bodies.

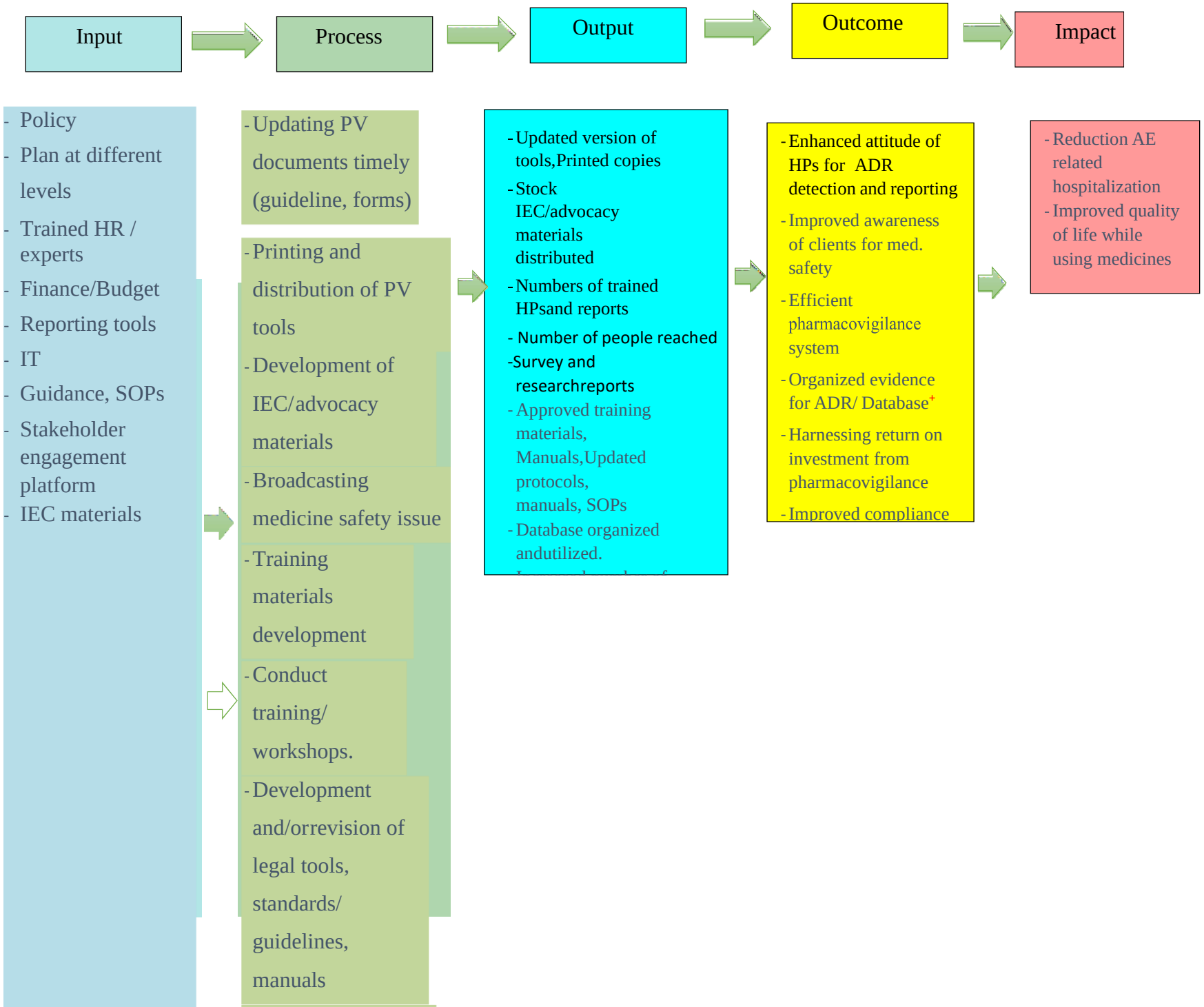
During monitoring and evaluation of the national pharmacovigilance system, it is preferable to use standardized and validated tools. The commonly used tools for assessing pharmacovigilance activities are the WHO pharmacovigilance indicator and/or Indicator-Based Pharmacovigilance Assessment Tool (IPAT). However, specific tools can be developed and used by the national PV center to monitor and evaluate PV activities at different levels.

The comprehensive M&E framework aims to monitor the resources invested, the activities implemented, services delivered as well as evaluate outcomes achieved and the long-term impact of the PV activities.

7.1. Logic Model for monitoring of pharmacovigilance performance

Monitoring the safety of medicines is a regulatory function and it is getting attention globally and nationally. Strengthening the pharmacovigilance system benefits the patient, the health system, the country, and the global community. This is supported by the regulatory strategic plan and the roadmap supported with different interventions to be implemented at different levels and individuals. Monitoring the performance of each level is an important task. Hence, this calls for understanding the problem and having a tracking mechanism using an appropriate M&E system.

The goal of monitoring and evaluation of pharmacovigilance activities is to strengthen the safety monitoring of medicines and contribute to the reduction of medicine-related problems. Monitoring the performance of the pharmacovigilance system should be conducted at all components of the system starting from the input to the impact level as described in the following diagram.


Input
Process
Output
Outcome
Impact
- Policy
- Plan at different levels
- Trained HR / experts
- Finance/Budget
- Reporting tools
- IT
- Guidance, SOPs
- Stakeholder engagement platform
- IEC materials
- Updating PV documents timely (guideline, forms)
- Printing and distribution of PV tools
- Development of IEC/advocacy materials
- Broadcasting medicine safety issue
- Training materials development
- Conduct training/ workshops.
- Development and/orrevision of legal tools, standards/ guidelines, manuals
- Updated version of tools,Printed copies
- Stock IEC/advocacy materials distributed
- Numbers of trained HPsand reports
- Number of people reached
-Survey and researchreports
- Approved training materials, Manuals,Updated protocols, manuals, SOPs
- Database organized andutilized.
- Enhanced attitude of HPs for ADR detection and reporting
- Improved awareness of clients for med. safety
- Efficient pharmacovigilance system
- Organized evidence for ADR/ Database+
- Harnessing return on investment from pharmacovigilance
- Improved compliance
- Reduction AE related hospitalization
- Improved quality of life while using medicines

7.2. Monitoring and Evaluation platforms and indicators

The performance of the pharmacovigilance system needs to be monitored to review the implementation of planned activities in quarters, half-year, and annually at regional and federal levels using existing platforms. While selecting indicators the following criteria were followed:

Useful: reflects an important dimension of performance

Practical: can be obtained timely, at a reasonable cost, and frequently enough to inform the progress andinfluence decisions

Clear: easily understood and calculated

Measurable: can be defined in quantitative or qualitative terms and used within existing constraints on information quality and availability

Reliable: permits consistent assessment over time among different observers

Valid: is a true measure of what it is meant to measureThe selected indicators include:

S.N	Name of Indicator	Type	Data Source	Frequency	level
1.	Dedicated budget available for pharmacovigilance-related activities	Input	Doc. Review	Quarterly	NPVC, Regional, Zonal, HFs
2.	A dedicated pharmacovigilance focal person	Input	Nomination letter	Annual	Regional, Zonal, HFs
3.	Incorporation of pharmacovigilance activities in annual plan	Input	Annual plan/report	Annual	Regional, Zonal, HFs
4.	Availability of reporting forms (AE and AEFI)	Input	Observation	Monthly	HFs
5.	Availability of guidelines (PV and AEFI)	Input	Observation	Quarterly	Regional, Zonal, HFs
6.	Availability of trained staff and	Output	Training	Half-year	Regional, Zonal,

	Healthcare professionals		record/ certificate		HFs
7.	Existence of procedures or SOPs for detecting and reporting AEs to the national PV center	Input	Doc. Review	Annual	HFs
8.	Existence of a pharmacovigilance or medicine safety bulletin	Output	Doc. Review	Quarterly	NPVC
9.	Total number of AE reported to the national PV center in the last calendar year (expressed as number per 100 000 people in the catchment area)	output	Archives/record	Quarterly	Regional, Zonal, HFs
10.	Number of investigated serious adverse event out of reported serious cases	output	Archives	Quarterly	Region and NPVC
11.	Number of cases assessed for causality out of investigated cases	output	Archives	Quarterly	NPVC
12.	Total number of AE reports received by the NPVC	output	Archives	annually	NPVC
13.	Total number of AE reports shared to global database (vigibase)	output	Archives	annually	NPVC
14.	Number of potential signals assessed	Output	Archives	Annually	NPVC
15.	Proportion of assigned QPPV per registered MAHs	Output	Archives	Quarterly	NPVC
16.	Number of pharmacovigilance inspections conducted at MAHs	Output	Archives	Annual	NPVC

17.	Number of PSURs/PBRERs and RMPs reviewed	outcome	Archives	Quarterly	NPVC
18.	Number of safety/quality alerts or regulatory recommendations issued to HCPs and stakeholders	outcome	Archives	Quarterly	NPVC

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Annexes

Annex 1. Adverse event reporting form

Ethiopian Food and Drug Authority (EFDA)

Suspected Adverse Drug Event (ADE) Reporting Form

Patient Name (Initial)	Card no/MRN	Age, Date of birth	Sex	Weight	Height

Report type □ Initial □ Follow up	Substance of abuse

Information on suspected drug

Drug name (write all information including brand name, batch no and manufacturer)	Dose/dosage form, route, frequency	Date drug taking was started (D/M/Y)	Date drug reaction started (D/M/Y)	Date drug taking was stopped (D/M/Y)	Indication (Reason for drug use)

Information on concomitant drug/vaccine, including herbal medicines

Drug name(write all information including brand name, batch no and manufacturer)	Dose/dosage form, route, frequency	Date drug taking was started (D/M/Y)	Date drug taking was stopped (D/M/Y)	Indication (Reason for drug use)

Adverse drug event description (include all available laboratory test results)

Was the reaction serious? □ YES □ No Reason for seriousness □ Death □ Hospitalization/prolonged □ Disabling □ Congenital anomaly □ Life threatening □ Other medically important conditions	**Reaction subsides after D/C of suspected drug, if D/C** □ YES, Date_____ □ No □ Unknown **Reaction reappears after restart (if so) of suspected drug.** □ YES □ No □ Information not available

Treatment of reaction

Outcome: □ Died □ Recovering □ Not yet recovered
□ Recovered without sequelae □ Recovered with sequelae* □ Unknown

*Sequelae

Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc

Reported by: Name	Profession:	Email address:	Telephone

Name of health institution	Date

Product quality problem: Color change, separating of components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling, etc (Write if anything different than given above)

Drug name	Batch No	Manufacturer	Dosage form and strength	Size /type of package

For office use only	
Received on:	Registration no:
Key: D/M/Y ; Date /Month/Year D/C; Discontinue treatment Y;YES N;NO	

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This ADE reporting form is prepared and printed by EFDA in collaboration with the Global Health Supply Chain Program- Procurement and Supply Management (GHSC-PSM) project with a financial suport from USAID

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What to report?

All suspected reactions to drugs
Unknown or unexpected reactions
Unexpected therapeutic effects
All suspected drug interactions
Product quality problems
Treatment failures
Medication errors

NB. Drugs includes

Conventional drugs
Herbal drugs
Traditional medicines
Biologicals
Medical supplies
Medicated cosmetics

From --

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Toll free telephone: 8482

P.O. Box 5681-Tel.0115-523142
Addis Ababa, Ethiopia

Annex II. WHO-UMC Causality assessment criteria of medicines

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