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ETHIOPIAN FOOD & DRUG AUTHORITY

Product safety Directorate,

Ethiopian Food and Drug Authority

Guideline for Adverse Drug Events Monitoring (Pharmacovigilance) of Medicines

EFDA/GDL/004

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ABBREVIATIONS AND ACRONYMS

ADE	Adverse Drug Event
ADR	Adverse drug reaction
AEFI	Adverse event following Immunization.
DLP	Data Lock Point
DTC	Drug and Therapeutic Center
DTP	Drug Therapy Problems
EFDA	Ethiopian Food and Drug Authority
EPI	Expanded Period of Immunization
GBT	Global Bench Marking 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 materials
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 Bureaus
RMI	Risk Minimization Intervention
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 population's health care needs is one of the priorities of our national health care system and medicines are one of the most essential components in the health care system. One part of this is ensuring the safety, efficacy and quality of medicines provided to the public. Worldwide, numerous numbers of medicines are being released into the market every day with incomplete knowledge as to their safety levels. Limited information from clinical trials on safety of medicines creates a concern. This concern calls for a Comprehensive pharmacovigilance system.

Through the mandate given to the Ethiopian Food and Drug Authority with proclamation no. 1112/2029 and articles under Part two, Article 4(9) and Article 38(3) and regulation no. 299/2013, on Article 31(1); as well as through the Pharmacovigilance directive No. 932/2022, the Authority has been implementing overall pharmacovigilance activities in the country. A complete pharmacovigilance system needs an up to date and practical guideline to provide information and guidance to the various partners of pharmacovigilance as to what their roles and responsibilities should be towards the maintenance of a national medicines safety monitoring system.

With the above context, I would like to present this revised pharmacovigilance guideline. This updated version addresses important stakeholders like the Market Authorization Holders with detailed elaboration of their involvement in medicine safety. Furthermore, International good pharmacovigilance practices including Pharmacovigilance Inspection guidance are incorporated.

I would like to take this opportunity to thank all those who contributed to developing and printing this Pharmacovigilance Guideline. I also call upon interested parties to continue their support by forwarding their comments and suggestions to the Ethiopian Food and Drug Authority (EFDA), p.o.box 5681 Addis Ababa, Ethiopia., Tel.251-115524122, e-mail: contactefda@efda.gov.et.

Heran Gerba

Director General, EFDA

GLOSSARY OF TERMS

Adverse drug event- means any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.

Adverse drug reaction- 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 for 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.

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

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

Identified risk – means an undesirable clinical outcome and 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.

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

Marketing authorization holder (MAH) – An individual or a corporate entity/company responsible for placing a pharmaceutical product in the market either through importation, donation, distribution, or sale in Ethiopia. This individual or company is responsible for all aspects of the product, including quality and 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. (National Coordinating Council for Medication Error Reporting and Prevention)

Medicine-means any substance or mixture of substance 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 a medicine obtained at defined times post marketing authorization.

Periodic Benefit-Risk Evaluation Report (PBRER) – means an update of the worldwide marketing experience of a medicine at defined times with focus on formal evaluation of benefit in special population at defined times during 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): a detailed description of the Pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products.

Product quality defect- means attributes of a medicinal product or component which may affect the 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 and for which there is scientific evidence to suspect the possibility of a causal relationship with the medical product.

Qualified Person Responsible for Pharmacovigilance (QPPV) - means a healthcare professional, usually an employee of a pharmaceutical manufacture or importer, who is personally responsible 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 or reaction -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 a 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.

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

Scope of the guideline

This guideline applies to all pharmaceutical products (conventional medicines, herbal medicines, other traditional and complementary products, biologicals other than vaccines) whose authorisation to market or distribution include requirements for safety monitoring or pharmacovigilance. The guideline is also written to outline the roles and responsibilities of stakeholders involved in manufacturing, importing, distributing, supplying, prescribing, dispensing, and administering medicines in the country.

The objectives of pharmacovigilance are listed below:

• detect previously unknown medicine-related problems as early as possible

• identify risk factors or risk groups of patients

• detect increased frequency of medicine-related problems

• improve knowledge of the clinical features of known serious adverse drug reactions

• Encourage reporting and strengthen of monitoring of ADEs

The findings are used to create awareness on and promote rational, safe, and more effective use of medicines by healthcare professionals, patients, and consumers.

The scope of the Guideline doesn't include the safety monitoring of medical devices.

II. INTRODUCTION

Background

The use of medicines is an important aspect of many health programmes that are designed to improve the health of a target population. Their cost to the health budget is between 6% in developed countries and 45% in some developing countries. Medicines are important not only because of their capacity to treat and prevent disease, to support health programmes, but also because the confidence of the public in the health policies of their countries is inextricably linked to their confidence in the availability of medicines that are safe and effective. Medicinal products have undergone 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. Pregnant

mother, children, elderly, and patients with certain diseases or on certain medicines have often been excluded in these studies. These conditions make it unfeasible 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 or product quality defects and self-medication. The post-marketing period is therefore a very important period 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/internationally, national post-marketing safety monitoring is necessary.

Moreover, the effect and safety of a medicine can also be affected by population specific genetics, diet, malnutrition, and nation specific disease prevalence. Social and cultural traditions, healthcare systems and health professional practices can lead to sub-optimal use of medicines with increased risks for harm. National drug production, distribution, and availability of medicines (or lack of availability) can also influence patient safety.

The drug delivery process is dependent on patients' and healthcare professionals' vigilance in real-life settings to detect potential problems that need to be communicated to the national drug authority in order for preventative actions be taken. Wherever medicines are being used, there should be a readiness to monitor and report unwanted and unexpected medicine-related problems. Therefore, all medicines carry some risk of harm, and it is important to monitor their effects, both intended 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, the 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. This is the role of pharmacovigilance. Information gathered during pharmacovigilance may also assist in selecting the most appropriate medicine for future use.

Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. In line with this general definition, underlying objectives for pharmacovigilance are:

- preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

The scope of pharmacovigilance on monitoring of 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.

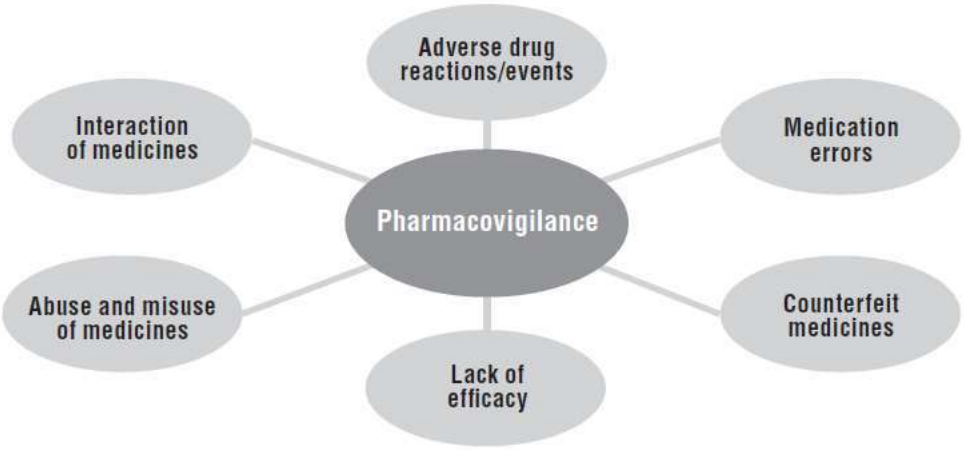


Figure 1: The scope of Pharmacovigilance. WHO pharmacovigilance indicators. A practical manual for the assessment of pharmacovigilance systems.2015

Monitoring medicines safety or Pharmacovigilance aims at achieving the following:

a. Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.

b. Improve public health and safety in relation to the use of medicines.

c. Detect problems related to the use of medicines and communicate the findings in a timely manner;

d. Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefits;

e. Encourage the safe, rational and more effective (including cost effective)use of medicines;

f. Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public.

There is an increasing burden of adverse events from adverse drug reactions (ADRs), poor quality products, adverse events following immunization, therapeutic ineffectiveness, medication errors, and irrational use of medical products and health technologies in addition to increase in antimicrobial resistance (AMR). These medicine-related problems not only contribute to morbidity and mortality but also result in higher treatment costs, loss of confidence in the health system, non-adherence to treatment, and economic losses to the pharmaceutical industry and patients. Monitoring the safety of medicines, their quality and effectiveness following market authorization, in addition to providing medicines safety information are essential functions of national healthcare systems.

So what are the types of safety issues that will be monitored in pharmacovigilance?

Adverse drug reactions/ADR

An ADR has been defined as "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 for the modification of physiological function."

Alphabetical categorization of adverse drug reactions shows that there are six types Of ADRs.

Type A (Augmented)- Related to the principal action of the medicine.

• Can occur in anyone

• Dose related

• Pharmacodynamic effects

• Common

• Skilled management reduce their incidence

Type B (Bizarre) - Not related to the principal action of the medicine

• Will occur in some people

• Not part of the normal pharmacology of the medicine

• Not dose related

• Unpredictable

• Include idiosyncrasy and drug allergy

• Account for most drug fatalities

Type C (continues)

• Reaction due to long term use of a medicine

Type D (delayed)

• This are reactions that are observed after a Effects like teratogenesis, carcinogenesis

Type E (ending of use)

• Abrupt discontinuation e.g., rebound adrenocortical insufficiency

Type F (failure of therapy)

these reactions occur when there is a failure of efficacy. Such reactions are common, may be dose-related and are often caused by drug interactions.

Medication errors

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.

Medication errors have been defined as “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."

It is important that healthcare professionals alert responsible staff at health facilities and the regulatory authority of medication errors and near-misses detected during prescribing, transcribing, dispensing and administration in order to prevent the error from occurring again. Important interventions to prevent medication errors are to provide oversight of physician

ordering, especially in intensive care units; to simplify, standardize, and rationalize hospital systems involved in medicine formulation and administration; and to promote adequate staffing so that errors caused by undue haste or fatigue can be avoided.

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

• **Human factors**

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

• **Workplace factors**

- Poor lighting, noise, interruptions

• **Pharmaceutical factors**

- Excessive prescribing
- Confusing medicine nomenclature, packaging, or labelling
- Frequency and complexity of calculations needed to prescribe, dispense, administer a medicine.
- Lack of effective policies and procedures.

Product quality defect

With new safety concerns such as illegal sale of medicines, irrational and potentially unsafe medicinal product drug donation practices, widespread manufacture and sale of counterfeit and substandard medicines, the vigilance for product quality problems is 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 under this category.

Chapter One

The National Pharmacovigilance System

The National pharmacovigilance system in Ethiopia was established in 2002 and Ethiopia become the 88th full member of the WHO Program for International Drug Monitoring in 2008.

The overall Adverse Drug Events monitoring is coordinated by the national pharmacovigilance center situated under the Ethiopian Food and Drug Authority.

The overall system includes:

- Regional Pharmacovigilance centers located at six University based referral hospitals at the country's different cities of Gonder, Mekelle, Hawassa, Haromaya, Jimma and Addis Ababa.
- Different tools (Guidelines, reporting tools and IEC materials)
- Use of passive and active surveillance systems.
- The national Pharmacovigilance database. Ethiopia uses WHO's global Individual Case Safety Report (ICSR) database which is the VigiBase.
- The national Pharmacovigilance safety advisory committee whose role is to provide technical assistance on causality assessment of ADEs and provide appropriate recommendations to EFDA.
- The system includes All levels of healthcare including the community-based health care providers, all medicines used in the country, all level healthcare professionals and any individual in the country suspecting an Adverse Drug Event following medicine use. The system also includes public health programs, pharmaceutical industry, and marketing authorization holders.

The key role of the pharmacovigilance center is safety monitoring of all health products available in the Ethiopian market. Its core activity is the collection and evaluation of ADE reports submitted by healthcare professionals, consumers, and pharmaceutical companies in the country. The goal is to 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 ADE reports, the flow of communication starts from patients with ADRs and moves directly to the healthcare professionals at health institutions/public health programmes 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 ADR reporters after a report is received.

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

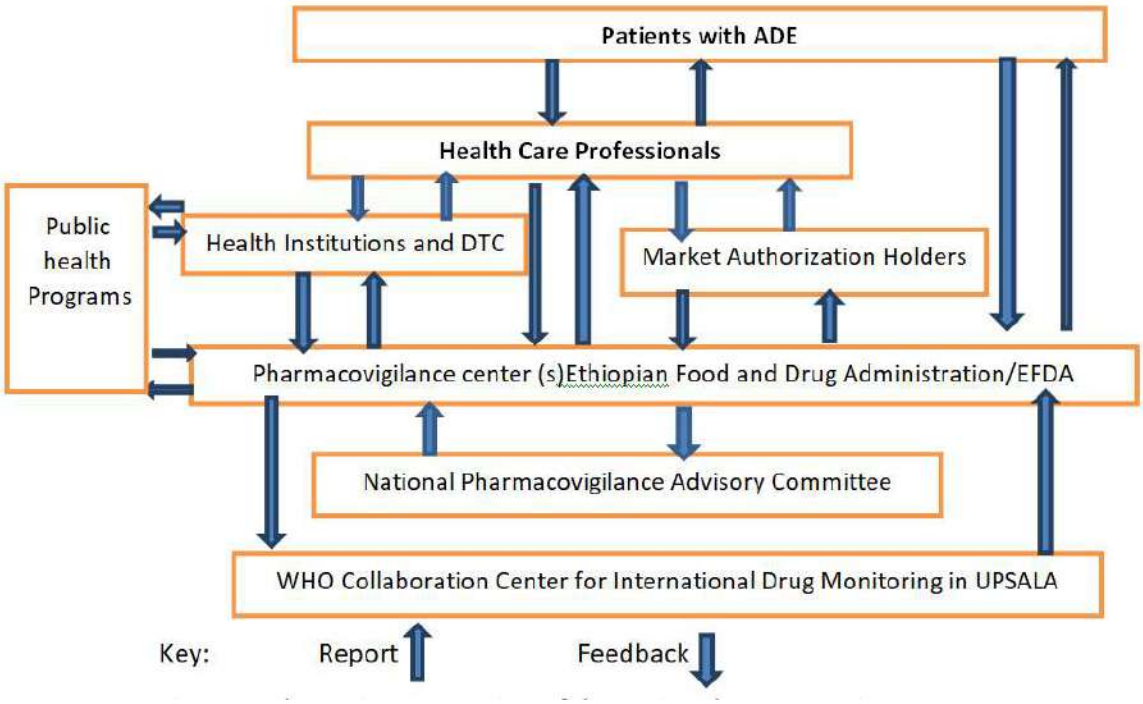


Figure 2. The National ADE reporting and feedback mechanism

Chapter Two

2. Guide to reporting adverse drug reactions (ADRs) and adverse drug events (ADEs)

2.1 Who should report Adverse drug events?

All Health care professionals including physicians, dentists, health officers, nurses, pharmacy professionals, and community health workers should report ADEs to regional/national PVcenter.

Reporting an adverse drug event does not constitute an admission that the health care professional or any other healthare professional contributed to or caused the event in any way and will have no negative consequences on the reporter in whatever way.

Market authorization holders: Being primarily responsible for safety of their products, they are obligated to report serious ADRs that they receive to national pharmacovigilance center. While

non-serious ADEs should be included in the periodic safety up-date reports (PSURs) that are also sent to EFDA.

2.2 What to report.

It is mandatory to report all adverse drug events which contain adverse drug reactions, product quality defects and medication errors.

Adverse drug reactions which include:

- All suspected reactions to medicines
- Unknown or unexpected reactions
- Serious adverse drug reactions
- Unexpected therapeutic effects
- All suspected drug interactions, including interactions with other medicines, chemicals and food.
- Treatment failures

Product quality defects

Product quality defect including adulteration or contamination, or falsified medicine (such as counterfeit or tampering) constitutes a significant safety issue.

Medication errors

- Medication error of any type

In addition, Abuse, overdose, and misuse of medicines are also reportable.

In addition, any Adverse Event Following Immunization (AEFI) should be reported according to the guideline for AEFI Surveillance in Ethiopia by Healthcare Professionals engaged in national expanded program for immunization /EPI.

2.3 When to report.

Any suspected ADR, medication error or quality defect should be reported as soon as possible after all relevant information is compiled. Delay 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 ADEs even when they do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction. However, healthcare professionals should note that even if all the facts are not available at the time of reporting, the minimum information required for a valid case (i.e. information about the patient, suspected medicine, the Adverse Event and information about the reporter) should always be included in the report.

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

The reporting timelines for Market Authorization Holder is described under chapter Four of this guideline.

When the reports have been received by the national Pharmacovigilance center, an acknowledgement letter will be sent to the reporter and follow-up questions will be answered.

Any follow-up information for an event that has already been reported can be sent on a new ADE form to the national pharmacovigilance center. Clearly indicate that the report concerns:

• follow-up information

• the report case number, (available on the acknowledgement letter), so that this information can be matched with the original report.

It is very important that follow-up reports are identified and linked to the original report to avoid duplications of reports in the pharmacovigilance database.

2.4 How to report a suspected ADEs.

The national PV system has reporting tools to receive encountered and observed ADEs from health care professionals. Reporting can be done using any of the four available mechanisms or tools described below:

- **The yellow prepaid report form available at the facility** (Annex 1). After the form is filled and folded, it needs to be sent to the post office so that it could reach EFDA
- **8482 (toll free line)**: Collect the necessary patient information, drug information, reaction information, reporter information call the number and inform the trained experts who can receive the report at the Health regulatory Information center of EFDA.

- **Online reporting**: Using online reporting system available from the website www.efda.gov.et-serivces-e-Reporting ADR, creating an account using an email address and then entering the required information in the reporting page (See instructions on Annex II).
- **Medsafety**: Using a mobile application Medsafety that can be downloaded from Google play store for Android phones or and the APP store for IOS users, creating an account using an email address and then entering through the "new report" button and filling the information on the adverse drug event that is going to be reported (See instructions on Annex III).

If the event occurred in the decentralized university hospital-based pharmacovigilance center, it is very important to communicate with focal person to get the necessary support in the reporting process.

2.5. To whom to report

All healthcare professionals are requested to report all suspected adverse Events to medicines particularly serious ADEs and those related to new medicines. It is vital to report an adverse drug Event to the EFDA's Pharmacovigilance center. Reports can also be shared to the Market Authorization Holder of the medicine.

Whenever the paper-based ADE reporting form is used, the reports should be sent to EFDA, national pharmacovigilance Center. The reports can be hand delivered, sent to the post office using the address mentioned below or scanned and sent through the PV center's e-mail address as follows:

Ethiopian Food and Drug Authority,
P.O.Box 5681, Addis Ababa, Ethiopia
Tel: +2515523142
Email Address: Pharmacovigilance@efda.gov.et
The available web-based, and mobile e-reporting tools can also be used to share the reports.

Confidentiality of ADR Reports

Any information related to the reporter and patient must be kept strictly confidential. The information should not be used for any other purpose besides for pharmacovigilance system. The

information is only meant to improve our understanding of safety in relation to the use of medicines in Ethiopia.

2.6. What happens to the report?

Once an adverse drug event is report has been received, the below activities will be performed.

1. Information validation, verification, and report entry

The recipient of the report will carefully review the report for the quality and completeness of the filled information obtained in the report form. The reporter might also be requested for information in case of missing pertinent data by using the address he/she has provided. Each report is classified as an adverse drug reaction, medication error or a product quality problem.

Pharmacovigilance experts enter the incoming reports into the WHO Pharmacovigilance database known as VigiBase®, where it is confidentially stored. This will be done using the VigiFlow.

2. Acknowledgment feedback to the reporter

The center then provides feedback in the form of an acknowledgment package to the reporter. The acknowledgment package contains formal letter from the authority and Information Education and communication materials prepared by pharmacovigilance center.

3. Investigation

Each individual case safety report is investigated further to gather further information on the case for further analysis. If it is ADR and medication error, then the occurrence of the case is searched and additional data is solicited from other health care facilities so that the rate and variety of the available data is increased to be subjected to analysis. If the case is a product quality defect further investigation is carried out by taking samples from other facilities and subjecting it to laboratory analysis.

All serious adverse drug event reports, any known or unknown cluster of events or adverse drug events of community concern should be investigated by the authority and regional regulatory bodies as appropriate to establish a diagnosis and identify the cause of the adverse drug event.
After receiving adverse drug event reports, the authority should check if the data in the report is complete and request for fulfillment of any incomplete data and conduct planning for investigation.

when the pre investigation concludes that the adverse drug event is a candidate for investigation, investigations should be started with in fifteen days from the day the report was received.

Investigation should be conducted by sub national Investigation teams; the national team may support whenever necessary.

Any serious adverse drug event report investigation should be performed according to the following steps-

1. Confirm the information received in the report by obtaining patient's medical file (or other clinical record), checking details about patient and event from medical file and documenting the information and obtaining any details missing from report.
2. Investigate and collect data about the patient's previous medical history including prior history of similar reaction or other allergies, family history of similar events and other concomitant medications taken including traditional medicines and food.
3. Investigate and collect data about the adverse drug event history, clinical description, any relevant laboratory results and diagnosis of the event and treatment, whether hospitalized and outcome of the treatment.
4. Investigate and collect data about the suspected medicine(s); conditions under which the medicine was purchased or obtained, its present storage condition, storage condition of the medicine at all levels before it arrived at health facility ,date of manufacture, expiry ,batch number and manufacturer and distributor.
5. Investigate about other people whether others have received the same medicine and developed similar adverse drug event and whether they need to be included in the investigation.
6. If the serious adverse event being investigated is death, investigate if an autopsy was performed and assess the result.
7. Assess the service provided and observe the service in action about;
   a. The medicine handling during prescribing, dispensing and administration.
   b. If it is injectable investigate about the reconstitution, diluents use.
   c. Formulate a working hypothesis on the likely/possible cause(s) of the event and
   d. Test working hypothesis if the case distribution match working hypothesis and occasionally, laboratory tests may help.

Report of the investigation on serious ADE will then be subjected to causality assessment.

4. Causality assessment

Causality assessment is performed, and the report is classified according to the WHO causality criteria (Annex IV)by the national Pharmacovigilance Advisory committee. Causality assessment can also be performed at the regional Pharmacovigilance centers that are sending reports to the national PV center. The assessment can then be verified and finalized at the WHO Vigiflow system while sending the report to Uppsala monitoring center of WHO and also to be used for recommendation for regulatory measure.

5. Report analysis

The outcome of the report, together with relevant information including background rate relating to the event will be used to analyze as to its rate and relevancy.

6. Assessing for potential signals

The Pharmacovigilance experts at the EFDA review each incoming report (adverse drug reaction, medication error, product quality defect) individually to detect any medicine-related problems that need immediate action.

The authority works towards detecting new potentially causal drug and event associations, or a new aspect of a known association, i.e., a signal which could be-

- Previously unknown adverse drug reactions
- Increases in frequency of known adverse drug reactions.
- Risk groups, risk factors and possible mechanisms underlying adverse drug reactions.

A signal can initially be detected in a single incoming report. The literature, the WHO Signal document and the WHO Pharmaceutical Newsletter should be regularly screened to detect medicine-related problems relevant for the nation. Each year, a summary of the reports received during the past year is produced and evaluated.

In addition, post marketing surveillance to detect product quality defects is performed by the EFDA. Samples of any product in the market are collected from various premises in a determined frequency per year. The samples are tested in the EFDA laboratory. Regulatory inspection is also carried out by regional responsible offices to detect product quality defects.

Each detected potential signal will undergo further evaluation. The WHO database published literature and information from the market Authorization Holder are reviewed for similar cases.

The National Pharmacovigilance Advisory Committee is provided summary information for evaluation. The committee recommends what action needs to be taken, i.e., if it is a signal that needs to be acted upon, it is not signal, or if further monitoring is needed.

7. Taking regulatory measures

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 will be taken on the specific medicine used so that appropriate actions are taken. The regulatory actions might range from warnings on the use of the specific medicine to the withdrawal or recall of the medicine and suspension from use.

Examples of regulatory actions include product label change; Dear healthcare professional letters (DHCPLs), press statements, medicines safety alerts, product restrictions (up-scheduling, limited packaging, limited prescribers), Educational programme and product withdrawal/suspension.

8. Communication with stakeholders

After all those processes are completed, the final decision and/ or regulatory measures will be communicated to all concerned bodies or stakeholders who are involved in the national pharmacovigilance system.

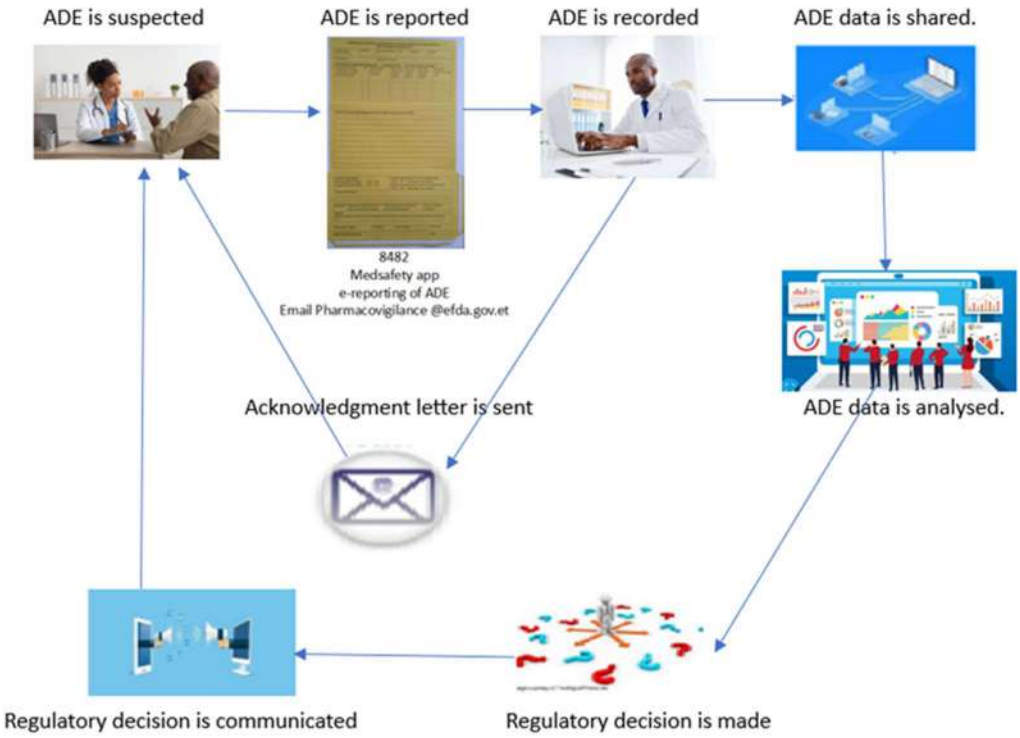


Figure 3. Flow diagram. Life cycle of an ADE information

Chapter Three

3. Roles and Responsibilities of key players

The well-functioning pharmacovigilance system works with the support of each healthcare provider, the regulatory bodies, the pharmaceutical industry, MAHs, PHPs, other stakeholders and the public at large. Hence, each of these have an important role to play and responsibility to bear:

3.1 Patient/Consumer

Patients who have experienced an adverse drug event or suspect are action to a drug or knows that an adverse drug event has occurred should report to the nearest health care facility, to regional regulatory body or to the Authority 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 nation have a very important role to highlight problems occurring when a marketed medicinal product is used. They need to alert the EFDA about suspected adverse drug reactions, medication errors and product quality problems in order for the authority to act in preventing or minimizing the occurrence of the medicine-related injury for other patients in the future. These activities include-

- Patient education on ADRs including counselling in order to promote adherence.
- Diagnosis/detection and appropriate clinical management and treatment of patients presenting with adverse Events.
- Being vigilant and detecting adverse drug events.
- Inspect the medicinal product to be dispensed or administered to patient.
- Identify medication errors and product quality defects.
- Adjust the dose or replace or stop the treatment for ADR suspected patient.
- Complete yellow (ADE reporting) form and/or other electronic reporting tools for all ADEs and submit them to national pharmacovigilance center (decentralized Pharmacovigilance centers)
- Document the management of suspected ADR on patient's history file.
- Analysis of the ADRs and/or events data for decision making at the facility level.
- Report SAEs to national pharmacovigilance center as soon as possible.
- 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 drug events to the authority or regional regulatory or the market Authorization holder of the medicine.
- appoint a pharmacovigilance focal person who will be assigned to coordinate adverse drug 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 drug events and have the appropriate knowledge and skill regarding adverse drug event monitoring.

b. Ensuring that adverse drug 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 on adverse drug events that occurred in the facility.

d. Analyze adverse drug event data, compile reports, and present it to the responsible body.

- Develop standard operating procedure/SOP/ on detection, management, and reporting of ADEs to regional or national pharmacovigilance center.
- Coordinate in service training on medicine safety and the national and global pharmacovigilance system for healthcare professionals in collaboration with national pharmacovigilance center and other partners.
- be vigilant and prevent any adverse event from occurring as a result of medication error and system flaws.
- maintain and document all records related to reported adverse drug events, share information when requested and collaborate on any pharmacovigilance activities with the authority.
- implement the regulatory measures taken by the authority after serious adverse events investigation and analysis.
- 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. Decentralized Pharmacovigilance centers

Pharmacovigilance activities will be more effective when it is decentralized. The decentralized centers should create awareness and provide trainings on pharmacovigilance for health care professionals, collect ADE reports, submit the reports by using Vigiflow and document the reports. In addition, they should conduct causality assessment of ADEs.

3.5. Professional Associations

Professional Associations need to play major role in pharmacovigilance through adapting and disseminating pharmacovigilance information to their respective members. They should work on Provide pre- and in-service trainings as well as Sensitization of their respective members on ADE reporting. Respective 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 and conduct monitoring of medicine safety activities in their respective public health programs. Ministry of health should include pharmacovigilance system and activities in their documents and ensure proper integration of pharmacovigilance system in documents and practices of lower levels. They need to ensure effective integration of pharmacovigilance system in their respective organizational structures, (RHB, ZHD, WoHO, health facilities), Policy documents, Guidelines, Annual plans, and practices. The public health programs should allocate appropriate budget for Pharmacovigilance related activities. Coordinate and provide Pharmacovigilance trainings to healthcare professionals and Ensure reporting of regular and quality ADE data from each health facilities to EFDA.

3.7. Pharmaceutical industry

Manufacturers are uniquely placed for monitoring the safety of medicines, from the start of drug development and thereafter throughout the lifetime of the drug. The below are major activities to be performed by pharmaceutical Industries/ MAHs:

- Pharmaceutical companies should establish pharmacovigilance system and employ a trained Qualified person for pharmacovigilance (QPPV) so that they are able to recognize, capture and report safety information appropriately.
- Develop and maintain the Pharmacovigilance System Master File (PSMF) in accordance with the guideline on good pharmacovigilance practices/GVP/
- Collect, compile and submit ADE reports to national PV center.
- Produce and submit periodic safety reports such as periodic safety update reports/PSUR/ to national PV center.
- Conduct specific studies on safety and effectiveness under specific conditions and as necessary cover the cost.

3.8. National Pharmacovigilance Advisory Committee

The advisory committee members is composed of different health professions. The current composition includes Internists, Neurologist, Forensic Pathologist, Epidemiologist, Obstetrics and Gynecologist, Pediatrician, Immunologist, Dermatologist, Pharmacologist, pharmaco-epidemiologist, cardiologist, clinical pharmacist and representative from the Regulatory Authority. Members of the National Pharmacovigilance Advisory Committee are appointed by the Authority pursuant to their professional competence.

The responsibilities of the committee contain but not limited to the below activities,

- Review individual serious and unusual ADE and other safety reports referred to it by the Secretariat in order to assess a potential causal link between the event and the medicine.
- Provide recommendations for further investigation, education, corrective action and communication.
- Advise the national program managers and Regulatory Authority about ADE 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 problem.
- 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. It has a comprehensive list of responsibilities which include the listed below:

- Develop and provide ADEs collection tools, methods and procedures for regional pharmacovigilance centers and healthcare professionals.
- Collection of ADEs reports from voluntary healthcare professionals.
- Perform active surveillance on selected drugs ADEs.

- Enter ADE reports to international pharmacovigilance data base,
- Disseminate new ADR information from global community to other stake holders and the public.
- Collaborative work with public health programs to maintain safety of their medicines.
- Analyze ADEs in collaboration with national pharmacovigilance advisory committee.
- Make regulatory decisions based on the results of ADEs analysis.
- Alert prescribers, manufacturers, and the public to new risks of adverse reactions.
- Communicate healthcare professionals, patients and the public about benefit, harm, effectiveness, and risk of medicines.
- Give feedback and acknowledgements for ADEs reporters.
- Conduct gap identification assessments of healthcare professionals and coordinate the capacity building training.
- Coordinate pharmacovigilance/drug safety/ harmonization meeting 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 drug safety or pharmacovigilance through teaching, training, research, policy development, clinical research, ethics committees and the clinical service they provide.

- ✓ Conduct research on pharmacovigilance/medicinal product's safety issues to generate evidence for policy making and priority setting.
- ✓ Facilitate and provide pre-service and postgraduate PV training in the field.
- ✓ Inclusion of basic pharmacovigilance topics in pre-service curriculum.
- ✓ Expansion of scientific knowledge in drug safety and create pharmacovigilance awareness.
- ✓ Recognize ADE monitoring as an essential quality assurance activity mainly of their clinical practices.
- ✓ Establish a system to extract information on DTP (Drug Therapy problems) 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 Centres 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 centres. It maintains the global ADR database (Vigibase) where ADR data from all member countries are collected and stored. WHO Analyses the reports from ADR data base 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 Pharmacovigilance center. In so doing, they support in sharing of global good practices in pharmacovigilance and mobilization of resources.

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

Other partners (media, advocacy group, consumer association, lawyer) in pharmacovigilance play a strong role in the monitoring of medicine safety. These partners advocate the importance of medicine safety monitoring to the public and Create awareness on pharmacovigilance policy and activities through appropriate platforms.

They should also Communicate preventive measures and regulatory actions on medicine safety to the public using appropriate channel. 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. Responsibilities of marketing authorization holders

According to Article 14 sub article 1-5 of the Ethiopian pharmacovigilance directive 932/2015, every market authorization holder should have a responsibility to set up a pharmacovigilance system of their medical products, to assign a Qualified person responsible 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 on adverse drug events to prevent and minimize the ADE's from harming the public.

4.1. Pharmacovigilance and appointment of the QPPV

MAH's 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 in accordance with national and international legislation and relevant guidance to the national competent authority. The MAH is responsible to appoint and have at its disposal permanently 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 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 including but 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 in order 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 Qualified Person for Pharmacovigilance (QPPV) should be healthcare professional with a minimum two years' experience on pharmacovigilance related activities.
  - The QPPV should receive a formal training in pharmacovigilance recognized by the Authority.
  - The QPPV should not be freelance, but an employee of the MAH or the Local Representative.
- Ensure that the responsibilities of the QPPV are executed appropriately.

4.1.1 Qualification of QPPV

The Marketing Authorization Holder should permanently and continuously have at his disposal an appropriately Qualified Person Responsible for Pharmacovigilance. The Qualified Person Responsible for Pharmacovigilance should be resident in Ethiopia.

4.1.2 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 which ensures that information about all suspected adverse drug reactions/events which are reported to the personnel of the marketing authorization holder, including to medical representatives, is collected, collated, processed, and evaluated and forwarded to the Authority in line with the timelines stipulated by the Authority.
- Prepare the following documents for submission to the Authority.
  - ✓ Adverse Drug Reaction reports
  - ✓ 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 and country specific Risk Management Plan when requested by the Authority.

- ✓ All RMPs submitted should be accompanied by a declaration to be signed by the QPPV. The declaration should indicate that the QPPV has read the RMP and will ensure implementation of all activities outline in the RMP.
- ✓ 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.

4.2. Reporting a safety information on medicines

Any Market Authorization Holder should report periodic safety update report, Periodic Benefit Risk Evaluation Report, Individual case safety report in line with the national Pharmacovigilance Directive 932/2015.

With respect to the reporting of safety information to the regulatory authority, the following timelines should be followed.

a. Unexpected and expected serious adverse drug 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 drug events must be reported within 90 days after the granted knowledge of the event.

c. All suspected serious adverse drug events in post-registration studies should be reported according to the timelines given in a & b of the previous section.

d. The market authorization holder should also inform the Authority of any significant safety issue (from other than single case reports) or action taken by foreign agency that affect the safety or use of 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.

e. Information on withdrawal of the registration status in any country because of safety issue must be noted to the Authority within 48 hours of the first knowledge by the market authorization holder.

For ICSRs, the MAH can use the yellow page ADE reporting form, electronic reporting tool, mobile application (med-safety) and e-mail. Other Safety Information reports (Example: PSURs, PBRERs) 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.

4.2.1. Periodic safety update reports

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product considering new or emerging safety information in the context of cumulative information on risk and benefits. PSURs summarize data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine, both in its authorized uses and in unauthorized uses. PSUR is therefore a tool for post-authorization evaluation at defined time points in the lifecycle of a product.

For new medicines that are registered and placed in the market in the country, a Periodic Safety Update Report 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 drug 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 drug event reports on their medicinal product.

The following timelines apply for the submission of PSURs:

i. Within 70 calendar days of the Data Log Point (Day 0) for PSURs covering intervals of 6 to 12 months.

ii. Within 90 calendar days of the DLP (Day 0) for PSURs covering intervals in excess of 12 months.

iii. Ad hoc PSURs should be submitted upon request within 90 calendar days of the DLP, unless otherwise specified.

The PSURs should emphasize on the following contents:

a. Scientific evaluation of the benefit-risk profile

b. Summaries of relevant scientific/clinical data including literature searches.

c. 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 in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

4.2.2 Periodic Benefit-Risk Evaluation Reports

The main objective of a Periodic Benefit-Risk Evaluation report (PBRER) 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.

The PBRER should contain an evaluation of new information relevant to the medical product that has become available to the MAH during the reporting interval, in the context of cumulative information by:

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

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

3. Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medical product's benefit and risk profile

4. Where important new safety information has emerged, conducting an integrated benefit- risk evaluation for approved indications. When appropriate, the PBRER should include proposed action(s) to optimize the benefit-risk profile.

The PBRERs should contain at a minimum the following data.

i. Summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization.

ii. A scientific evaluation of the risk-benefit balance of the medicinal product.

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

iv. Collection of adverse drug reaction (ADR) information (i.e. local serious ADRs, local non-serious ADRs, foreign serious ADRs, foreign non-serious ADRs, case reports published on international or local literatures including academic conferences);

v. A comprehensive, concise, and critical analysis of product's known or emerging important risks and to evidence of emerging important benefits;

vi. Summary of relevant new safety information that could have an impact on the benefit-risk profile of the product;

vii. Summary of any important new efficacy/effectiveness information that has become available during the reporting interval;

viii. Assessment of whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the product's benefit and risk profile;

ix. Conducting an integrated benefit-risk evaluation for approved indications in case a new safety information that has emerged;

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

The MAH should submit PBRERs as prescribed in the current ICH guidelines, E2C and as per the following timelines;

1. every 6 months for the first two years after marketing authorization; within 70 calendar days

2. annually for two years or thereafter annually; within 90 calendar days

3. thereafter every two years for products that have been marketed for several years and considered to have an established and acceptable profile or considered to be low risk; within 90 calendar days

4. ad hoc PBRERs may also be requested by the Authority and should be submitted within 90 calendar days unless specified otherwise.

5. 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.

4.3. 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 products important risk.
To this end, the RMP 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 also on 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');

The Pharmacovigilance plan should be developed by the MAH and will be submitted to the EFDA during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises post marketing.

The structure for 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:

i. Summary of Ongoing Safety issues

ii. Routine Pharmacovigilance Practice

iii. Action Plan for Safety issues

iv. Summary of Actions to be completed, including milestones.

The structure and details regarding pharmacovigilance plan should be as prescribed in current version of ICH E2E Pharmacovigilance planning guideline.

3. the planning and implementation of risk minimization measures, including the evaluation of the effectiveness of these activities (the 'risk minimization plan').

The MAH should have RMPs for their medicinal products throughout their lifecycle. The RMPs should be proportionate to the identified risks and 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 removal of safety concerns in the RMP should be under the following circumstances:

i. Removal of a safety concern for important potential risks:

a. when accumulating scientific and clinical data do not support the initial supposition, or the impact to the individual has been shown to be less than anticipated.

b. when there is no reasonable expectation that any pharmacovigilance activity can further characterize the risk.

ii. Removal of a safety concern for important identified risks:

a. 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 integrated into standard clinical practice such as inclusion into treatment protocols or clinical guidelines.

iii. Removal of a safety concern for missing information:

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

4. The risk management system should be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post authorization safety data.

5. Format of Risk management plan

The MAH should prepare and submit to the Authority RMP containing the below minimum information.

a. Safety Specifications: identification or characterization of the safety profile of the medical product and/or the health technology, 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 quantify clinically relevant risks, and to identify new adverse reactions.

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

The RMP document is expected to be submitted as one single document including all sections and annexes, as relevant.

4.4. Pharmacovigilance system master file (PSMF)

The objective of the Pharmacovigilance system master file (PSMF) is to provide an overview of the pharmacovigilance system, which may be requested and assessed by the EFDA during marketing authorization application(s) or post market authorization. It should also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorizations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by the EFDA.

Through the development and maintenance of the PSMF, the marketing authorization holder and the QPPV should be able to:

i. gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;

ii. confirm aspects of compliance in relation to the system;

iii. obtain information about deficiencies in the system, or non-compliance with the requirements;

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

MAHs should be required to maintain and make available a pharmacovigilance system master file (PSMF) upon request by the EFDA.

The PSMF should include documents to describe the pharmacovigilance system; the content of the PSMF should reflect the global availability of safety information for medicinal products authorized in the country. The PSMF to be presented should fulfill the minimum international requirements and hence content should be presented as per the attached format (Annex V)

4.5. Case reports from published scientific literature.

The authorized representative or MAH should report published suspected ADRs/events related to the active substance(s) of their medical products, occurring in and outside Ethiopia. The relevant published article should be provided.

The ADR report should be completed for each identifiable patient (with an identifiable adverse drug reaction) and submitted to the EFDA.

If more than one medicine is mentioned in the literature report, only the MAH whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s).

4.6. Post-Authorization Safety Studies.

A post-authorization safety study (PASS) is any study relating to an authorized medical product and conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring 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 is the issue 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 most up-to-date methods that are relevant and applicable.

The EFDA may require MAHs to conduct post-authorization studies on safety and on efficacy as a condition at the time of the granting of the marketing authorization or later.

The Notification may be in writing and should include the objectives and timeframe for the submission and conduct of the study. The request may also include recommendations on key elements of the study (e.g., study design, setting, exposure(s), outcome(s), and study population).

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

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

i. To quantify potential or identified risks, e.g., to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a nonexposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;

ii. 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);

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

iv. To provide evidence about the absence of risks;

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

vi. To measure the effectiveness of a risk management measures.

2. The PASS can be imposed due to the following concerns;

i. imposed as an obligation in accordance with Risk Management Plans stipulated in this guideline because they are key to the risk-benefit profile of the product.

ii. Imposed as a specific obligation in the framework of a marketing authorization granted under exceptional circumstances.

iii. 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.

3. The Market Authorization Holder should submit the PASS protocol for review and approval. The study protocol should be developed by individuals with appropriate scientific background and experience.

4. If the necessity for amendment arises, the PASS protocol should be amended and approved by the Authority as needed throughout the course of the study

5.. PASS should be initiated, managed or financed by a marketing authorization holder voluntarily or pursuant to 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.

6. Any new information that may affect the risk-benefit balance of the product should be communicated as an emerging safety issue to the EFDA. The reporting should be as per reporting requirements described in section 2 (reporting of event) of these guidelines.

7. The MAH initiating, managing or financing a PASS should communicate to the EFDA, the final manuscript of the article within two weeks prior to submission for publication in order to allow the EFDA to review in advance the results and interpretations to be published.

4.7 Clinical trials

The Pharmacovigilance system uses safety information obtained through clinical trial studies. Such safety reports will be treated as per the national regulations and requirement for clinical trials.

Chapter Five

5. Pharmacovigilance inspections and self-audits

Articles 21(1) of the Pharmacovigilance directive 932/2015 gives EFDA the responsibility to perform pharmacovigilance inspections and regulate market authorization holders with respect to their monitoring of safety and quality of their medicines.

EFDA 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:

i. to determine that the marketing authorization holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;

ii. to identify, record and address non-compliance which may pose a risk to public health;

iii. to use the inspection results as a basis for regulatory/enforcement action, where considered necessary.

5.1 Inspection types

There are four types of post authorization pharmacovigilance inspections that would be conducted by 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 3 years respectively 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. These inspections should focus on specific pharmacovigilance processes or include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. These inspections may arise when, for example, one or more of the triggers listed below are identified:

a. Risk-benefit balance of the product:

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

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

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

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 fulfil requests for information.

d. Delays or failure to carry out specific obligations relating to the monitoring of product safety and the fulfilment 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 be appropriate when it is known from a previous inspection that the inspected party 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 remote from the premises of the marketing authorization holder or firms employed by the marketing authorization holder. 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 or travel 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 has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

5.2 Inspection planning

The Authority plans the inspection and informs the MAH with a preliminary notification about the scheduled inspection. Relevant documents will be requested to facilitate the inspection at least 7 calendar days to the scheduled inspection date.

5.4 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.

5.5 Reporting and Follow-Up

Deficiencies found during the Pharmacovigilance inspections are graded as follows:

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

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.

5.6 Regulatory Measures

After the report is finalized, the Authority should inform the MAH regarding the non-compliance and advised on how this can be remedied. 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 932/2015.

5.7. Self-Audit

The MAH are expected to perform audits of their pharmacovigilance systems including risk-based audits 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

Safety communication aims at providing timely, evidence-based information on the safe and effective use of medicines; facilitating changes to healthcare practices (including self-medication practices); changing attitudes, decisions, and behaviors in relation to the use of medicines; supporting risk minimization behavior and facilitating informed decisions on the rational use of medicines.

In addition to the above, effective, high-quality safety communication can support public confidence in the regulatory system.

As stated in Article 21 of the pharmacovigilance directive 932/2015, the authority provides information on adverse drug events and signals to the public and other stakeholders on a timely basis.

The objectives of safety communication by the Authority are;

- To increase the awareness of the public about medicine related harm that could arise as a result of medicines at a time before taking a medicine and after an encounter of an adverse drug event (adverse drug reactions, medication errors and poor quality or defective medicines) and to ensure that they inform to EFDA about it when they experience the adverse event.
- To ensure that stakeholders of pharmacovigilance(consumers, health care professionals, health care facilities, MAH, public health programmes, academic institutions, professional associations, the media) understand their roles on the monitoring of safety and quality of medicines and carry out their share of responsibility accordingly.

6.1 Target audience

The target audiences for EFDA safety communication include but not limited to,

• The patient, client

• The general public

• Healthcare facilities

• Healthcare professionals

• Medicine manufacturer, importer, distributor, exporter ,retail outlet

• Regional Health bureaus/Regional regulatory bodies

• Development partners, donors

• International organizations such as WHO, UNICEF

• Professional associations

• Consumer associations

• The Media

• Governmental organizations

• Staff in general

• All Head Office directorates

• Branch managers

• Management

Hence, the findings obtained through the rigorous pharmacovigilance activities of detecting, investigating and analyzing adverse drug events which are used to educate and promote rational, safe and more effective (including cost effective) use of medicines by healthcare professionals and patients/clients will only be effective if it is done through appropriate strategies of communication.

6.4 Communication channels

Based on the analysis of the target audiences, the specific objectives of the communication and key messages to be transmitted, communication channels will be determined. Selecting channels takes into account the audience's preferred media, source of information, preferred languages and similar factors. The channels of safety communication are-

- Mainstream Media
- Social Media
- Website
- Newsletters

- Interpersonal Communication
- Emails, SMS messages
- Media Campaigns
- Formal correspondences (Dear Health Care Professional letters,)

6.6 Safety communication by the marketing authorization holder

Prior to making a public announcement, relating to new information on safety concerns on the use of a medicines, the MAH is be required to inform the Authority of its intension to make, such an announcement. The MAH is required to get approval from the Authority before disseminating the information. The MAH should ensure that information to the public is presented objectively and is not misleading.

Chapter Seven

7. Monitoring and Evaluation

Background

Monitoring and evaluation is a critical component of every effort in life and so for the Comprehensive Pharmacovigilance system. Routine tracking or monitoring of the activities by appropriate tools regularly needs to be carried out and communicated with all responsible persons to know whether activities are implemented according to plan, the progress to interim and final target is promising or need some amendment. Such effort will be evaluated at specified period, usually in the mid-term and at terminal phase. The monitoring data could be used in evaluation that will be accompanied by the reasons or justifications for positive or negative deviations from targets, and evaluation leads to conclusion and recommendation.

The regulatory sector has developed its strategic plan that states “Improve Pharmacovigilance Systems” as one sub-initiative having different interventions and targets. Besides, there is roadmap that runs from 2019 -2023 to strengthen the pharmacovigilance system. It is known that pharmacovigilance is a regulatory function, the Global Benchmarking Tool (GBT) and Indicator-Based Pharmacovigilance Assessment Tool (IPAT) are appropriate global tools for monitoring and evaluation that can be aligned with the targets in the strategic plan, roadmap and the annual plans. The comprehensive M&E framework aims to monitor the resources invested, the activities implemented, services delivered as well as evaluate outcomes achieved and long-term impact made. Mechanisms are being put in place to improve data collection and flow mechanisms to ensure quality, valid, and accurate data. Existing data collection mechanisms are being enabled

and new systems are being developed to respond to the data needs imposed by the plan. The mechanisms are also designed in a manner that ensures data confidentiality. Data collection, validation and use from the service point level up to the national pharmacovigilance center as well as the global database rely on existing expertise, commitment and dedication of members of the health team to use the different tools of PV and reporting channel diligently.

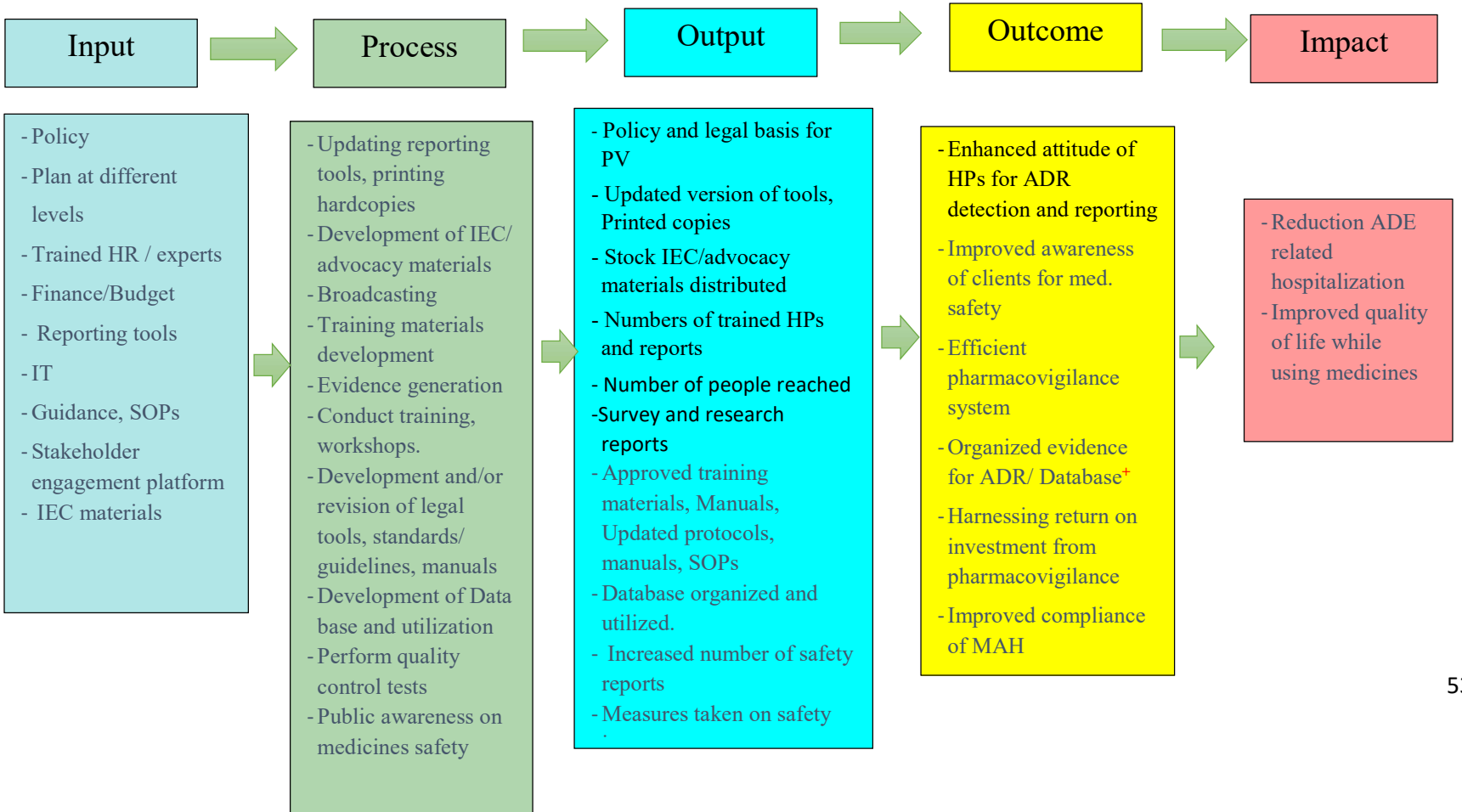
The pharmacovigilance indicators are categorized into five as per IPAT components cascaded to core (26) and supplementary (17) while the GBT states six major indicators cascaded to 36 sub-indicators. All these documents considered while designing the logic model for the M&E of pharmacovigilance guideline. The indicators will be from structural, process and outcome/impact perspectives and emphasis could be given for public health programs vis-à-vis the current context. This can be summarized in the logical framework as indicated below.

Logic Model for monitoring of pharmacovigilance performance

Problem Statement – 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 tracking mechanism using appropriate M & E system.

Goal – To strengthen the safety monitoring of medicines and contribute for reduction of ADE related risks of medidnes

Monitoring the performance of pharmacovigilance system should be comducted at all the components of the system starting from the input to the impact level as described in the following diagramme.



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 reasonable cost, frequently enough to inform the progress and influence 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 measure

The selected indicators include:

S. No	Name of Indicator	Type	Data Source	Frequency
1.	Dedicated budget available for pharmacovigilance-related activities	Input	Doc. Review	Quarterly
2.	Availability of reporting forms for ADR, PQD, ME and AEFI	Input	Observation	Monthly
3.	Trained staff and Healthcare professionals	Out put	Proceeding	Half-year
4.	Existence of updated protocols or SOPs for improving patient safety relating to medicine use	Out put	Doc. Review	Annual
5.	Existence of a pharmacovigilance or medicine safety bulletin*	Output	Doc. Review	Quarterly
6.	Number of ADR Reports received as per WHO standard*	output	Archives	Quarterly
7.	Number of serious adverse event investigated and causality assessment performed*	output	Archives	Quarterly
8.	Number of Signals detected*	Output	Archives	Annually
9.	Existence of functioning database for tracking pharmacovigilance activities	Process	Observation	Quarterly
10.	Percentage availability active QPPV in MAHs (Compliance level)	Out put	Archives	Quarterly

*For federal level (or National PV center) only

It is to be noted that some pharmacovigilance requirements that are already accomplished, yet included in different known reference are not included such as the policy and legal environment, updating to the dynamic environment is included in lower tools like guidelines and SOPs. Similarly, the indicators included in this guideline could be updated during the revision of the guideline.

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4. Strengthening Pharmaceutical Systems (SPS) Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool (IPAT): Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health
5. Federal Negarit Gazette of The Federal Democratic Republic of Ethiopia, Food and Medicine Administration Proclamation No.1112/2019
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7. EFDA, Pharmacovigilance Directive No 932/2022, Sept 2022
8. Ethiopian Food, Medicine and Healthcare Administration and Control Authority. Guideline for Adverse Drug Event monitoring (Pharmacovigilance) third edition. 2014
9. WHO. WHO pharmacovigilance indicators. A practical manual for the assessment of pharmacovigilance systems.2015
10. Ghana Food and Drug Authority. Guidelines for reporting adverse drug reactions.2013
11. Kenya Pharmacy and Poisons Board. Guidelines on the Safety and vigilance of medical products and Health technologies.2019
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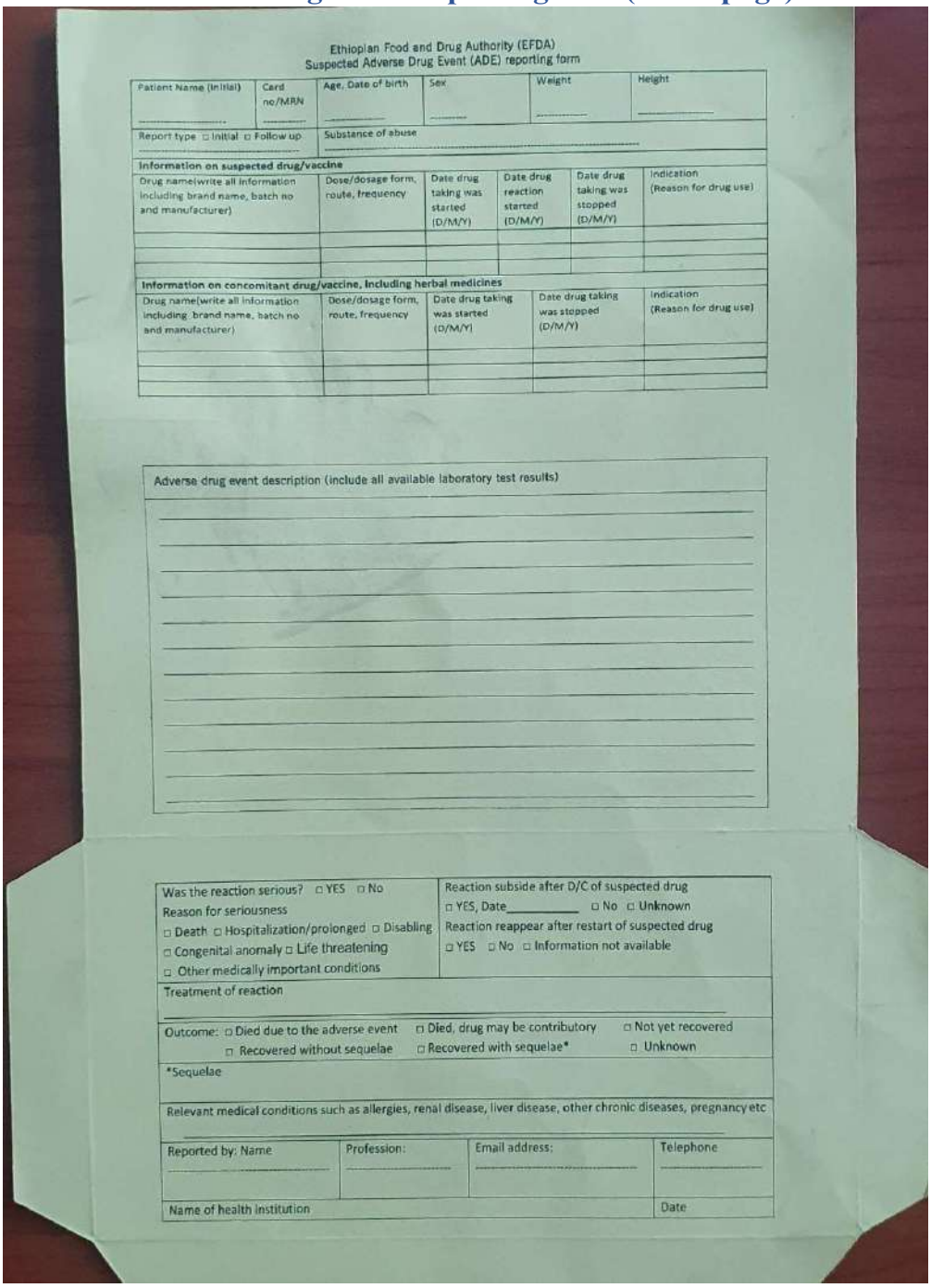
13. European Medicine Agency. Guideline on good pharmacovigilance practices (GVP) modules.2013
14. NAFDAC. Good Pharmacovigilance practices Guidelines.2016
15. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilancepractices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

16. South African Health Products Regulatory Authority, Guideline for Adverse Drug Reactions (ADRs) Reporting for Healthcare Professionals, March 2020.

Annexes

Annex 1. Adverse Drug Event reporting form(front page)



Ethioplan 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/vaccine

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 subside after D/C of suspected drug
□ YES, Date_____ □ No □ Unknown
Reaction reappear after restart of suspected drug
□ YES □ No □ Information not available

Treatment of reaction

Outcome: □ Died due to the adverse event □ Died, drug may be contributory □ Not yet recovered
□ Recovered without sequelae □ Recovered with sequelae* □ Unknown

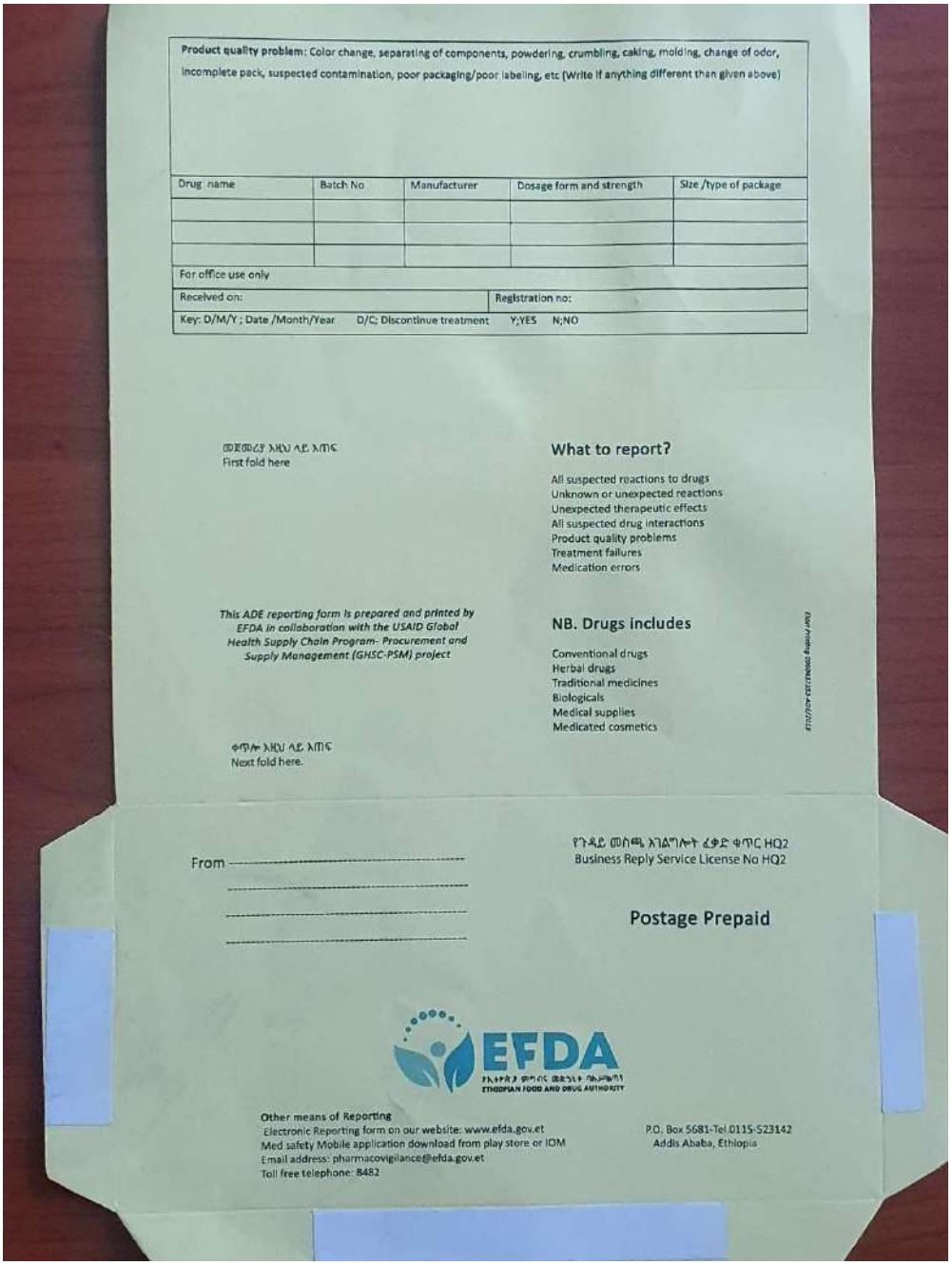
*Sequelae

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

Adverse Drug Event reporting form(back page)



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

መጀመሪያ እዚህ ላይ እጠፍ
First fold here

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

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

NB. Drugs includes

Conventional drugs
Herbal drugs
Traditional medicines
Biologicals
Medical supplies
Medicated cosmetics

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From _____

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Business Reply Service License No HQ2

Postage Prepaid

EFDA
ETHIOPIAN FOOD AND DRUG AUTHORITY

Other means of Reporting
Electronic Reporting form on our website: www.efda.gov.et
Med safety Mobile application download from play store or IOM
Email address: pharmacovigilance@efda.gov.et
Toll free telephone: 8482

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

Direction for completing the ADE reporting form

General

The ADE reporting form (Annex I) can be used to report ADR, ME in the first page and PQD at the back of the page. It comprises basic information about the patient, the drug, the adverse event, the action taken and the outcome.

• The age, sex, description of the adverse reaction, information on suspected medicine, and outcome are all considered essential and should be completed.

• The form can be completed by all Healthcare Professionals in the country such as Physicians, Pharmacists, Nurses, Health Officers, Dentist, etc.

• Complete the form to the best of your abilities.

• Avoid non-standard abbreviations.

• Use a separate form for each patient.

• Write legibly.

Specific

The patient's identity

Information about the patient's identity, and habit should be provided. It is not necessary to write patient's full name. Use Patients name initials only. E.g. ASZ for Addis Solomon Zerga. The card number have to be stated as the card number and patient's identity are useful to solicit additional information if necessary and also for retrospective and prospective study of adverse drug reaction.

Description of the adverse event

Clear and brief description about the nature of adverse event, the date of onset, duration, time course and laboratory test results including "negative" and normal results of any relevant test performed should be reported. The severity of the reaction i.e. weather it has necessitated prolonged hospitalization or not, discontinuation of the medicine or not, etc. have to be reported.

Information on suspected medicine

Drug Information

Write all drug identifying information i.e.; the brand name of suspected medicine(s),batch number, manufacturer and manufactory and expiry dates. Avoid non-standard abbreviations.

such as PPF, CAF, MTC, TTC, etc.

The dosage form such as tablet, capsule, syrup, suspension, elixir, emulsion, injection, eye drop/ointment, topical crème/ ointment, otic drop, nasal drop, suppositories rectal/ vaginal etc. should be stated. The strength must also be expressed in metric system. e.g. 500mg tab, 250mg/5ml syrup,1gm rectal suppository etc. Sometimes strength can be expressed in % e.g. 2% hydrocortisone ointment.

Frequency of drug administrations should be clearly notified using standard abbreviations. e.g. 3 times a day as tid or 8 hrly , 2 times a day as bid or 12hrly, 4 times a day as qid or 6 hrly etc. Route of administration expressed using standard abbreviation. E.g. Per os as PO, Intra- muscular as IM, Intra-Venus as IV, Per-rectal as PR, Topical as TO etc.

It is also useful to indicate whether the medication is taken before or after meal.

Date

The date the medicine was started and discontinued is an important data to assess the cause-and-effect relationship of the medicine and adverse reaction. Therefore, it has to be stated clearly on the report form as date/ month/ year. If the medicine has not been discontinued at the time of reporting, write continuing.

Dechallenge and Rechallenge

If the reaction subside after discontinuation of the suspected medicine (dechallenge), check Y (yes) and if not, check N (No). If the reaction reappear after the suspected medicine is restarted (if rechallenge done),, check Y (yes) and if not, check N (No). If there is no dechallenge and rechallenge then check NA (Not available).

Drug used concomitantly

List any other prescription or non- prescription medicines used concomitantly (designated as

‘C’) with the suspected (designated as ‘S’)medicine with all description i.e. brand name, route, dosage form, strength, frequency, indication, date started and date stopped. This information is useful for evaluation of possible drug interaction.

Indication

Write the reason why the medicine was used or the diagnosis for which the medicine prescribed for both suspected medicine and other medicines concurrently used.

Treatment

The treatment of the reaction, the final outcome of the reaction and sequelae has to be entered.

Additional information

Any reaction the patient may have experienced previously, particularly similar to the current adverse event, either caused by the same or different medicine has to be reported. Other relevant medical history, such as allergy, chronic disease, pregnancy and other factors, which may contribute i.e. herbal products, foods and chemicals, should be included under this heading

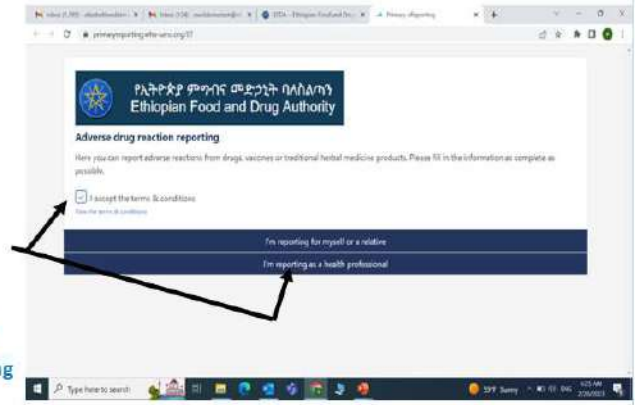
For medication error use the above-mentioned data elements as appropriate and fill the form

For product quality defects-use the back side of the reporting form and fill the required data elements. If there is additional information please use the space provided for narrative and describe the observed medicine quality defect

Annex 2.Instructions on how to use the e-reporting system to report an adverse drug event.

Healthcare professional can report ADE by using e-reporting by following the below procedures.

- Go to EFDA website www.efda.gov.et
- Click on services.
- Click on the link e-reporting of ADR and then
- you will find the page that is attached here that says ADR reporting.
- Accept the terms and conditions and select whether you report for yourself or /relative or as a healthcare Professional
- Start filling the information required by starting at user of the medicine, initial, sex, weight, date of birth....and clicking next until you finish filling all the required Information

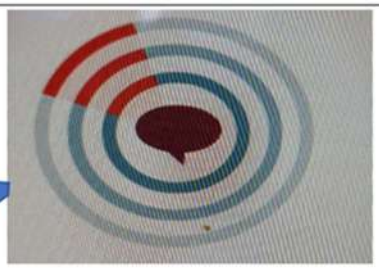


- Finally submit the filled reports to EFDA by entering data requested and protect the public from adverse drug reactions!!!!

Annex 3. Instructions on how to use the mobile app of Medsafety to report an adverse event.

Healthcare professionals can report ADE by using their MOBILE PHONES by following these simple procedures.

1. To access the Med safety app for IOS users go to the APP store for Android users go to google store search for Med safety app in the search bar (found as in the diagram above)
2. Click on the Med safety icon app to select it
3. click install to install the app
4. Once the app has been successfully installed click open on your device
5. Create a user account.
6. once the account has been created you come to the home page where the full page is provided
7. Then You can now report an ADE



Annex IV. 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

Annex V. Content of a PSMF

The main principle for the structure of the content of the PSMF is that primary topic sections contain information that is fundamental to the description of pharmacovigilance system.

PSMF Cover Page should include:

• The unique number assigned by the NMRA
• The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
• The name of other concerned MAH(s) (sharing the pharmacovigilance system).
• The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system)
• The date of preparation / last update

1 PSMF section on qualified person responsible for pharmacovigilance (QPPV)

The information relating to the QPPV, and back-up provided in the PSMF should include:

• job descriptions of the QPPV with responsibilities guaranteeing that he/she has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;

• a summary curriculum vitae with the key information on the role of the QPPV,

• contact details; including name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV

• details of back-up arrangements to apply in the absence of the QPPV

• The list of tasks that has been delegated by the QPPV and to whom these have been delegated

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

2 PSMF section on the organizational structure of the MAH

A description of the organizational structure of the MAH relevant to the pharmacovigilance system including the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations.

The PSMF should describe:

• Diagrams showing the organizational charts and the position of the QPPV in the organization may be particularly useful; the name of the department or third party should be indicated

• The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production,

signal detection and analysis, risk management plan management, pre- and post-authorization study management, and management of safety variations to product particulars.

Delegated activities

• Description of the activities and/or services subcontracted by the MAH in any country relating to the fulfilment of pharmacovigilance obligations should be provided.

• List/table to show the parties involved, the roles undertaken and the concerned product(s) and territories, including: service providers (e.g. medical information, auditors, patient support programme providers, study data management, etc.), commercial arrangements (distributors, importers/ agents, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.).

• Individual contractual agreements should be made available at the request of NMRA or during inspection and audit and the list provided in the Annexes.

3 PSMF Section on the sources of safety data

• The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in Ethiopia.

This should include medical information sites as well as affiliate offices.

• Flow diagrams indicating

- Inflow of adverse reaction reports and safety information

- Description of the stages involved in the processing of ICSRs including the timelines for submission to regulatory authorities including the NMRA

- Outflow of safety data to regulatory authorities including the NMRA

List of sources of safety data including any studies, registries, surveillance or support programmes sponsored by the MAH through which ICSRs could be reported. The list should be comprehensive for products authorized in the Ethiopia, irrespective of indication, product presentation or route of administration. The list should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should be organized per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex. Such list will support inspection, audit and QPPV oversight.

4 PSMF section on computerized systems and databases

Description of the location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose should be described in the PSMF in such a way that the extent of computerization within the pharmacovigilance system can be understood.

The validation status the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described.

For paper-based systems (where an electronic system may only be used for expedited submission of

ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

5 PSMF section on pharmacovigilance processes

• A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects should be included in the PSMF:

- Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection, and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc;

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

ICSR collection, collation, follow-up, assessment, and reporting; the procedures applied to this area should clarify what are local and what are global activities;

- PBRER scheduling, production and submission, if applicable

- Communication of safety concerns to consumers, healthcare professionals and the NMRA;

- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications. In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.

• A list of specific procedures and processes related to the pharmacovigilance activities, as well as interfaces with other functions including, but are not limited to, the roles and responsibilities of the QPPV, responding to NMRA requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. This list should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

6 PSMF section on pharmacovigilance system performance

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The

PSMF should include a description of the targets and monitoring methods (metrics) applied and contain as a minimum:

• An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;

• A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by authorities regarding the quality of ICSR reporting, PSURs or other submissions.

• An overview of the timeliness of PBRER reporting to NMRA in Sri Lanka (the annex should reflect the latest figures used by the MAH to assess compliance);

• An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and NMRA deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;

• Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

A list of performance indicators must be provided in the Annex to the PSMF alongside the results of (actual) performance measurements over the past year.

7 PSMF section on quality system

A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance. This should include:

Document and Record Control

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

Procedural documents

• A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc), the applicability of the various documents at global, regional

or local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.

• Information about the documentation systems applied to relevant procedural documents under the control of third parties.

Training

Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports and individual whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, telephone operators, receptionists, medical information, sales and marketing, regulatory affairs and legal affairs.

The PSMF should provide:

• description of the resource management for the performance of pharmacovigilance activities: the organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities,

• A description of the training organization in relation to the personnel and site information;

• A summary description of the training concept, planning including a reference to the location training Files

Updated training materials, training plan and evidence of training (training records) should be provided including assessment of the effectiveness of the training programmes as an Annex in the PSMF

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of

local distributers, service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the pharmacovigilance obligations and cover a rolling 5 year period.

The PSMF should also contain a note associated with any audit where significant (major or critical) findings are raised and to provide a brief description of their corrective and/or preventative action(s), the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In case corrective and preventative action plan(s) have not yet been agreed for a particular audit or finding, the PSMF should include the note required and stating that "corrective and preventative action plan(s) are to be agreed".

In the annex, in the list of audits conducted, those associated with unresolved notes in the PSMF, should be identified. The note and associated corrective and preventative action(s), should be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file should also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

8 Annex to the PSMF

An annex to the PSMF should contain the following documents which should be presented with the following headings and, if hardcopy, in the order outlined below:

Where there is no content for an Annex, it should simply be described as 'unused' in the indexing so the recipients of the PSMF are assured that missing content is intended. In these cases, the Annexes that are provided should still be named according to the format described below without reordering.

The qualified person responsible for pharmacovigilance, Annex A

• The list of tasks that have been delegated by the QPPV, or the applicable procedural document

• The curriculum vitae of the QPPV and associated documents

• Contact details supplementary to those contained, if appropriate

The Organizational Structure of the MAH, Annex B

• The lists of contracts and agreements

Sources of safety data, Annex C \

• Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

Computerized systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

• Lists of procedural documents

Pharmacovigilance System Performance, Annex F

• Lists of performance indicators

• Current results of performance assessment in relation to the indicators

Quality System, Annex G

• Audit schedules

• List of audits conducted and completed

Products, Annex H

• List(s) of products covered by the pharmacovigilance system

• Any notes concerning the MAH per product

Document and Record Control, Annex I

• Logbook

• Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself.

7.9 Logbook and history of changes

• All changes to the PSMF must be recorded in a descriptive way (include date and nature of change). and recorded in the logbook that is available in Annex I. The record for history of changes encompasses the pharmacovigilance safety database, significant pharmacovigilance service provider, merger and delegation of PSMF management.

• The QPPV should always be kept informed of such changes as well.

• The history of changes in each related Annex (e.g. product list, standard operating procedure list and compliance figures) should also be regularly updated.

• The superseded versions of such content may be managed outside of the PSMF content itself and made available to the Authority if requested. As a basis for audit and inspections, the PSMF should provide a description of the pharmacovigilance system at the current time, though the function and scope of the pharmacovigilance system in the past may need to be understood.

• MAH should have document control procedures in place to govern the maintenance of the PSMF, including those who have engaged a third party on the PSMF service.