# TIMOR-LESTE PHARMACOVIGILANCE MANUAL

**First Edition**
**May 2025**

## MINISTRY OF HEALTH
## NATIONAL DIRECTORATE OF PHARMACEUTICAL AND MEDICINES

Ministério da Saúde

# TIMOR-LESTE PHARMACOVIGILANCE MANUAL

**First Edition**
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World Health Organization
Timor-Leste

ADB

# PHARMACOVIGILANCE MANUAL

**Timor-Leste 2025**

# Message from the Minister of Health

In 1961, the world was shaken by the "Thalidomide Disaster." Thalidomide was sold in the market as a sedative and medication for morning sickness. Four years after launch, a dramatic increase in the frequency of Phocomelia, a rare birth defect, was observed in several countries, resulting in children without limbs and with severe deformities.

Epidemiological studies show that the cause of the incident was the exposure of pregnant women to medication during pregnancy. This tragedy remains a pivotal moment in medical history, emphasizing the critical role of Pharmacovigilance in protecting public health. One way to prevent these events is to monitor the safety of drugs through Pharmacovigilance, which over the past 40 years has become a top priority of health systems across the world. The health and well-being of our population depend not only on access to medicines but also on the continuous monitoring of their effects. This manual serves as a comprehensive resource for healthcare professionals, regulatory authorities, and all stakeholders involved in the safe use of pharmaceutical products.

This edition of the Pharmacovigilance Manual is the result of unwavering efforts and a highly consultative process with inputs from national and international health professionals and technical experts led by the Department of Pharmacovigilance and Control under the National Directorate of Pharmacy and Medicines. Strict adherence to the formatted Pharmacovigilance Manual remains a mandatory requirement.

The objective of this manual is to harmonize Pharmacovigilance practices, thereby ensuring the safety of the medicines used in our country. I urge all healthcare professionals and relevant authorities to utilize this manual effectively, ensuring the safety of every patient. Let us work together to uphold the highest standards of medicines safety and vigilance in Timor-Leste.

**dr. Élia A. A. dos Reis Amaral, SH**
**Minister of Health**
**Democratic Republic of Timor-Leste**

# Content

# Acknowledgment

The Ministry of Health of Timor-Leste acknowledges the efforts of all the experts for their contribution to the development of this Pharmacovigilance Manual.

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## World Health Organization

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## Asian Development Bank

1. **Stefania Dina,** Country Director, Asian Development Bank.
2. **Dr. Kyi Thar,** Regional Pharmacovigilance Expert (Consultant), Asian Development Bank.
3. **Dr. Alexo Esperato,** Senior Health Specialist, Asian Development Bank.
4. **SECURE Project Team,** Asian Development Bank.

Lastly, the Ministry of Health, Government of Timor-Leste, would like to express its sincere appreciation to the World Health Organization and the Asian Development Bank for providing financial and technical support for the development of this document.

# List of Abbreviations

- **ADR**: Adverse Drug Reaction
- **AE**: Adverse Event
- **AEFI**: Adverse Event Following Immunization
- **AERS**: Adverse Event Reporting System
- **AMTL**: Medical Association of Timor-Leste
- **AETL** : Association Nurse of Timor-Leste
- **ASFARTIL**: Pharmacists Association of Timor-Leste
- **ATC**: Anatomical, Therapeutic and Chemical Classification
- **CAPA**: Corrective Action and Preventive Action
- **CEM**: Cohort Event Monitoring
- **CSMPEM:** Commission for the Selection of Medicines, Products and Medical Equipment.
- **CHC:** Community Health Centers
- **CIOMS:** Council for International Organization of Medical Sciences
- **CPPV:** Contact Person for Pharmacovigilance
- **DA**: Drug Alert
- **DPHO**: District Public Health Officer
- **DHS**: District/Municipal Health Services
- **DNFM**: National Directorate of Pharmacy and Medicines
- **DFV**: Pharmacovigilance Department
- **EU-EMA:** European Medicine Agency of European Union
- **FIP:** International Pharmaceutical Federation
- **GCP**: Good Clinical Practice
- **GDP**: Good Distribution Practice
- **GLP**: Good Laboratory Practices
- **GLARS**: Cabinet of Licensing and Registration of Health Professional Activities
- **GMP**: Good Manufacturing Practice

- **GxP**: Good Practice ‘‘Quality Guidelines And Regulation”
- **HNGV**: Hospital Nacional Guido Valadares
- **ICH E2A:** International Council for Harmonization Clinical safety data management: definitions and standards for reporting.
- **ICH E2C:** International Council for Harmonization Periodic Benefit-Risk Evaluation Report
- **ICH E2D**: International Council for Harmonization of technical requirements for pharmaceutical for human use Guidelines.
- **ICH E2F**: International Council for Harmonization (ICH) guidelines for Development Safety Update Report.
- **ICSR**: Individual Case Safety Report
- **INS**: National Institute of Health
- **ISO**: International Organization for Standardization
- **INFPM**: National Institute of Pharmacy and Medical Products
- **NITAG - TL**: National Immunization Technical Advisory Groups Timor-Leste
- **LEE**: Lack of Expected Efficacy
- **MAHs**: Marketing Authorization Holders
- **ME**: Medication Error
- **MoH**: Ministry of Health
- **NCE**: New Chemical Entity
- **NM**: New Medicine
- **NPC** : National Pharmacovigilance Centre
- **NRA** : National Regulatory Authority
- **PASS** : Post Authorization Safety Study
- **PV** : Pharmacovigilance
- **PL** : Package Leaflet
- **PIL** : Patient Information Leaflet
- **PBRER**: Periodic Benefit Risk Evaluation Report
- **PSUR**: Safety Update Report

- **PSMF**: Pharmacovigilance System Master File
- **PSRM**: Product Safety and Risk Management
- **QPPV**: Qualified Person for Pharmacovigilance
- **RMP**: Risk Management Plan
- **SAE/R**: Serious Adverse Event/Reaction
- **SE**: Side Effect
- **SmPC**: Summary of Product Characteristics
- **SR**: Spontaneous Reporting
- **SRS**: Spontaneous Reporting System
- **SSRI**: Selective Serotonin Reuptake Inhibitors
- **USFDA**: United States Food and Drug Administration
- **TRG**: Technical Review Group
- **UMC**: Uppsala Monitoring Centre
- **WHO-ART**: WHO Adverse Reaction Terminology

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# Definitions and Terminologies

**Abuse of Medicinal Products**: Intentional, permanent, or sporadic excessive use of a drug that is accompanied by harmful physical or psychological effects.

**Adverse Drug Reaction (ADRs):** Response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans.[1]

**Adverse Event (AE):** Refers to any untoward (unpleasant) medical occurrence that may present during treatment, but which is not necessarily related to the treatment.[2]

**Adverse Event Following Immunization (AEFI).** Any untoward medical occurrence which follows immunization, and which is not necessarily related with the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. (CIOMS-WHO).

**Alert or Signal:** Information communicated of a possible causal relationship between an adverse event and medication, when this relationship was previously unknown or incompletely documented. Usually more is required of a notification to generate a signal, depending on the severity of the event and the quality of the information.

**Anatomical Therapeutic Chemical Classification (ATC):** Coding system of medicines, according to their pharmacological effect, therapeutic indications, and chemical structure. (WHO)

**Audit:** A systematic, disciplined, independent, and documented process for evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled (ISO 19011)

**Compliance:** Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements

**Corrective Action and Preventive Action (CAPA):** Tool to implement corrective and preventive actions resulting from the investigation of complaints, product rejections, non-performances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.[3]

**Drug Alerts:** Notification to the general population by the Pharmacovigilance Centre of a suspected association between a drug and an adverse reaction.

**Fake/Falsified Drug:** Drugs or substances that are wholly or partly an imitation of genuine drugs, or which have a false expiry date, false location, are registered with the wrong formula, and with a strength lower than the minimum or higher than the maximum standards.

**Good Pharmacovigilance Practices (GVP):** A set of measures to facilitate the performance of the safety monitoring of medicines. (EU-EMA)

**Herbal Drug:** A drug derived from a plant, animal or mineral that has not yet been compounded, dispensed, or denatured.

**Individual Case Safety Report (ICSR):** A document/form providing complete information on an individual case. The information is provided by a primary source (the healthcare worker who suspected and reported) and describes the suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient. (EU-EMA)

**Lack of Expected Efficacy:** An unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.

**Marketing Authorization Holders (MAHs):** An authorized entity to manufacture or import medicinal products into Timor-Leste.

**Medication Error:** An unintended failure in the drug treatment process that leads to, or has the potential to harm the patient. (EU-EMA)

**Minimum Criteria for Reporting Suspected Adverse Reactions**: These include an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect medicinal product (ICH-E2D).

**Missing Information:** Gaps in knowledge about a medicinal product, related to the safety or use of patient populations, which could be clinically significant (ICH-E2C).

**National Pharmacovigilance Centre:** The Department of Pharmacovigilance in the DNFM in the Ministry of Health.

**Notification Forms (see also Yellow Card):** The communication of a suspected adverse drug reaction to a Pharmacovigilance Center. Usually, notifications are made through the adverse reaction collection forms (Yellow Card), seeking the necessary means in each case to maintain data confidentiality.

**Periodic Safety Update Report (PSUR):** Format and content for evaluating the risk-benefit balance of a medicinal product for submission by the marketing authorization holder at defined time points during the post-authorization phase (EU-EMA).

**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.

**Post-Authorization Safety Study (PASS):** Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures. A post-authorization safety study may be a clinical trial or may follow an observational, non-interventional study design (EU-EMA).

**Potential Risk:** An untoward occurrence for which there is a basis for suspecting an association with the medicinal product of interest but where this association has not been confirmed (ICH-E2F).

**Quality Control and Assurance:** Monitoring and evaluating how effectively the

structures and processes have been established and how effectively the Pharmacovigilance processes are being carried out (EU-EMA-GPV)

**Registry:** An organized system that collects uniform data on the disease, conditions, or exposures by a population.

**Risks Related to the Use of Medicinal Products:** Any risk relating to the quality, safety, or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.

**Risk Management System:** A set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent, or minimize risks relating to a medicinal product.

**Risk Management Plan (RMP):** A structured set of activities to reduce the risks of medicinal products. The risk management plan established by MAH shall contain the following elements: (a) identification or characterization of the safety profile of the medicinal product(s)

(b) indication of how to characterize further the safety profile of the medicinal product(s) (c) documentation of measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) documentation of post-authorization obligations that have been imposed as a condition of the marketing authorization.

**Risk Minimization Measure:** 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.

**Safety Concern:** An important identified risk, important potential risk, or missing information. It is noted that the ICH definition of safety concern is an important identified risk, important potential risk, or important missing information, i.e., includes the qualifier "important" in relation to missing information (ICH-E2C).

**Serious Adverse Event or Reaction** Any untoward medical occurrence that at any dose results in death is life-threatening, requires hospitalization, or results in disability.

**Side Effect:** Any unintended effect (usually unpleasant) of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the medicine.

**Signal:** Reported information on a possible causal relationship between an adverse reaction and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the reaction, the quality of the reaction and the quality of the information.

**Signal Detection:** The process of looking for and/or identifying signals using data from any source (CIOMS VIII).

**Signal Management Process:** To properly manage signals, this process includes

the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritization, signal assessment and recommendation for action. (EU-EMA)

**Signal Validation:** Evaluation of whether a detected signal demonstrates the existence of a causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. (EU-EMA)

**Spontaneous Reporting:** A system whereby case reports of adverse drug reactions are voluntarily submitted by health care professionals and workers, pharmaceutical manufacturers/importers to the DNFM.

**Spontaneous Reporting System:** Pharmacovigilance method, based on the communication, collection and evaluation of notifications conducted by healthcare professionals on suspected adverse drug reactions, dependence on drugs, drug abuse and misuse.

**Stakeholders:** An institution, organization, individual, or group of individuals, with a legitimate interest, role, and responsibility in Pharmacovigilance.

**Substance:** Any matter irrespective of origin which may be human (e.g. human blood and human blood products), animal (e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (e.g. micro-organisms, plants, part of plants, vegetable secretions, extracts), or chemical (e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis).

**Traditional Medicine:** The sum of the knowledge, skills and practices from indigenous cultures, used in the diagnosis and treatment of health conditions.

**Vigiflow**: A web-based data management tool for ADRs. It is a complete Individual Case Safety Report (ICSR) management system created and maintained by the Uppsala Monitoring Centre (UMC) based in Sweden and strongly associated with the WHO Collaborating Centre for International Drug Monitoring. It can be used as the national database for countries in the WHO Program as it incorporates tools for report analysis and facilitates sending reports.

**Vaccine Pharmacovigilance:** The science and activities for the detection, assessment, understanding and communication of adverse events following Immunization (CIOMS-WHO). **UMC:** Uppsala Monitoring Centre located in Uppsala, Sweden.

**WHO-ART** (The WHO Adverse Reaction Terminology): A of terminology of adverse drug reactions containing a coding system for themselves.

# I. Introduction

In 2016, the National Directorate of Pharmacy and Medicines (DNFM) was established by Ministerial Decree No. 29/2024 Article 17 of this decree designates the Department of Pharmacovigilance of Medicines as the competent authority to develop a Pharmacovigilance Manual with an aim to increase the knowledge and awareness of Adverse Drug Reactions (ADRs) among health professionals and to encourage them to report all ADR problems to the Pharmacovigilance Department under DNFM.

In Timor-Leste, Decree-Law No.2/2025 defines the regime for the Import, Storage, Distribution, Sale and Export of Pharmaceutical Products and Medical Equipment within the country.

This Manual provides background on Pharmacovigilance in Timor-Leste and aims to strengthen the reporting of ADRs by the Department of Pharmacovigilance. The concepts and reporting requirements in this manual are based on the adaptation of international guidelines to Timor-Leste, a country substantially progressing from low to middle income status. The manual has been considered and acknowledged as similar to those in use by other low- and middle-income countries.

The Manual is intended for healthcare professionals to improve their awareness and understanding of Pharmacovigilance in their daily practice. It contains instructions for healthcare professionals to detect and report challenges with medicines, particularly ADRs. The healthcare workers include doctors and other prescribers, nurses, and pharmacists in the National Hospital of Guido Valadares (HNGV), referral hospitals, community health centers, health posts and private pharmacies.

Timor-Leste is using ADRs reporting systems to monitor adverse events following immunization (AEFI). This manual also describes practical solutions to integrate the ADRs and AEFI systems in Timor-Leste.

Timor-Leste's public health care system has demonstrated remarkable progress improving the health outcomes by enhancing access to medicines and medical products for the population. Pharmacovigilance is another effort of the public healthcare system to improve the quality and safety of medicines, and rational utilization of medicines in Timor-Leste.

The definition of Pharmacovigilance has evolved with time. According to the World Health Organization (WHO), it is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems" This definition has progressed into a systematic approach for monitoring and improving the safe

use of medicines. Another definition of Pharmacovigilance is the science of monitoring the safety of medicines and taking action to reduce risk and increase benefit. The assessment of benefit versus risk must begin from the development of the medicine to its uses and withdrawal when more effective drugs become available.[4]

Both definitions emphasize Pharmacovigilance as ultimately improving the use of medicines. However, the means of "Improving the Use of Medicines" varies from country to country. The inclusion of "any other drug-related problem" in the WHO definition of Pharmacovigilance has enlarged the scope of Pharmacovigilance.[5]

While exploring the development and use of medicines globally, new medicines (New Chemical Entities – NCEs) are introduced in high-income countries through intensive monitoring and vigilance to ensure their safety and efficacy. In contrast, low- and middle-income countries rely mainly on "Essential Medicines" which still face several challenges, including substandard and falsified medicines, improper or unsafe dosage (medication errors), and loss of efficacy of medicines including failures in storage (resulting in degradation).

As a developing country, Timor-Leste's Pharmacovigilance focus has so far been concerned with the ''Essential Medicines'' used in the health care system. The introduction of clinical trials and new medicines into the country will undoubtedly bring changes in the Pharmacovigilance system.

## Scope of Pharmacovigilance in Timor-Leste

In Timor-Leste, Pharmacovigilance comprises the following areas:

- To improve public health and safety in relation to the use of medicines.
- To detect problems related to the use of medicines by health care professionals, communicate the findings in a timely manner to DNFM, and take measures to correct those problems.
- To detect problems in medical products, investigate their causes and rectify them.
- To assess the risks and benefits of medicines through the identification of effectiveness, risks and costs of medicines.
- To promote understanding, education and clinical training in Pharmacovigilance and its effective communication to health care providers and the public.

As the Pharmacovigilance system is being established, priority is given to the first four areas: data collection, signal detection, risk assessment, and communication strategies to ensure the ongoing safety of medications.

## Pharmacovigilance Activities in the Ministry of Health

- Identifying medication errors (e.g., failure in pediatric malaria treatment due to incorrect dosage)
- Identifying fake medicines (e.g., illegally manufactured medicine with little or no active ingredient)
- Identifying substandard medicines (e.g., the medicine does not meet the required standard; the local anesthetic did not provide sufficient analgesia)
- Identifying adverse drug interactions (e.g. three drugs were given together of which two should not have been given at the same time).
- Identifying reasons such as adverse reactions, which can lead to medicines not being taken (non-compliance, non-adherence, e.g., nausea due to anti-TB drugs) [6]

These core functions of Pharmacovigilance address the medicines and medical products to ensure patient safety. Examples are the detection of poor-quality products such as spoiled medicines (e.g., discolorations in tablets, variation in the color of liquids in syrups), and cloudy liquids in injection vials. Conventionally these are seen as supply chain problems and other countries may have separate systems for them. However, in a country like Timor-Leste with limited human and financial resources, the Pharmacovigilance system can be used to monitor the quality of the products in the system, provide feedback and improve the medicines quality. Pharmacists are particularly important in this and there is a section addresses this issue.

## WHO Program for International Drug Monitoring

Pharmacovigilance is an international global effort; countries need to cooperate and pool their resources, as well as the reports of adverse drug reactions to build a comprehensive picture of the risks and benefits of medicine use. WHO's Program for International Drug Monitoring started in 1968 to pool existing data on ADRs. It was endorsed at the 20th World Health Assembly which adopted a resolution to initiate an international system of monitoring adverse drug reactions. The Uppsala Monitoring Centre (UMC) in Sweden began in 1968 and is the apex of the WHO Collaborating Centre for Pharmacovigilance. As of November 2019, there were 136 full member countries, and 30 associate members participating in this system.[7]

Timor-Leste became an associate member in 2019 and currently progressing towards achieving a full member status. Establishing the National Pharmacovigilance System and regular reporting of ADRs to UMC is an essential requirement to upgrade from associate member to full member status. This

Manual is critical and will contribute to the improvement of regular reporting of suspected ADRs and other medicines problems to the Department of Pharmacovigilance in DNFM.

# II. Steering and Expert Advisory Committees on Pharmacovigilance

Establishing the National Pharmacovigilance Steering and Expert Advisory Committees is a necessary component of any Pharmacovigilance system. These include stakeholders who can provide adequate and timely advice on medicine safety for Timor-Leste. The existence of the steering and advisory committees is one of the core structural indicators (CSTs) of a Pharmacovigilance system according to the World Health Organization.

## Goals and Objectives:

The overall goal of the committee is to improve policy awareness, support regulatory measures and strengthen reporting and management of Adverse Drug Reactions (ADRs) among all relevant health care professionals including public and private sectors.

## The Specific Objectives of the Steering and Advisory Committees are to:

- Provide stewardship, policy, and legal advice to improve the Pharmacovigilance system.
- Generate awareness about ADRs among policy-makers and healthcare providers.
- Identify and report ADRs in the health care setting and public to appropriate authorities.
- Assess the quality and safety of medicine and drugs including rapid alert notification and identification of falsified drugs and take necessary regulatory actions.
- Undertake scientific and research activation pertaining to ADR signal detection and signal management process.
- Support other activities to strengthen the ongoing national Pharmacovigilance system such as audits, safety reporting, quality control, risk management and regulatory compliance.

## Scope of the Committees

The Steering and Advisory have the following scope of activities:

**1. National Steering Committee:** shall be responsible policy, governance, and stewardship of the entire Pharmacovigilance system.

The proposed members of the Pharmacovigilance Steering Committee are:

**Chairperson:** H.E. Vice Minister of Health, Ministry of Health

**Vice Chairperson:** Director General of Hospital Services

**Secretary:** Director, DNFM

**Members:**

- Health Professionals: from DNFM, Department of Health Services/Hospitals, Disease Control Program, National Immunization Program, Supply Chain Management, and Health Information System, as well as Finance and Budget.
- Representatives from other ministries: Ministry of Agriculture, Ministry of Education, Ministry of State Administration, Ministry of Finance, Ministry of Commerce and Trade
- Representative from the Consumer Care Association
- Representative from the Health Professional Association. AMTL (Medical Association of Timor-Leste), ASFARTIL (Pharmacists Association of Timor-Leste) and AETL (Nursing Association of Timor-Leste).
- Representative from an academic institution
- Representatives from state media and civil society
- Representative from key development partners (WHO, UNICEF, DFAT- PHD, ADB)
- Representative from a private/community pharmacy

**2. National Expert Advisory Committee:** shall be responsible for planning, implementing, and monitoring various activities.

The proposed members of the National Expert Advisory Committee are:

**Chairperson:** Director General of Hospital Services

**Secretary:** Director, DNFM

**Members:**

- Head of PV department
- Pharmacy Advisor of the Ministry of Health
- Representative from the National Directorate of Pharmacy and Medicine
- Representative from the Clinical Department of Medical Services (Hospitals)
- Representative from the National Immunization Program
- Representative from the Disease Control Department
- Representative from the General Practitioner Association
- Representative from the Nursing Association

- Representatives from the Academic Institutions
- PV experts from the Development partners (WHO, ADB, Therapeutic Good Administration)

## Functions and Terms of Reference (ToRs) of the Steering Committee

The National Medicine Policy and Standard Operating Procedures (SOPs) for the Pharmacovigilance system will provide overall guidance and support for implementing the following Pharmacovigilance committee functions.

**Oversight Function:**

- Offer support and advocacy for policymakers and stakeholders.
- Provide policy decisions to ensure reliable performance and safety practices.
- Organize meetings to review the performance of the Pharmacovigilance system.

**Legal Responsibility:**

- Coordinate the formulation of legislation and regulations and address legal issues related to Pharmacovigilance systems.
- Coordinate other functions of the National Regulatory Authorities.
- Oversee customer complaints and public communication on ADRs and AEFI.

**Regulatory Affairs:**

- Notify health authorities on matters related to the safety of pharmaceuticals.
- Provide regulatory information and notify safety-related label changes.
- Maintain information to market authorization regulatory data based (product approval, suspension, and withdrawal).
- Rapidly alert to and take necessary actions for falsified and sub-standard drugs.

## Functions and Terms of Reference (ToRs) of Expert Advisory Committee :

- Develop procedures and standards, as well as patient support, knowledge, management and studies.
- ADRs signal detection and management, market surveillance, and causality assessment.

**Product Safety and Risk Management (PSRM)**

- Coordinate with stakeholders to minimize medical product risks.
- Monitor Pharmacovigilance system performance, safety, and risk-benefit of medicinal products.
- Establish the Pharmacovigilance System Master File (PSMF) and develop Pharmacovigilance guidelines.
- Provide Pharmacovigilance training and refresher training to public and private health care professionals.
- Promote knowledge and awareness of ADRs and safety reporting to MAHs.

- Provide specific actions to maintain safety issues (recall, suspension, withdrawal)
- Share safety information and Pharmacovigilance data to regulatory authorities (DNFM) and the public.

**Quality Operation:**

- Implement quality systems, procedures, and standards.
- Establish mechanisms and databases to ensure product quality complaints as well as reconciliation.
- Coordinate with PSRM regarding risk assessment and product recall.
- Communicate with the public about the quality and safety of medicine.

## Operational Mechanism of Pharmacovigilance Committees

- The Steering Committee shall meet once in every 6 months.
- The Expert Advisory Committee shall meet more frequently, once in every 3 months.
- A full-term DNFM staff is required to be assigned as the Secretariat of the steering committee and advisory committee.
- The tasks of the Secretariat include the following:

✓ Communicate with committee members via email or departmental letter.
✓ Plan and budget steering committee meetings and advisory committee meetings in the annual Pharmacovigilance system budget.
✓ Prepare and disseminate the reports and recommendations of the Pharmacovigilance committee meetings to all committee members.
✓ Other ad-hoc and emergency functions assigned by the Pharmacovigilance Committee

## Relations of Pharmacovigilance Centre with the Stakeholders

i. The Drug Regulatory Authority in the country (DNFM in Timor-Leste) must be informed about suspected adverse reactions promptly, especially when they are unusual (e.g., reactions not listed in the approved Summary of Product Characteristics) or serious.
ii. The Pharmacovigilance Centre should seek the support of professional medical and pharmacist associations, as well as healthcare institutions (HNGV, Referral Hospitals). In case of an emergency, these associations and institutions should be informed promptly.
iii. Establish links with the National Pharmacovigilance Centers in nearby countries, such as Australia and Indonesia, for information exchange and capacity development.
iv. Engage with academic institutions that offer pharmacology and related

courses for research and learning. This manual can serve as a reference for students and teaching faculty.

v. Maintain effective communication channels with journalists and media outlets to increase public awareness and support Pharmacovigilance efforts.

# III. Minimum Criteria for Quality Pharmacovigilance System

According to the WHO Global Benchmark Tools (2021)[8], there are four levels of maturity for Pharmacovigilance. Timor-Leste is now at maturity level 1 and aims to achieve maturity level 2. Expertise in Pharmacovigilance encompasses several key criteria, including comprehensive clinical monitoring, safety reporting, signal detection and management, risk management, data safety, and the designation of a qualified person responsible for Pharmacovigilance.[9]

**Figure 1. Key Components of Pharmacovigilance Expertise[10]**

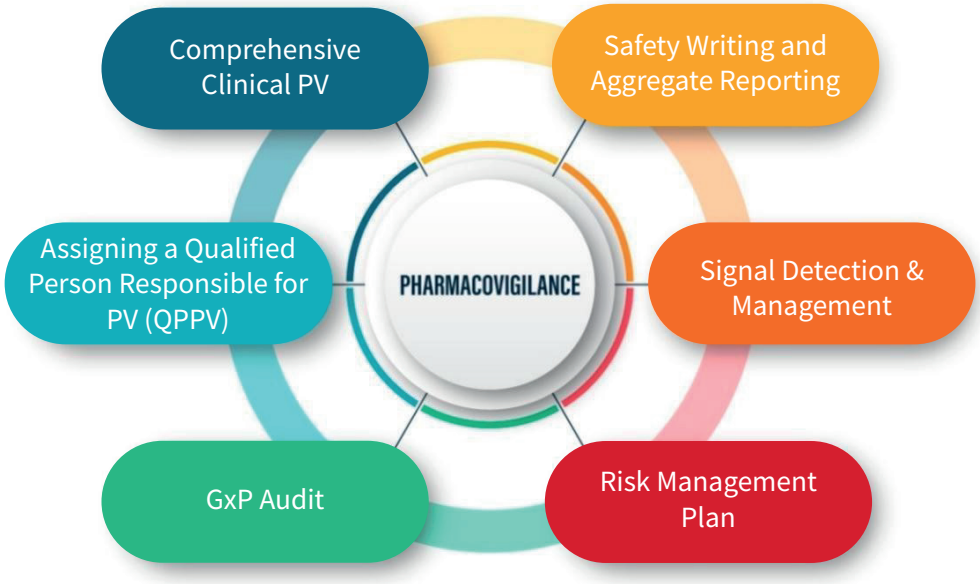


Figure 1

According to the European Union Good Pharmacovigilance Practice (GPV) and USFDA guidelines, a quality Pharmacovigilance system needs to meet the follow minimum quality criteria/standards.[11]

**Table (1) Minimum Criteria and Functions of the Pharmacovigilance System**

| Minimum Criteria/ Standards | Functions of Pharmacovigilance Systems |
|---|---|
| **Quality Pharmacovigilance System** | • The Pharmacovigilance system must identify the scope of products for all registered drugs and medicines.<br>• Adequate facilities and equipment for quality inspection and post-market surveillance. |
| | • Training programs and training plans for Pharmacovigilance.<br>• Standard operation procedures and record management system.<br>• Monitoring system for performance and effectiveness of the Pharmacovigilance system |
| **Pharmacovigilance System Master File (PSMF)** | • There should be a designated person responsible for the Pharmacovigilance system and master file.<br>• The terms of reference and roles of Qualified Persons for Pharmacovigilance (QPPV) and Contact Person for Pharmacovigilance (CPPV) by Market Authorizing Holders (MAHs) should be documented.<br>• Documented information on Market Authorizing Holders MAHs (Company details and organizational structures)<br>• Recording of product safety data (databases – electronic or paper-based)<br>• Pharmacovigilance processes and procedures must be documented and available for dissemination.<br>• The Pharmacovigilance unit must keep performance records.<br>• There should be PSMF logbooks, and all information related to the quality system of Pharmacovigilance mentioned above should be kept in PSMF. |

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| **Inspection and Audits** | • The Pharmacovigilance team should understand various inspection types and scopes of the products.<br>• Documentation related to inception and process, classification of findings and preparation of inspection of reports.<br>• Roles and responsibilities of inspectors (Assessor and MHA) should be documented.<br>• The Pharmacovigilance team also has the annual audit plan in collaboration with the auditor inspection general office.<br>• Actions and follow-up from audits should be documented.<br>• The competence of auditors should be promoted through necessary training and quality improvement. |
| **Signal Detection and Signal Management** | • The Pharmacovigilance system has documented standard operation procedures for signal detection and signal management process.<br>• There should be an ADR reporting format, as well as procedures and various stakeholders responsible for ADR reporting.<br>• The ADR reporting should be integrated into AEFI signal detection and management and reported to the global reporting system through Vigiflow or similar reporting platforms.<br>• Pharmacovigilance staff should be regularly trained for signal detection, validation, prioritization, and management.<br>• There should be collaboration with medical teams to provide appropriate treatment for adverse drug reactions. |
| **Data Management** | • The Pharmacovigilance system should have a data management system to protect data privacy and analyze Pharmacovigilance data.<br>• For resource-limited settings, a transitional system could be applied where an electronic data-based system is established at the central level and a paper- |

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| | based reporting system can be applied at the sub-national level.<br>• A designated focal person for data management and reporting at various levels should be assigned by DNFM.<br>• Challenges and gaps in data management systems (technical, human resource and IT should be regularly assessed. Request Development Partners and MoH to support as necessary |
| **Risk Management** | • Stakeholders should be advocated for minimizing risk and the principle of risk management in Pharmacovigilance.<br>• The Pharmacovigilance Centre should designate a person for risk management.<br>• Risk management can be considered as a routine activity on Pharmacovigilance or additional activities depending on the available human resources, data, and information.<br>• Risk minimization measures and activities should be documented, and safety concerns should be regularly updated |
| **Safety Communication** | • The Pharmacovigilance system should have documented protocols and principles for safety communications, such as setting the target audience, type and contents of safety communications.<br>• Safety communications should have at least two mechanisms, routine communications and emergency and crisis communications.<br>• The effectiveness of communication mechanisms (media, website, social media, and alert messages) should be regularly assessed. |

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| **Safety Reporting** | • The Pharmacovigilance system should use various channels of safety reporting such as types of events or reactions, types of product monitoring and reporting.<br>• The common types of reporting are (1) Individual case safety reports (ICSR) and (2) Periodic benefit-risk evaluation reports (PBRER)<br>• There should be designated qualified reporters proficient in the information and minimum criteria for safety reports.<br>• Safety studies (e.g. clinical trials, epidemiology studies and population studies) can incorporate scientific methods to identify causes and effects.<br>• Periodic safety studies need a trained Pharmacovigilance expert, with a research background and an adequate budget for the studies. |

# IV. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a harmful and unwanted reaction that occurs after the administration of drugs at the doses commonly used in the human species to prevent, diagnose, or treat a disease or modify any biological function.[12]

## Classification of Adverse Drug Reaction (ADR)

## Clinical Epidemiological Classification or RAWLINS and THOMPSON Classification (Types of Adverse Drug Reactions)

An ADR is a response to a drug that is noxious (unpleasant) and unintended, occurring at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or the modification of physiological functions. Note that diagnostics (e.g., X-ray contrast media) and oral contraceptives (which modify physiological function to regulate fertility) are also included in the definition of a drug. There are multiple classifications of ADRs, but the following classification is the most widely accepted (see Table 2). [13]

### Table 2. Classification of Adverse Drug Reactions

| Type of Reactions | Mnemonic | Features | Examples | Management |
|---|---|---|---|---|
| A: Dose-Related | Augmented | • Common<br>• Related to a pharmacolog-ical Action of the drug.<br>• Predictable<br>• Low mortality | • Toxic effects: Digoxin toxicity syndrome with SSRIs<br>• Side effect: Anticholinergic effect of tricyclic antidepressant | • Reduce dose or withhold.<br>• Consider the effects of concomitant therapy |

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| C. Dose-Related and Time-Related | Chronic | • Uncommon<br>• Related to the cumulative dose | • Hypothalamic pituitary-adrenal axis suppression by corticosteroids | • Reduce dose or withhold; withdrawal may have to be prolonged |
| D: Time-Related | Delayed | • Uncommon<br>• Usually is related.<br>• Occurs or becomes apparent after the use of the drug | • Teratogens (e.g., vaginal adenocarcinoma with diethylstilbestrol)<br>• Carcinogenesis<br>• Tardive dyskinesia | • Often intractable |
| E: Withdrawal | End of use | • Uncommon<br>• Occurs soon after withdrawal of the drug | • Opiate withdrawal syndrome<br>• Myocardial ischemia (B-blocker withdrawal) | • Reintroduce and withdraw slowly |
| F: Unexpected Failure of Therapy | Failure | • Common<br>• Dose related.<br>• Often caused by drug interactions | • Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers | • Increase dosage.<br>• Consider the effects of concomitant therapy |

**a) Type A Effects: Dose Related**

Augmented (increased) pharmacologic effects-dose dependent and predictable (medicine actions) are those which are due to (exaggerated) pharmacological effects. Type A effects tend to be common, dose-related (e.g., more frequent, or severe with higher doses) and may often be avoided by using doses that are appropriate to the individual patient. Such effects are often already identified before marketing.

**b) Type B Effects: Non-Dose Related.**

Unusual (bizarre) effects (or idiosyncratic)-dose-independent and unpredictable (patient reactions) characteristically occur in only a minority of patients and display little or no dose relationship. They are rare and unpredictable and may be serious. Type B effects can be immunological or non-immunological and may occur in patients with predisposing conditions. Immunological reactions may range from rashes, anaphylaxis and vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Allergic reactions to penicillin are examples of such Type B immunological reactions.

Type B effects occur in a minority of predisposed, intolerant, patients, e.g., because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or accumulation of a toxic metabolite. The Grey Baby Syndrome due to chloramphenicol in neonates is due to immature liver enzymes. However, the mechanism of chloramphenicol-induced aplastic anemia is still unknown although it was first reported over 50 years ago. It has been reported only in oral and parenteral administration and topical administration remains safe.

***Type A and Type B are the Most Common Adverse Effects.***

**c) Type C Effects: Dose-Related and Time-Related.**

Chronic effects refer to situations where the use of a medicine, often for unknown reasons, increases the frequency of a "spontaneous" disease. Type C effects may be both serious and common (and include malignant tumors) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long-term effects; there is often no suggestive (indicative) time relationship, and the connection may be difficult to prove. (e.g., Adrenal suppression with corticosteroids).

**d) Type D Effects: Time-Related**

Due to prolonged use of a drug it does not tend to accumulate in the delayed effects that are dose- independent. Adverse Drug Reaction is marked by effects that manifest after treatment has stopped, such as ophthalmopathy linked to

chloroquine or pulmonary/peritoneal fibrosis caused by thioridazine. Some of these are carcinogenesis due to immunosuppressants (azathioprine) and teratogenesis due to antineoplastics, thalidomide and tetracyclines.

e) **Type E Effects: Withdrawal.**

End-of-treatment effects. e.g. - Opiate withdrawal syndrome.

f) **Type F Effects Unexpected Failure of Therapy. e.g., -** Inadequate dosage of an oral contraceptive; standard does but used with enzyme inducers which increased the metabolism of the oral contraceptive.

## Classification of Adverse Reactions According to Severity

a) **Fatal:** The reaction directly or indirectly leads to the death of the patient.

b) **Severe:** The reaction directly threatens the patient's life.

c) **Moderate:** The reaction causes hospitalization or care in the emergency service or sick leave from work or school, without directly threatening the life of the patient.

d) **Mild:** The reaction exhibits easily tolerated signs and symptoms, does not need treatment, does not prolong hospitalization and may or may not require drug suspension

### Classification of Adverse Reactions According to Frequency

The RAM classification is based on the frequency of events as follows:

a) **Very Common:** They occur with a frequency greater than or equal to 1 case in every 10 patients who encounter the drug. It is expressed ≥ 1/10 and ≥10%.

b) **Common:** Occur with a frequency greater than or equal to 1/100 and < 1/10 but less than 1/10 and ≥1% and <10%.

c) **Infrequent:** Occurs with a frequency greater than or equal to 1/1000 but less than 1/100 and ≥ 0.1% and < 1%.

d) **Rare:** Occurs with a frequency greater than or equal to 1/10,000 but less than 1/1,000 and ≥0,01% and <0,1%.

e) **Very Rare:** Occurs with a frequency of less than 1/10,000 and < 0.01%.

## Adverse Events Following Immunization (AEFI)

Vaccines used in national immunization programs are highly safe and effective. But, no vaccine is perfectly safe, and adverse events can occur following

immunization. In addition to the vaccines themselves, the immunization process is a potential source of adverse events. An adverse event following immunization (AEFI) is any adverse event that occurs after immunization and is believed to be caused by the vaccine. Reported adverse events can be either actual adverse events or perceived adverse events.

One challenge for the MoH is to integrate the AEFI information system with the ADR reporting system, given the different management structures across various departments (DNFM and EPI program), differing reporting pathways and data management, and distinct budgets. The Global Center, reporting through the Vigibase/Vigiflow reporting system, can capture both AEFI and ADR information on the same platform, which is a possible solution to combine the two systems. However, there are designated responsibilities required between DNFM and EPI to link the ADR and AEFI data in the Vigiflow system.

To achieve the integration of ADR and AEFI, the following are required:

- Obtain strong political commitment from the Pharmacovigilance steering committee, which can provide clear direction for synchronizing data from different focal departments.
- Raise awareness between stakeholders from the Ministry of Health, EPI and DNFM, through regular Pharmacovigilance expert meetings every quarter.
- Establish communication mechanisms between EPI and DNFM (either email, electronic reporting, WhatsApp, Viber etc. and define responsibilities for information sharing and collaboration.
- Nominate focal points at EPI and DNFM for data sharing, interpretation, and analysis.
- Share information and data management tools. No new additional data collection mechanism is required. EPI can share existing monthly AEFI data sets with DNFM, and DNFM can upload AEFI data into the Vigiflow system.
- Establish an electronic data format interoperable with EPI and DNFM (either Excel templates or any other data information system DHIS-2).
- Implement education and hands-on training on data collection, compilation, analysis and data management.
- Seek and explore support from development partners on vaccine information, training and dissemination of SOPs and forms (WHO, UNICEF and ADB).

# V. Reliable Medicine Information System for Pharmacovigilance

## Registration of Medicines

Every country has a registration system for medicinal products. Registration is based on the dossier submitted by the applicant. Adequate submission requires detailed information of the product's name, manufacturer, dosage, and form (e.g., amoxicillin, brand name ABC™, made by manufacturer XYZ Company, 250 Mg Capsule). The applicant would usually be:

- A manufacturer or
- An officially nominated agent/importer of the manufacturer (Market Authorization Holders MAHs).

Since there are no pharmaceutical manufacturers in Timor-Leste, all applicants are MAHs. Typically, the medicine must be registered in the country of origin to demonstrate to the importing country that it is of adequate quality and safety.

There are two aspects to evaluating and approving a dossier.

- The first is the quality of the product, including the Active Pharmaceutical Ingredient, Good Manufacturing Practices, Quality Assurance Systems, and Quality Testing, as well as relevant certificates.
- The second is the information on how to use the medicine correctly.

## The Information on the Use of Medicine

The information required for registering each medicine includes the name of the product, indications, dose, contraindications, adverse effects, and use in special situations such as pregnancy, renal, and hepatic failure. This information is considered "Approval Information" as it must be evaluated and approved by the country's Medicines Regulatory Authority. The information is legally binding, frames the use of the product, and can be broadly considered the "birth certificate" of the product. This document is known as the Summary of Product Characteristics (SmPC), also referred to as SmPC. When there are multiple versions (generics) of the same medicine, a common Summary of Product Characteristics (SmPC) usually applies. The approval of the two dissimilar parts of the dossier illustrates that medicine is not only a physical product but also includes comprehensive information on how to use it correctly.

## Summary of Product Characteristics (SmPC)

SPCs provide comprehensive information on how to use the medicine safely and effectively. However, some products are unable to provide SPCs, primarily when they are imported in bulk quantities. Some SPCs of medicines registered by Regulatory Authorities of high-income countries are available on the internet and websites and are a handy source of complete information. The Product Information Leaflet, also known as the Prescribing Information Leaflet, contains a summary of the Summary of Product Characteristics (SPC). There are also Patient Information Leaflets, which are written in non-technical language and aimed at patients, providing useful sources of information.

### Smartphone Apps

The most useful sources of medicines' information are in the two smartphone Apps referred below. When there is an unfamiliar/unusual reaction to a medicine, these can be checked for further information on the potential adverse effect.

**British National Formulary (BNF):** Based on the UK pharmaceutical reference book, this app can be downloaded from the Google Play Store in Timor-Leste. BNF is considered the gold standard in medicines information and a very authoritative source. The BNF App also has the advantage of not requiring data once installed; therefore, it can be used off-line by prescribers in the wards or clinics, including in rural areas with limited Internet connectivity.

**Therapeutic Guidelines (Formerly eTG Complete):** A digital resource from Australia, this app provides treatment notes as well as information on medicines. While the information is aimed at Australian prescribers, most of the information is useful for prescribers in Timor- Leste. Again, when searching for information on medicine, eTG would be an extremely useful source. Therapeutic Guidelines provide free access for prescribers in Low- and Middle- Income Countries (LMICs) including Timor-Leste.[14]

# VI. Product Inspection

Inspection is the key step in ensuring the safety and quality of products, and this chapter guides the planning, conducting, reporting, and follow-up of inspections. An overview of various processes and parties involved in inspection is described. Assessors from DNFM should conduct regular Pharmacovigilance inspections to fulfill the obligation of quality and safety requirements and to ensure MAHs comply with Pharmacovigilance obligations established in Timor-Leste.

## The Objectives of Pharmacovigilance Inspections

- To determine that the MAHs have personnel, systems, and facilities in place to meet their Pharmacovigilance obligations. To identify, record, and address non-compliance.
- To use the inspection results as a basis for enforcement action if necessary.

## 1. Types of Inspections

### i. 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 regulatory Pharmacovigilance obligations. This may include some products to demonstrate the Pharmacovigilance operation.
- Product-Related Pharmacovigilance inspection**s** are primarily focused on product- related issues, including product-specific activities and documentation, rather than a general system review. However, some aspects of the general system may still be examined as part of a product-related inspection.

### ii. Routine and “for-cause” Pharmacovigilance Inspections

- Routine Inspections are scheduled as part of inspection programs. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are typically system inspections, but one or more specific products may be selected as examples to verify the system's implementation.
- Cause-Specific Inspections are conducted when a specific problem or trigger is identified. This type of inspection is considered an appropriate way to examine and solve the issues. Cause inspections are more likely to focus on specific Pharmacovigilance processes or include an examination of identified compliance issues. Common causes include:

- ✓ Delays or failure to identify or communicate a risk.
- ✓ Communication of Pharmacovigilance information to the public without notification to the NRA
- ✓ Non-compliance or product safety issues identified during the monitoring of Pharmacovigilance activities by the NRA.
- ✓ Suspension or product withdrawal with no advance notice to NRA delays or omissions in reporting inferior quality or incomplete reports, inadequate quality, or inadequate data to fulfill NRA information requests.
- ✓ Inconsistencies between reports and other information sources failure to provide the requested information within the NRA-specific deadline.
- ✓ Delays in the implementation or inappropriate implementation of corrective and preventive actions (CAPA)
- ✓ Information such as non-compliance or product safety issues from other types of inspections (All GxP; GCP, GMP, GLP and GDP)

**iii. Pre and Post Authorization Inspections**

- Pre-Authorization Inspections are performed before a marketing authorization is granted. These inspections are to examine the existing or proposed Pharmacovigilance system as it described by the applicant in support of a marketing authorization application. In most cases, a risk assessment based on a combination of product-specific and system- related issues should be performed before a pre-authorization Pharmacovigilance inspection is requested.
- Post-Authorization Inspections are performed after a marketing authorization is granted and are intended to examine whether the MAHs comply with their Pharmacovigilance obligations.

**iv. Announced and Unannounced Inspections**

- Inspections are usually announced in advance to the inspected party to ensure the availability of relevant individuals for the inspection. However, unannounced inspections, or inspections announced at short notice, may be conducted due to urgent safety reasons.

**v. Remote and on-site Inspections**

- Remote Inspections are performed by inspectors far away from the firms employed by the MAHs. Communication technologies encompass live or real-time streaming video, screen sharing, and other means of real-time communication. This approach may also be used when an on-site inspection would be complex logistically due to exceptional circumstances.
- Onsite Inspections at the firm of MAHs. This is based on the risk assessment,

size of the company, and complexity of the Pharmacovigilance system & process.

## 2. Scope of Inspections

The scope will depend on the inspection objectives, the result of previous inspections and whether it is a system or product-related inspection. Additional data should be requested in advance before the inspection to select appropriate sites or clarify aspects of the Pharmacovigilance system. The following elements should be considered for the inspection scope:

- ✓ Information in the Pharmacovigilance system master file (PSMF)
- ✓ Compliance data and reports from NRA and data quality audits
- ✓ Individual case safety reports (ICSRs) collecting, receiving, and exchanging reports.
- ✓ Assessment follow-up and outcome recording
- ✓ Reporting and timeliness record and archiving
- ✓ Periodic benefit-risk evaluation report (PBRER), (as applicable):
- ✓ Formatting, timeliness of submission, and completeness and accuracy of the data
- ✓ Addressing safety topics and ongoing safety evaluation signal detection analysis
- ✓ Implementation of the RMP or other commitments
- ✓ Timely response to specific NRA requests for data
- ✓ Implementation of safety communications

## 3. Processes of Inspections

Preparation for product inspection includes the following steps:

- Resource allocation
- Trained and experienced inspector(s) should be appointed for an inspection.
- Announcing the inspection
- NRAs should have the right to inspect at any time. In some cases, an inspection may be performed without prior notice. This could arise, for example, in the conduct of a “for cause” inspection to investigate an immediate public health or compliance concern.
- However, routine practice is to provide advance notice of the intent to inspect a Pharmacovigilance system to the MAH. The 6-8 weeks of notice should be sufficient for MAHs to enable logistical arrangements and review of relevant data.

- Announcement could include the name of the inspector(s), MAH, the objectives and type of the inspection, and the address of the inspection site(s). Additional information, including specific product authorizations, is to be reviewed if applicable.
- The announcement should be issued to the relevant contact person, requesting confirmation of the inspected entity's availability and that access to all required documents/databases will be provided. The timeline and method of submission of documentation should be clearly defined for the inspected entity.

## 4. Conducting Inspection

Information to fulfill the inspection can be collected by examination of computer systems, the conduct of interviews, and review of internal and external communication e.g., logbooks, registries, communication with authorities etc. The opening meeting must take place between the inspection team and the company being inspected. The chair of the meeting should be the lead inspector. The purpose of the opening meeting is to introduce the inspection team:

- Explain the regulatory framework for the inspection.
- Provide the scope and the objectives of the inspection.
- Clarify logistics and other references.
- Introduce the MAH representatives who will be attending the inspection.
- Allow the company to present an overview of the Pharmacovigilance system.
- Review of documentation, processes, and systems

The processes and documents to be reviewed during an inspection will depend on the type, scope, and focus of the inspection; for example, a "for cause" inspection may focus on issues of concern. All inspection observations should be documented. If appropriate, copies should be made of records that contain inconsistencies or illustrate non-compliance. Closing meetings with the inspected entity explain the findings grading, timelines for distributing the report, response, and follow-up measures to provide the inspected party with the necessary information to correct misconceptions and misunderstandings in response to the findings.

**Classification of Inspection Findings**

- **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 or that represents a serious violation of applicable legislation and guidelines.
- **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 or that represents a violation of applicable legislation and guidelines.

- **Minor**: a deficiency in Pharmacovigilance systems, practices or processes that would not adversely affect the rights, safety, or well-being of patients.

## 5. Report of Inspection

The inspection report should be issued thirty working days after the end of the inspection (the time is calculated from the last day of the last inspection or from when the last post-inspection document has been received). Corrective and preventive actions (CAPA) should be provided by the MAHs within thirty working days after receiving the report. When the CAPA proposed by the MAHs is acceptable, the inspection may be closed.

## 6. Record Management and Archiving

Pharmacovigilance system inspections should preferably be maintained for as long as the system is in place. Advanced Pharmacovigilance systems in developed countries archive the inspection record for at least 10 years after the system had ceased to exist.

## 7. Role of MAHs in Inspection

MAHs should always be ready for regulatory inspections and be aware of these activities during the Pharmacovigilance inspection. Its role is as follows:

- To ensure that the sites selected agree to Pharmacovigilance inspections.
- To make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection.
- To ensure that relevant Pharmacovigilance staff are present and available for interviews or clarification.
- To ensure that relevant Pharmacovigilance data is accessible.
- To ensure that appropriate and timely corrective and preventive action plans are implemented to address findings.

# VII. Audits

An audit can be defined as a systematic, disciplined, independent, and documented process for gathering evidence and objectively evaluating it to determine the extent to which the audit criteria are met, thereby contributing to the improvement of risk management, control, and governance processes. Audits in Pharmacovigilance should verify the appropriateness and effectiveness of a Pharmacovigilance system's implementation and operation, including its quality, through examination and evaluation of objective evidence.[15]

In Timor-Leste, Pharmacovigilance audits are usually conducted in collaboration with other departments. Therefore, Pharmacovigilance staff must fully understand the key aspects to be focused on by the Pharmacovigilance audit. Internationally recognized auditing standards or principles are essential during the audit process, which are established by relevant local and international auditing standardization organizations, such as the International Organization for Standardization (ISO). All organizations involved in Pharmacovigilance activities should conduct regular audits of their Pharmacovigilance systems to ensure the achievement of Pharmacovigilance quality commitments.

## Level of the Audit Plan

The risk-based approach is applied in Pharmacovigilance audits to focus on high-risk areas within an organization's Pharmacovigilance system, including its quality system. Risk can be assessed at the following levels:

- Strategic Level (Long-Term Plan)
- Tactical Level (Audit Program)
- Operational Plan (Fieldwork & Report)

## Strategic Level (Long-Term Plan)

The audit strategy is a high-level plan outlining the audit approach for 2-5 years. The audit strategy should outline the risk areas, audit topics, methods, and assumptions (including risk assessment) for the proposed audit program. It should encompass the governance, risk management, and internal controls of the Pharmacovigilance system, including all its processes, the quality control system, interactions with other stakeholders, and activities conducted by affiliated or third-party entities. The following are examples for a strategic audit risk assessment:

- Changes to legislation and guidance
- Major change in organization Change in key managerial function(s)

- Availability & turnover of Pharmacovigilance staff
- Changes since the last audit
- First medicinal product on the market
- Specific risk minimization or safety conditional implementation
- Outcome of previous audits
- Identified gaps relating to the specific area.
- Other organizational changes (information technology function)

## Tactical Level (Audit Program)

This is a set of audit programs for a year. The audit program should include the audit type, scope, objectives, timing, and periodicity. The tactical audit program should focus on:

- ✓ Pharmacovigilance quality system and critical processes
- ✓ Key control systems
- ✓ High-risk areas (after controls are put in place)
- ✓ Planning and fieldwork
- ✓ Reporting for corrective actions

The findings should be documented in an audit report and communicated promptly to the auditee and upper management. Audit findings should be graded to indicate their relative criticality to risks impacting the Pharmacovigilance system, processes, and parts of processes:

- **Critical:** a fundamental weakness in more than one Pharmacovigilance process that adversely affects the entire system, safety, or well-being of patients or that poses potential public health risks or causes a serious violation of regulatory requirements.
- **Major**: a significant weakness or fundamental weakness in more than one Pharmacovigilance process that is detrimental to the system, which could potentially affect the safety or well-being of the patients or pose potential public health risk or violation of regulatory requirement (however not considered serious)
- **Minor:** a weakness in one or more Pharmacovigilance processes that is not expected to adversely affect the overall system and/or the rights, safety, or well-being of patients.

## Operational Level (Fieldwork and Report)

The organization should have procedures for planning and conducting audits. The auditor identifies and assesses the risk to employ the appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan.

## Actions and Follow-Up of Audits

Actions within a reasonable timeframe and issues need to be communicated urgently so that relevant parties can take corrective actions.

- ✓ Corrective actions and preventive actions (CAPA) of serious issues should be prioritized.
- ✓ The upper management of the organization (DNFM or MOH) should have a mechanism to adequately address the issues arising from Pharmacovigilance audits.
- ✓ Actions should include a root cause analysis and impact analysis of audit findings, as well as the preparation of a Corrective and Preventive Action (CAPA) that is appropriately and effectively implemented.
- ✓ Evidence of action completion needs to be recorded.

## Competence of Auditors

The qualifications, skills, and experience of auditors should be obtained through a combination of education, work experience, training, and sharing knowledge and skills among the auditing team members. Auditors must understand the audit laws, principles, procedures, techniques, and technical knowledge relevant to Pharmacovigilance activities, processes, systems, and management.

- ✓ Audit activities should be independent, and the organization should ensure this independence and objectivity in documented approaches.
- ✓ Auditors should be free from interference when determining the scope of their audit.
- ✓ The main reporting line of the internal auditor should be to the upper management.
- ✓ Auditors can consult technical experts and personnel involved in Pharmacovigilance processes.
- ✓ Auditors should maintain an unbiased attitude when performing audits to ensure quality is not compromised.

- The organization may use an outsourced audit service provider to perform Pharmacovigilance audits.

### Quality of Audit Activities

- Quality of audit work can be evaluated by periodic assessment of all audit activities, auditee feedback, and self-assessment.

# VIII. Pharmacovigilance System in Timor-Leste

The quality, safety and efficacy of medicines play a key role not only in curing and controlling diseases but also in promoting well-being and prolonging the life expectancy of the population. Consequently, numerous studies and tests are required to prove their efficacy and safety, thus ensuring their effectiveness in the general population. Regulatory authorities are bodies responsible for overseeing all products imported into the country. Timor-Leste has prioritized the distribution of safe and effective medicines to the health care system since its independence on 20 May 2002 (the formal declaration of independence). The country relies on the system established by the INFPM (prequalification of suppliers, monitoring of quality supervision) to ensure the quality of medicines in the state health sector, which is the main importer of medicines in the country. The INFPM imports and procures medicines for the National Hospital (HNGV), referral hospitals, community health centers and health posts.

DNFM is the main agency responsible for the regulation of medicines in the public and private sectors in Timor-Leste. The Department of Pharmacovigilance is established within DNFM, and the national focal point has been identified to oversee the Pharmacovigilance system to communicate with the Uppsala Monitoring Centre and to detect falsified and substandard medicines.

DNFM is also responsible for the registration of medicines for both the government and private sector. However, DNFM managed databases of medicinal products imported by the private sector. Databases on the import of medicine for the public sector belong to the National Institute of Pharmacy and Medicine Products (INFPM). It is anticipated that there will be an integrated central database system established in Timor-Leste, accessible to DNFM, INFPM and other relevant departments. This would provide an enormous asset to the Pharmacovigilance activities in the country in the future. If all imported medicines are reported to the central database, it would be possible to estimate the quantity of medicines that have been imported and estimate the potential incidence of ADRs in Timor-Leste.

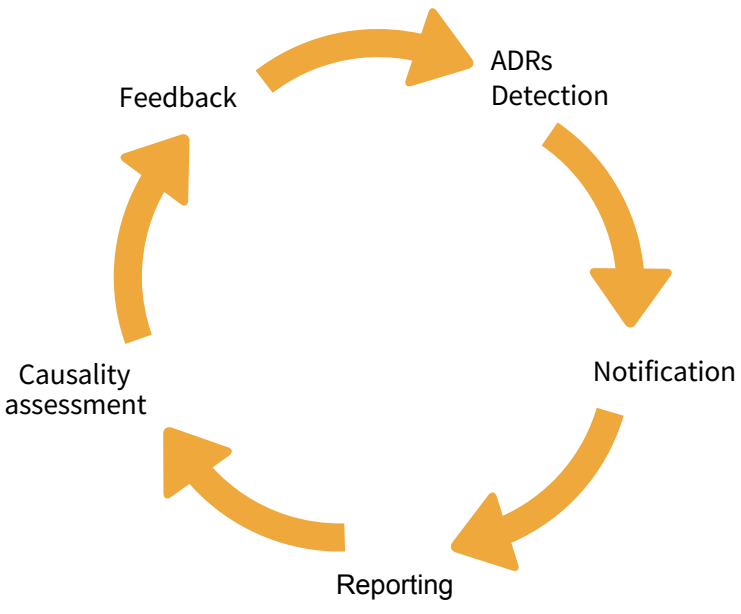
Although INFPM is the major importer of medicines in the country, Pharmacovigilance activities are the responsibility of DNFM, and adverse drug reactions and other reports related to patients are mandatory to report to DNFM. Reports of falsified medical products, sub- standards and medicines that are of inferior quality should also be sent to the Department of Pharmacovigilance.

## Adverse Drug Reactions (ADRs)

Spontaneous reporting of suspected adverse drug reactions and poor-quality products is a major source of information in Pharmacovigilance. Spontaneous reporting is voluntary, and the forms included in this manual are used to collect the information. In each adverse drug reaction, a report is generated and is also called Individual Case Safety Report (ICSR). The holistic process of Pharmacovigilance is defined as a system to detect, report, collect, evaluate, understand, and respond to the ADRs with timely feedback mechanisms. The data collected can be shared with the WHO to improve regional and global medicine safety and research. ADR Pharmacovigilance also helps to initiate causality assessments on suspected ADRs. Furthermore, signals, an adverse health event previously not identified as ADRs for a medicine, can be detected and investigated.

In Timor-Leste, the ADR reports are collected and evaluated by the Pharmacovigilance Department of DNFM and disseminated to the global reporting system. DNFM is planning to expand its capacity to establish a Pharmacovigilance program to sub-national levels, municipal health services, health centers and referral hospitals. The ADR reports from sub-national level facilities will be reviewed and assessed at the Pharmacovigilance department and necessary feedback will be provided to the reporting institutions at various levels. The following process cycle in Figure (2) shows the ADR reporting process in Timor-Leste.

**Figure 2. ADR Pharmacovigilance Cycle**



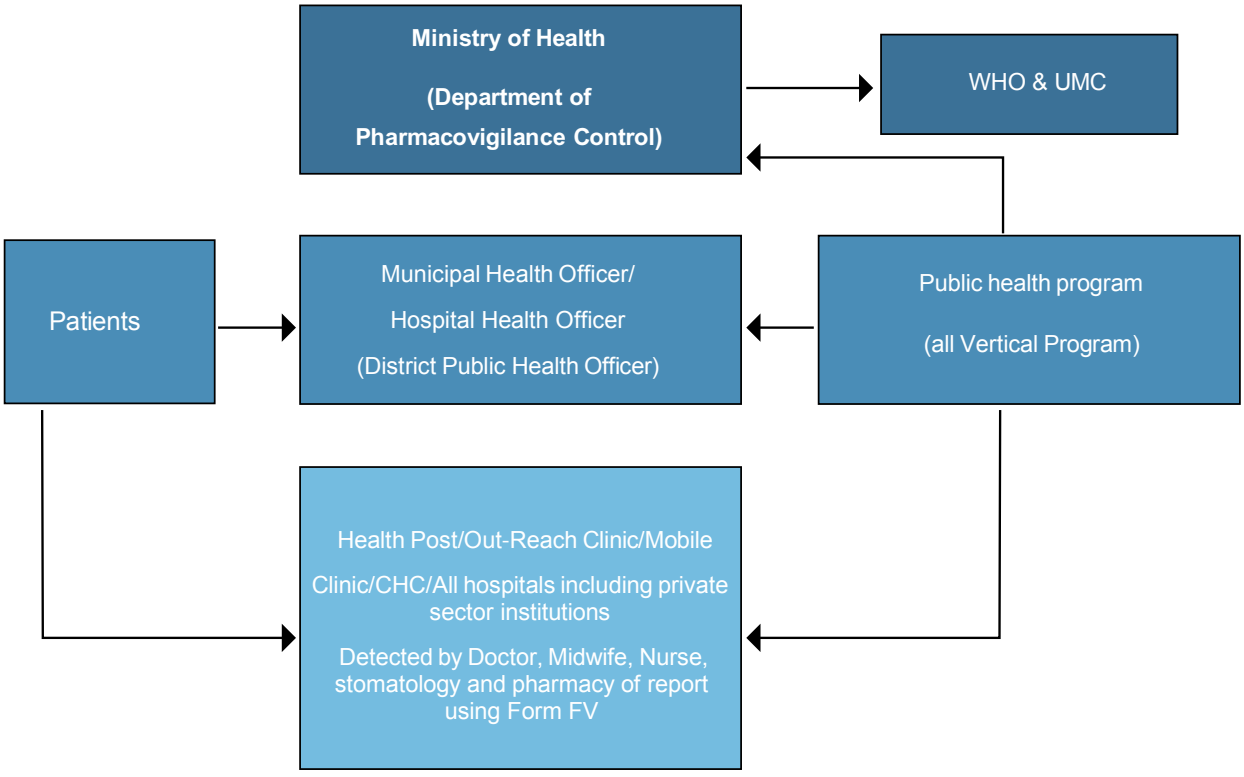
## Process of ADR Reporting

The institutes involved at each level and the ADR reporting system are described below. The reporting system includes the following institutes:

- National Hospital
- Referral Hospital
- Regional Hospital
- Community Health Centers (CHC)
- Health Posts (HP)
- Mobile clinics
- Outreach clinics
- All private sector clinics and hospitals

This manual describes procedures and requirements for ADR reporting. The reporting form is described in the appendix and an electronic copy is available on the DNFM website. The Pharmacovigilance department is highly encouraged to download the ADR reporting form and submit it electronically through email from the reporting units. DNFM also receives and acknowledges paper-based reporting from facilities when it is not feasible to send electronic reports.

**Figure 3. Pharmacovigilance Levels for ADRs in Timor-Leste**



The notification system and reporting flow of ADR cases are described in Figure 3. It is expected that all ADR cases will be reported to these institutes as follows:

## At the Sub-national Level:

- All reported ADR cases must be notified, and an ADR notification form must be completed by the health personnel (doctor, midwife, nurse, stomatology, or pharmacy) who attends an ADR case using the ADR Form (Annex 1).
- Copies of the ADR Form must be prepared for each ADR case detected. A copy of the ADR form must be submitted to the corresponding reporting unit under the custody of the officer in charge of the reporting Health Center.
- The person in charge of the Health Center would send a copy of the ADR report to the respective Municipality Health Directorate and a copy to the National Directorate of Pharmacy and Medicines (DNFM) Pharmacovigilance Department.
- At the end of each month, the collected data from the Municipality Health Directorate should be analyzed according to the guidance provided in the ADR data analysis chapter of this manual. The electronic ADR form must be sent to the National Department of Pharmacovigilance in the following month by email.

## At the National Level:

- The National Pharmacovigilance Department must maintain an electronic database (a spreadsheet) of ADR forms. All printed copies of the ADR Form must be filed in agreement with the municipality and kept in a safe place.
- At the end of each month, an analysis must be conducted to monitor the safety profile of the drugs used in the essential medicine list of Timor-Leste. This analysis report along with the list of ADR lines and the ADR inquiry forms must be shared with the Centers.
- A quarterly report must be prepared with the breakdown by the district of the reported ADRs. During quarterly Pharmacovigilance technical advisory meetings, the National Pharmacovigilance Department, in consultation with CSMPEM, NITAG and NRA, should decide the need for causality assessments for reported ADRs.

**Content of ADR Reporting**

**a) Who Should Report Adverse Drug Reactions?**

- Healthcare professionals who are prescribers such as Medical Officers and

Dentists.

- Nurses and other health workers who administer medicines.
- Pharmacists play a significant role in reporting and providing additional information (for example, on co-medication and previous medicine use).
- Medicines importers can be informed of problems with their products by healthcare professionals and workers. They have an obligation to get the full information and report it to the Department of Pharmacovigilance.

**b) Who Should Report Medical Products Suspected to be of Poor Quality?**

- The reporting of products suspected to be inferior quality is the responsibility of the pharmacists, but others could also submit reports.
- Medicines importers are required to have registered pharmacists to report products that have been reported to them as being suspected of inadequate quality.

### c) What to Report?

- All suspected ADR of medicinal products from whichever source. These could include medicines supplied by INFPM in the state's health sector and those from private pharmacies. Suspected adverse drug reactions (ADRs) from medicines obtained from informal suppliers or sources must also be reported.
- The reports can be from wards, clinics, and outpatient departments. They can be from general outpatient departments or vertical programs such as Malaria, TB, HIV, and Others. For medical products suspected to be of inferior quality, reports should be made for products from any of the sources (government, private sector, or informal suppliers).

**d)How, What, and Where to Report?**

- An Adverse Drug Reaction Form is enclosed in these guidelines. Requests for ADR forms and ADR information may be obtained from the Department of Pharmacovigilance or by visiting the DNFM webpage. The adverse drug event form should be completed with as much detail as possible and returned to the Department of Pharmacovigilance. There are four sections to validate the individual case report (ICSR) as follows: (Refer to ADR form Annex I)

  **An Identifiable Patient:**

  - Patient initials
  - Sex
  - Weight

- Age at time of reaction or date of birth
- Race
- Past medical history (PMH)
- Number of Clinical History (CH)

- **Suspected Medicine**
  - Name (Generic and Brand Name)
  - Strength (Concentration)
  - Dose, Frequency (Dose Daily)
  - Dosage Form
    - Route of Administration
    - Indication for Use
    - Duration of Use, Date Started, Date Stopped.
    - Batch Number and Expiry Date.
- **Suspected Adverse Reaction.**
  - Description of the Reaction
  - The Seriousness of the Reaction
  - The Date of the Reaction Started Stopped.
  - Date the drug withdrawn or continued after ADR.
  - Treatment Provided for the Reaction.
  - Relevant Tests/Laboratory Data (if available)
- **An Identifiable Reporter**
  - Name, initials
  - Address
  - Gender
  - Contact Details - Mobile phone and Email.
  - Qualification (if Healthcare Professional)

**e) How to Recognize ADRs in Patients?**

ADRs can be difficult and sometimes impossible to distinguish from the disease being treated, as they may act through the same physiological and pathological pathways. However, the following approach helps assess a possible drug-related ADR:

1. Ensure that the medicine prescribed is the same as the medicine received and taken by the patient at the prescribed dose.

2. Record a detailed history, including a thorough examination of the patient.
    - A complete medical history should be taken.
    - An ADR should be considered wherever possible.
    - Consider whether this adverse reaction can be attributed to any other cause, such as the patient's underlying disease, other medications (including over the counter and traditional medicines), toxins, or food allergies.
    - A medicine-related cause should be considered, especially when other causes do not explain the patient's condition.
3. Establish Relationships with Time by answering the following question:
    - Did the adverse reaction occur immediately following the administration of the medicine? Some reactions occur immediately after the medicine is administered, while others take time to develop.
4. When Evaluating the Patient, further consider the following:
    - Only a few medicines produce distinctive physical signs.
    - Distinctive ADRs include skin eruptions, steroid-induced dermal atrophy, and acute extrapyramidal reactions (involuntary movements).
    - Laboratory tests are essential. They may indicate severity (e.g., elevated liver enzymes) and aid in follow-up.
    - Try to describe the reaction as clearly as possible - where possible, provide an accurate diagnosis of the underlying condition.
5. De-Challenge and Rechallenge, if it occurs, should be described.
    - De-Challenge (withdrawal of the suspected medicine)
    - Rechallenge (re-introducing the suspected medicine after a Rechallenge)
    - Rechallenge is only justifiable when the disease requires the reintroduction of the medicine. It is not justified to reintroduce a medicine to see whether an adverse drug reaction will occur.
6. Check the Known Pharmacology of the Medicine.
    - Check if the reaction is known to occur with the suspected medicine as stated in the Medicines information sources.
    - If the reaction is not documented in the Medicines Information sources, it could still be due to the drug.

**f). Will the Reporting have any negative consequences for the Reporter?**

- No, reporting of suspected ADR is to be commended. Reports of suspected ADR will be considered best and responsible practice by the healthcare professional/worker and in no way the individual be disciplined or rebuked.
- Feedback to the reporter. The outcome of the report, together with any important or relevant information relating to the reported reaction, will be communicated to the reporter as appropriate.
- The details of the report will be stored in a database at the Department of Pharmacovigilance and analyzed. Where relevant the report will be sent to the Uppsala Monitoring Center (UMC) to be evaluated and if appropriate, added to the Global Database.
- The names of the reporters or any other health professionals named in the report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others.

**g). The Basic Principles of Efficient Reporting**

- Timely reporting: report the suspected adverse drug reaction as soon as it occurs. Please send the report promptly to the Department of Pharmacovigilance. The report involves less work and is more accurate when reported promptly.
- Strong suspicion and follow-up: Continue your strong suspicion of the medicine. Induced illness in the same patient and other patients.
- Keep vigilance for signs and symptoms: This enhances or excludes the possibility of a medicine-induced reaction. All follow-up and supplementary information should be documented and submitted to the Pharmacovigilance Center, with “Follow-up Report” clearly indicated on the top right corner of the form.
- Accuracy and completeness: Ensure that the ADR Reporting Form is filled with accurate and complete information, which is particularly important for assessing the causality of the medicine in causing the reaction.

## Causality Assessment

Causality assessment is a method by which the suspected reaction under investigation is linked to existing medical knowledge. Several methods can be used to assess the causality of ADR reports. Causality assessment includes identification of (dose-reaction, temporal relationship, and other confounding factors) biological mechanism and pharmacological plausibility, case pooling (case series) analysis, seriousness and severity of the reaction, and reversibility of the reaction. Additional insight on a known adverse reaction included:

- Severity, duration, outcome, incidence, reversibility, and the potential for prevention
- Reaction in vulnerable populations (such as pregnant women, children, or the older population, or in patients with pre-existing risk factors).
- Reactions in different patterns of use (overdose, abuse, misuse, off-label use, medication errors, falsified products).
- Patient exposure and frequency of adverse reaction
- Consequences of discontinuation of the disease under treatment and the availability of other options.
- Expected regulatory intervention (addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation).
- Apply to other substances of the same class of medicinal products.
- Media attention and/or public concerns (adverse events on mass immunization).
- Urgency for further signal management (depending on the prioritization).

Data is essential for a proper assessment or additional data may be required under examination. The prescriber submitting the form may comment on the causality assessment, but it is not essential. A formal causality assessment will be done by the Pharmacovigilance Center. The table given below summarizes the strength of the link that can be established.[16]

**Table 3: WHO Probability Scale for Suspected Adverse Drug Reactions**

| Term | Description |
|---|---|
| Certain | A clinical reaction, including laboratory test abnormality, occurs in a plausible time relationship to medicine administration and cannot be explained by concurrent disease or other medicines or chemicals. The response to withdrawal of the medicine (dechallenge) should be clinically plausible. The reaction must be definitive pharmacologically or phenomenologically, (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) Using a satisfactory challenge procedure if necessary. |
| Probable/ Likely | A clinical reaction, including laboratory test abnormality, with a reasonable time sequence to administration of the medicine. Unlikely to be attributed to concurrent disease or other medicines or chemicals, and which Follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. |
| Possible | A clinical reaction, including laboratory test abnormality, with a reasonable time sequence to the administration of the medicine, but which could also be explained by concurrent disease or other medicines or chemicals.<br>Information on medicine withdrawal may be lacking or unclear. |
| Unlikely | A clinical reaction, including a laboratory test abnormality, with a temporal relationship to medication administration that makes a causal relationship improbable, and other medications and chemicals.<br>Or underlying disease provides plausible explanations. |
| Conditional/ Unclassified | A clinical reaction, including laboratory test abnormality, |
| Un-assessable/ Unclassified | More data is essential for a proper assessment, or the additional data are under examination. |

# IX. Signal Management

Pharmacovigilance aims to ensure patient safety. National Pharmacovigilance centers or MAHs need to screen and detect any harm caused by medicines early on. Signal Detection is crucial for achieving this objective. Effective communication of signals is necessary for minimizing harm, a primary goal of Pharmacovigilance. This chapter aims to guide any organizations that engage in Pharmacovigilance on the direction of signal management, particularly in organizations with restricted databases and resources. Typically, in such scenarios, the quantity of Individual Case Safety Reports (ICSRs) will be low, and the range of medicinal products and event profiles may be specific to the location.

## Signal

A signal is a hypothesis of risk associated with a medicine, based on data from one or more sources and supporting arguments. The signal may be a new causal association arising from observations or experiments. It may reveal new aspects of known associations that are adverse or beneficial, including changes in frequency, distribution, duration, severity, or outcome. Signals apply to medicinal products containing the same active substance, including combination products. They may be relevant to a specific medicinal product or indication, strength, pharmaceutical form, route of administration, or a whole class of medicinal products.

## Signal Management Process

Figure 4. Signal Management Process[17]

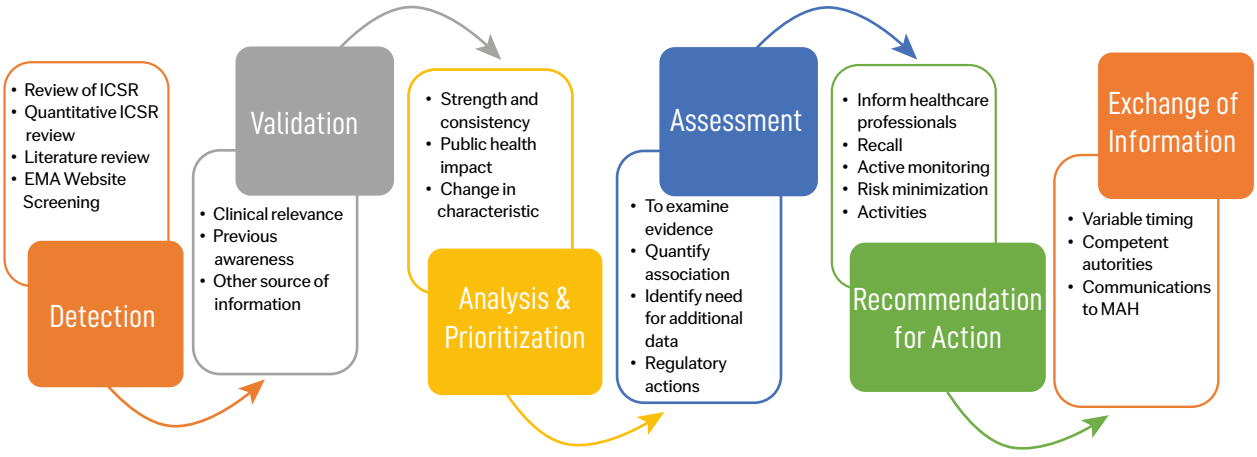



**Figure 4**

The process of evaluating Individual Case Safety Reports (ICSRs), data from passive or active surveillance systems, scientific literature, and other sources to determine if there are any new risks associated with a medicinal product or active substance, or

if any known risks have changed. This includes making recommendations and decisions and communicating any findings, as well as tracking the outcomes of these actions. The signal management process includes the following activities: (i) signal detection, (ii) signal validation, (iii) signal confirmation, (iv) signal analysis and prioritization, (v) signal assessment, and recommendation for action.

## Structures and Processes

### Sources of Data

Signals can come from various sources including scientific data related to medicinal product use and outcomes. These sources include spontaneous reporting systems, active surveillance systems, studies, digital media, national regulatory safety databases, and scientific literature. Adverse reaction databases are periodically monitored to detect signals, which can vary in size and scope. This chapter focuses on signals from spontaneous reporting systems, but all relevant sources should be considered during signal management. These sources may be included:

- Safety Database from Marketing Authorization Holders (MAHs)
- DNFM Database
- Public Health Program Database
- WHO Vigiflow Database
- Clinical Trials
- Regulatory websites & newsletters
- WHO pharmaceutical newsletters
- Scientific meetings
- Scientific literature
- Traditional and social media

### Signal Detection

Signal detection requires specific methodologies to consider the nature of data and characteristics of medicinal products. All relevant data should be considered, and clinical judgment applied. Signal detection may involve a review of ICSRs, statistical analyses or both. Organizations should document the process adequately. In Pharmacovigilance systems that rely on spontaneous reporting, there are two types of signal detection methodology.

- **The qualitative method** involves a manual screening process, followed by a medical review of individual case safety reports (ICSRs) or a review of a series of cases.
- **The quantitative (statistical) method** screens the database by using simple cross-tabulation data-mining algorithms. Their goal is to identify disproportionality when the number of reports of a suspected drug-ADR

combination is higher than expected. Disproportional analysis will help for hypothesis generation, not for hypothesis testing. After discovering disproportionality, medical experts review individual case safety reports and case series.

**Signal Validation**

The review of ICSR data should consider these elements for signal validation.[18]

- ADR is already included in the product information, specifically in the Summary of Product Characteristics (SmPC) and the package leaflet.
- Signal/adverse reaction already known to the SmPC for other medicinal products containing the active substance of interest,
- Association already assessed in the initial application for marketing authorization, the risk management plan (RMP), the periodic safety update report (PSUR)
- Assess the strength of the evidence and total number of related cases (exclusion of duplicates)
- number of cases per patient exposure (prevalence/incidence)
- Additional cases reported with related terms.
- consistency of the evidence across cases (characteristics of cases)
- quality of the data and their documentation
- Cases that match internationally agreed-upon case definitions, if applicable.

**Signal Prioritization**

The signal management process within organizations can involve multiple expert discussions and decision levels, resulting in varied outcomes. It is important to document any decision trees as part of the signal management process description. During the signal management process, organizations should evaluate whether signals imply risks that could significantly affect the health of patients, public health and/or the risk-benefit balance of the medicinal product. The following should be considered when evaluating this impact:

- Signal detection
- Signal validation
- Further assessment
- New or changed risk.
- Propose risk minimization activities Refuted signal
- Non-validated signal

**Quality Requirements for Signal Management**

- Develop, document, and implement the process for managing signals, including the rationale for the method, periodicity of signal detection, tracking system activities, and process control for all steps.

- Conduct regular audits of signal management activities, just as with any critical process. This ensures that any errors in the process can be identified and corrected in a timely manner.
- Ensure confidentiality, security, and validity of data and documents per applicable laws and regulations, including data integrity during inter-organizational transfers.
- MAHs should describe their signal management process in the Pharmacovigilance System Master File and monitor system performance with performance indicators in the annex.
- MAHs should implement a record management system for Pharmacovigilance documents. This system should ensure easy retrieval and traceability of measures taken during the investigation.

# X. Risk Management

A medicinal product is authorized based on its positive benefit-risk balance at a specific time for a target population within its approved indication(s). However, not all ADRs and risks can be identified at the time the initial marketing authorization is granted; it must be acknowledged that safety information generated by clinical trials is limited and that ADRs may become apparent only once the product is used. In addition, there are risks that can result from medication errors, misuse, abuse, or off-label use. To ensure that the benefits of the medicinal product continue to outweigh the risks when used in real-world settings, a risk management strategy is essential.

A Risk Management Plan (RMP) is a document submitted as part of the dossier that is evaluated by regulatory authorities before a medicinal product can be authorized and is regularly updated as the latest information becomes available. The RMP explains the system necessary to identify, characterize, and minimize a medicinal product's Risk. RMP is part of global Pharmacovigilance standards but there are variations depending on country contexts and regulatory requirements. In Timor-Leste, RMP is focused on Pharmacovigilance methods and risk minimization activities in accordance with its existing capacity.

## Classification of Risks

**Identified Risk:** An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples: (i) an adverse reaction demonstrated in non-clinical studies and confirmed by clinical data, (ii) an adverse reaction observed in well-designed clinical trials or epidemiological studies that show a causal relationship, (iii) an adverse reaction suggested by well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility.

**Potential Risk:** An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest, but where this association has not been confirmed. Examples: (i) non-clinical toxicological findings that have not been resolved in clinical studies, (ii) adverse events observed in clinical trials or epidemiological studies, but with no definite evidence of a causal relationship, (iii) a signal arising from a spontaneous adverse reaction reporting system, (iv) an event known to be associated with other active substances within the same class of product.

**Missing Information:** Gaps in knowledge about the safety of a medicinal product for an anticipated utilization or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized at the time of submission of a particular RMP. For example, missing information may pertain to certain populations, such as pregnant women or patients with severe renal impairment, or to scenarios with a high likelihood of off-label use.

**Important Identified Risk and Important Potential Risk:** An identified or potential risk that could have an impact on the risk-benefit balance of the product on the individual, the seriousness of the risk and the impact on public health.

## Objectives of the Risk Management Plan (RMP)

Risk management is a step-by-step process that involves evaluating the balance between the benefits and risks of a product, implementing measures to minimize the risks while maintaining its benefits, assessing the effectiveness of these measures, and adjusting them as needed. The main aim of an RMP is to optimize a medicinal product's benefit/risk balance for the individual patient and the target population. The objectives of an RMP are to:

- Identify or characterize the safety profile of the medicinal product(s).
- Indicate how to characterize the safety profile of the medicinal product(s).
- Document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions.
- Document post-authorization obligations of the marketing authorization.

The RMP includes three essential elements:

- Identification or characterization of the safety profile of the medicinal product, with emphasis on significant identified and potential risks, missing information, and safety concerns that require management or further study. (safety specification).
- Planning Pharmacovigilance activities to quantify clinically relevant risks and identify new adverse reactions (Pharmacovigilance plan).

- Planning and implementing risk minimization measures, including evaluating the effectiveness of these activities. (risk minimization plan).

During the product's life cycle, it is crucial to consider the following issues for a critical review:

- What are the hazards associated with the product's properties, considering the manufacturing and control processes?
- Which groups in the target population are more susceptible to the highest risks?
- Are the risks identified by independent scientific assessment predictable?
- Are there any uncertainties surrounding the assessment of risks?
- How can the risks be effectively mitigated?
- How effective are risk mitigation activities?

## Responsibilities for Risk Management

The NRA and MAHs are directly involved in risk management. The RMP is drafted by the MAHs and evaluated by the regulator. The MAHs are responsible for having an appropriate risk management system in place and ensuring that the knowledge and understanding of the product's safety profile following its use in clinical practice are critically reviewed.

- Developing and updating the RMP as the latest information emerges.
- Implementing the activities and interventions outlined in the RMP.
- Monitoring and reporting Pharmacovigilance data to NRA for changes in medicinal product risks and benefits,
- Collecting and analyzing information to monitor the effectiveness of these activities.
- Actively updating and promptly communicating with the NRA when new safety information becomes available.

### Content of the RMP

- Product(s) Overview
- Safety specifications (epidemiology, target population, non-clinical part, clinical trial, population not studied in a clinical trial, post-authorization experience, identified and potential risks, a summary of safety concerns)
- Pharmacovigilance plan (including post-authorization safety studies)
- Plan for post-authorization efficacy studies
- Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
- Summary of RMP

### Routine Risk Minimization Activities

- Summary of product characteristics (SmPC)
- Package leaflet (PL),
- Patient information leaflet (PIL)

- Product labeling (outer packaging)
- Legal status of the product
- Pack size & design, product design.
- Instruction for use document
- Stability and cold chain management

**Additional Risk Minimization Activities**

- Consider population, frequency, severity, context, impact, and preventability.
- Healthcare professionals should be advised on patient selection and monitoring during treatment, to detect and manage early adverse reactions.
- Healthcare professionals and patients should be guided to follow specific behaviors for each step of the treatment process.
- The effectiveness of such activities should be weighed against the burden they may impose.
- MAHs must review and assess risk minimization measures regularly and notify regulatory authorities of any subsequent changes before implementation.
- Educational programs for professionals and patients.
- Control access program to regulate access to medicine beyond routine control measures.
- Pregnancy prevention program: to avoid pregnancy during the treatment, restriction of medication, and counseling for unplanned or adverse pregnancy outcomes.

# XI. Safety Reporting

Pharmacovigilance is essential to improving patient care and safety and holds the potential to reduce the financial burden of adverse reactions on the healthcare sector and society. Therefore, Safety reporting is a crucial aspect of Pharmacovigilance activities. Pharmacovigilance methods for safety reporting and data collection are classified as passive or active.

**Passive Pharmacovigilance:** No active measures are taken to look for adverse reactions other than encouraging healthcare professionals and others to report safety concerns. Reporting is entirely dependent on the reporters. It is commonly called “spontaneous” or “voluntary” reporting.

**Active Pharmacovigilance**: Active measures are taken to monitor adverse events. This is actively organized to follow up after treatment, and the events can be obtained by asking patients directly or screening medical records. The most comprehensive method is cohort event monitoring (CEM). The other methods include the use of registries, record linkages, and screening laboratory reports in medical records.

Sufficient safety information is required to demonstrate that the product is of high quality, effective, and safe for the intended use before obtaining marketing authorization from NRA. It is accepted that Pharmacovigilance has become an essential component of drug regulation to monitor the safety of medicinal products in the post-marketing phase.

## The scope of safety reporting includes the following domains:

- ADR or Adverse reactions
- Individual Case Safety Reporting (ICSR)
- Periodic Benefit-Risk Evaluation Reports (PBRER)
- Other product-related problems, e.g., lack of efficacy.
- Misuse and/or abuse, or off-label use.
- Medication error or minimization error-related reactions, including overdose.
- Interaction between medicinal products or with other products; or
- Counterfeit or substandard medicines, including vaccine quality defect-related reactions.
- Pregnancy and lactation exposure and outcomes.

## Minimum Criteria for ICSR Reporting

All ICSRs should be completed as much as possible and aligned with the following requirements before submitting them to the NRA.

- Patient Identification

- Identifiable Reporting Sources
- At least one suspected substance/product
- At least one adverse event/reaction

## Periodic Benefit-Risk Evaluation Report (PBRER)

The primary objective of a PBRER is to provide an updated, comprehensive, and critical assessment of new or emerging information regarding the risks and benefits of the medicinal product in its approved indications. The report should evaluate the latest information obtained by MAHs during the reporting interval, which includes:

- Summarizing relevant safety and efficacy data
- Assessing consistency with the known benefit and risk profile
- Conducting an integrated benefit-risk evaluation for approved indications
- Proposing actions for optimizing the benefit-risk profile as appropriate

**The type of products for monitoring and reporting** includes products with marketing- authorized license approvals and license exemptions.

- Medicinal products for human use including biological products and vaccines.
- Narcotic drugs and psychotropic substances
- Herbal products for human use include herbal medicine and health supplements.

All manufacturers and importers of medicinal products are responsible for safety reporting. They are required to monitor and report any product safety issues that arise locally or internationally to DNFM, in accordance with the safety reporting regulations for medicinal products.

## Post Authorization Safety Study (PASS)

A post-authorization safety study (PASS) is a study designed to identify, characterize, or quantify safety hazards, confirm the safety profile of a medicine, and assess the effectiveness of risk-management measures. PASSs can be clinical trials (intervention trials) or non- interventional studies and are conducted either voluntarily or obligatory by the NRA. Individuals with scientific backgrounds should develop the study protocol.

There are various sources of data to be used in the PASS: primary data (e.g. interview or paper-based medical records) or automated data (e.g. medical records, diagnosis, prescription, and referral information). Various study designs used in PASS are as follows:

**Active Surveillance**

- Intensive monitoring schemes
- Prescription event monitoring
- Registries

**Observational Studies**

- Cross-sectional study
- Cohort study
- Case-control study
- Case-only design

**Clinical trials**

- Large simple trials
- Drug utilization studies

# XII. Annexes

## Annex 1. Form for Spontaneous Reports of Suspected ADRs

| A. PATIENT INFORMATION | | | | |
|---|---|---|---|---|
| Unit reporting:_____ | | District: _____ | | |
| Patient initial: _____ _____ _____ _____ _____ _____ _____ | Date of birth: __/__/_____ PMH: _____ _____ _____ _____ _____ | Weight: _____ kg | Sex: M ____ F___, if female, is she pregnant? No: Yes unknown____ Age: _____ | Race:___ |
| Relevant medical history: | | | Relevant test/lab. Data (if any): | |

| B. SUSPECTED DRUG(S) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Drug name generic/brand | Prescribed for/ indication | Dose/ strength | Daily dose | Route | Manufactured | Lote/ batch no exp date | Date started | Date stopped |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

| C. SUSPECT DRUG REACTION(S) | | | | | | |
|---|---|---|---|---|---|---|
| Please describe reaction | Data reaction started | Data stopped | Urgent care | | Emergency care | |
| | ____/____/_____ | ___/____/___ | Yes | No | Yes | No |
| | | | | | | |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |

**Treatment and action taken:**

**Additional information:**

| **OUTCOME: Tick all that is appropriate** | | | | Do you consider the reaction to be serious? Yes, _____No____ If yes, please indicate why the reaction is considered to be serious (tick all that is appropriate) | | |
|---|---|---|---|---|---|---|
| **Recovered _____** | **Recovering _____** | **Continuing___** | **Others (specify):_** | **Life threatening: _** | **Patient died: _____** | **Prolonged hospitalization: _____** |
| | | | | **Significant disability: ___** | **Congenital anomaly: _** | **Overdose: ____** |

**D. OTHER MEDICATIONS (INCLUDING SELF-MEDICATION, (HERBAL AND TRADITIONAL MEDICINES)**
Did the patient take any other medicines prior to this reaction? Yes: _____No: _____

| **Drug name (both generic & brand)** | | **Dosage** | | **Route** | | **Date started** | | **Data stopped** | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

| **E: REPORTER DETAILS** | | **F: FOR OFFICIAL USE BY:** |
|---|---|---|
| Name: _____ | Contact: _____ | Date of receipt of the report: _____/ __/____ |
| Designation_____ | Date: _____ | Report ID no: _____ |
| Gender: M: _____F: _____ | Email: _____ | Received by: _____ |
| Signature: _____ | | Action taken: _____ |

- If you suspect an unusual or severe adverse drug reaction, please use this form to report it immediately to the Department of Pharmacovigilance DNFM.

## Annex 2. Naranjo Algorithm for Assessing Probability an Adverse Drug Reaction (ADR)

| No | Question | Yes | No | Do not know | Score |
|---|---|---|---|---|---|
| 1 | Are there previous conclusive reports in this reaction? | +1 | 0 | 0 | |
| 2 | Did the adverse event appear after the suspected medicines were administered? | +2 | -1 | 0 | |
| 3 | Did the adverse reaction improve when the medicine was discounted, or a specific antagonist was administered? | +1 | 0 | 0 | |
| 4 | Did the reaction reappear when the medicine was administered? | +2 | -1 | 0 | |
| 5 | Are there alternate causes (other than the medicine) that could solely have caused the reaction? | -1 | +2 | 0 | |
| 6 | Did the reaction appear when a placebo was given? | -1 | +1 | 0 | |
| 7 | Was the medicine detected in the blood (or others fluid) in a concentration know to be toxic? | +1 | 0 | 0 | |
| 8 | Was the reaction more severe when the dose was increased or less severe when the dose decreased? | +1 | 0 | 0 | |
| 9 | Did the patient have a similar reaction to the same similar medicines in any previous exposure? | + | 0 | 0 | |
| 10 | Was the reaction event confirmed by objective evidence? | +1 | 0 | 0 | |

**Total score ADR probability classification:**

**> 9 = probable  5- 8 = probable  1- 4 = possible  0 = doubtful**

medicines to describe products suspected to be of inferior quality.

This document has been modified from a document that has been produced by FIP (International Pharmaceutical Federation). It is designed to help health professionals (especially pharmacists) to carry out a visual inspection of medicines for signs of poor quality.

## Annex 3. Physical Characteristics of Medical Product

| | | | |
|---|---|---|---|
| All types of medicine can be and have been counterfeited from inadequate quality tablets and capsules. to injections.<br>This checklist has some of the common features of poor work quality medicines; it should be submitted along with the details of the person reporting it. | | | |
| **1. PACKAGING** | | | |
| | Yes | No | Other Observations |
| 1.1 Container and Closure | | | |
| Does the container and closure protect the product from the outside environment; e.g. is the container properly sealed? | | | |
| Do they assure that the product will meet the proper specifications throughout its shelf life? | | | |
| Are the container and the closure appropriate for the product inside? | | | |
| Is the container safely sealed? | | | |
| 1.2 Label<br>The information written on the label is very important. The information can be printed on a label adhered to the container, or printed directly onto the container itself, but all information must be legible and indelible. | | | |
| If there is a carton protecting the container, does the label on the carton match the label on the container? | | | |
| Is all information on the label legible and indelible? | | | |
| 1.2.1 The trade (brand) name | Yes | No | Other Observations |
| Is the trade name spelled correctly? | | | |
| Is the medicinal product (trade name) registered in the country by the Drug Regulatory Authority)? | | | |
| Is the product legally sold in the country? | | | |

| | | | |
|---|---|---|---|
| Does the symbol follow the trade name? | | | |
| For blister or foil strip packed products, is the trade name indelibly impressed or imprinted onto the strip? | | | |
| 1.2.2 The active ingredient name (scientific name/generic name): | | | |
| Is the active ingredient name spelt correctly? | | | |
| Do the trade name and the active ingredient names correspond to the registered product? | | | |
| 1.2.3 The manufacturer's name and logo: | | | |
| Are the manufacturer's name and logo legible and correct? | | | |
| Does the logo or hologram (if applicable) look authentic? | | | |
| Does the logo or hologram (if applicable) change color when viewed from different angles? | | | |
| 1.2.3 The manufacturer's name and logo: | | | |
| Are the manufacturer's name and logo legible and correct? | | | |
| Does the logo or hologram (if applicable) look authentic? | | | |
| Does the logo or hologram (if applicable) change color when viewed from different angles? | | | |
| 1.2.4 The manufacturer's full address:<br>All manufacturers are required by international law to print their complete address on the label. Many companies making substandard or counterfeit products do not have a traceable address on the label. | | | |
| Is the manufacturer's full address legible and correct? | | | |
| Has this company or its agent registered the product in the country? | | | |

| | | | |
|---|---|---|---|
| 1.2.5 The medicine strength (mg/unit): | | | |
| Is the strength - the amount of active ingredient per unit - clearly stated on the label? | | | |
| For blister or foil strip packed products, is the medicine strength indelibly impressed or imprinted onto the strip? | | | |
| 1.2.6 The dosage form (e.g., tablet/capsule): | | | |
| Is the dosage form clearly indicated on the container label? | | | |
| Does the dosage form stated on the label match the actual dosage form of the medication? | | | |
| Is the indicated medicine under this dosage form registered and authorized for sale in the country? | | | |
| 1.2.7 The number of units per container: | | | |
| Does the number of dosage units listed on the label match the number of dosage units stated on the container? | | | |
| 1.2.8 Dosage statement (if appropriate) | | | |
| Is the dosage clearly indicated on the label? | | | |
| Is the dosage stated on the label appropriate for the medicine in this form and strength? | | | |
| Is the product registered and authorized for sale in the country with this dosage? | | | |
| 1.2.9 The batch (or lot) number:<br>Medicines with the same batch/lot number are expected to be equivalent. In a continuous process, a batch corresponds to a defined portion of the production, based on time or quantity. Products from the same batch number should have the same history of manufacturing, processing, packing, and coding. All product quality control testing should be based on batch/lot numbers. | | | |

| | | | |
|---|---|---|---|
| Does the numbering system on the package correspond to that of the producing company? | | | |
| For blister or foil strip packed medicines, is the batch number indelibly impressed or imprinted onto the strip? | | | |
| 1.2.10 The date of manufacture and the expiry date: An expired product should not be sold under any circumstances. | | | |
| Are the manufacture and expiry dates clearly indicated on the label? | | | |
| For blister or foil strip packed products, is the expiry date indelibly impressed or imprinted onto the strip? | | | |
| 1.2.11 Storage information: | | | |
| Are the storage conditions indicated on the label? | | | |
| Has the product been properly stored? | | | |
| 1.3 Leaflet or package insert:<br>All product packs contain a leaflet explaining dosage, the medicine content, the adverse affects, the medicine's actions, and how the medicine should be taken. The only exceptions are where the packaging includes all the information that would otherwise be in the leaflet | | | |
| Is the package insert printed on the same colored or same quality paper as the original (If available to compare) or does it look familiar? | | | |
| Is the ink on the package insert or packaging smudge-proof? | | | |
| Does the information on the package insert match the information on the product container? | | | |
| **2. PHYSICAL CHARACTERISTICS OF TABLETS/CAPSULES** | | | |
| ***2.1 Uniformity of Shape:*** | Yes | No | Other Observations |
| Are the tablets/capsules uniform in shape? | | | |

| | | | |
|---|---|---|---|
| ***2.2 Uniformity of Size:*** | | | |
| Are the tablets/capsules uniform in size? | | | |
| ***2.3 Uniformity of Color:*** | | | |
| Are the tablets/capsules uniform in color? | | | |
| ***2.4 Uniformity of Texture:***<br>Tablets can be film-coated, sugar-coated, or enteric-coated. | | | |
| Do the tablets have a uniform coating? | | | |
| Is the base of the tablets fully covered? | | | |
| Are the tablets uniformly polished, free of powder, and non-sticking? | | | |
| ***2.5 Markings (scoring, letters, etc.):*** | | | |
| Are markings uniform and identical? | | | |
| ***2.6 Breaks, Cracks and Splits:*** | | | |
| Are the tablets/capsules free of breaks, cracks, splits, or pinholes? | | | |
| ***2.7 Embedded surface spots or contamination:*** | | | |
| Are the tablets/capsules free of embedded?<br>Are there surface spots and foreign particle contamination? | | | |
| ***2.8 Presence of empty capsules in the case of a sample of capsules:*** | | | |
| Is the sample examined free of empty capsules? | | | |
| ***2.9 Smell*** | | | |
| Does the medicine smell the same as the original (If available)?<br>Does it smell peculiar? | | | |

If possible, include a picture (taken from a smartphone would be adequate) of the suspect medical product. Please keep the suspected tablets in safe and secure (locked cupboard) standard storage (storage between 15-25 Degrees Centigrade).

## Annex 4. Details of Healthcare Professional/Worker

| Last Name | Other Names | Title |
|---|---|---|
| Address (Hospital/Community Health Centre/Health Post) | | |
| Telephone Number | Email | |
| Signature | Date | |

Thank you for submitting this form.

**Reporting of poor-quality medical product**

If, after conducting the above visual inspection, you suspect you have discovered a medical product of poor quality, you should report it immediately to the Department of Pharmacovigilance DNFM.

This form can be submitted electronically as an attachment (pharmacovigilance16gmail.com) or sent by post to the National Pharmacovigilance Centre, National Directorate for Pharmacy and Medicines (DNFM), Dili ( Edificio Salaun SPK Rua de Lahane Ocidental Caixa postal 374 Dili Timor Leste)

## Annex 5. Application for Access to Electronic Therapeutic Guidelines

| | | | |
|---|---|---|---|
| Name (title, first name, surname) | Click here to enter your title (e.g., Dr, Ms., Mr.) | Click here to enter your first name | Click here to enter your surname |
| Job title/occupation | Click here to enter your title/occupation | | |
| Country/country of work (if different) | Click here to enter your home country | | Click here to enter your country of work |
| Organization/workplace | Click here to enter your organization/workplace | | |
| Address | Click here to enter your full address | | |
| Phone number | Click here to enter your phone number including your country code | | |
| Email address for login | Click here to enter your preferred email address | | |
| I have read and agree to **the license agreement provisions** stated on page 2 | Yes ☐ No ☐ | | |

## Annex 6. Therapeutic Guideline Use

| **Please explain how Therapeutic Guidelines will be used in your line of work – check all that apply** | ➹ |
|---|---|
| As primary treatment guidelines | ☐ |
| As secondary treatment guidelines (for those patients not covered by existing local guidelines) | ☐ |
| As a model for writing local treatment guidelines (please read **adaptation policy statement**, page 3) | ☐ |
| For training purposes (please list the occupation of those who would be trained, e.g., doctors, nurses' pharmacists, pharmacy support staff) Click here to enter details for people you will train | ☐ |
| As a point of reference | ☐ |

| Other (please provide details): Click here to enter details | ☐ |
|---|---|
| **Who will be using Therapeutic Guidelines in response to this request?** | ➹ |
| Just you | ☐ |
| You and others working at your facility: Click here to enter facility name Occupation of staff who will use TG (check all that will apply):<br>Doctors ☐ Nurses ☐ Pharmacists ☐ Other ☐ | ☐ |
| Other (please provide details): Click here to enter details | |

## Annex 7. The List of Variables, Their Line List, and Order for the ADRs.

1. Case ID
2. HP/CHC/Hospital
3. District
4. Patient name
5. Date of birth
6. Sex
7. Address
8. Telephone number
9. Medical history
10. Batch number of the primary suspect medicine
11. Expiry date of primary suspect medicine
12. Batch number of secondary suspect medicine
13. Diluent batch number
14. Diluent expiry date
15. Reconstitution time
16. Date of medication
17. Time of medication
18. Adverse event
19. Date of onset
20. Serious
21. If serious
22. Outcome of the ADRs
23. If died, Date of death.
24. Name of the first reporter of ADRs
25. Institution
26. Position
27. Department

29. Telephone number
30. Date of notification
31. Date received by Municipal Health Office
32. Date received by National Pharmacovigilance Department

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**Timor-Leste Pharmacovigilance Manual 2025**
**Guidelines for Implementation**

**Democratic Republic of Timor-Leste**
**Ministry of Health**

**Supported by :**

World Health Organization Timor-Leste

Asian Development Bank

Ministério da Saúde


**First Edition**
**2025**

World Health Organization
Timor-Leste

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