Doc. No. TFDA/DMC/PV/001

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH AND SOCIAL WELFARE

TANZANIA FOOD AND DRUGS AUTHORITY

NATIONAL GUIDELINES FOR MONITORING MEDICINES SAFETY

(Made under Section 5 (c) of the Tanzania Food, Drugs and Cosmetics Act, 2003)

Second Edition

November 2010

P. O. Box 77150, Mabibo External, Off Mandela Road, Dar es Salaam, Tel: +255-22-2450512/2450751/ 2452108, Fax: +255-22-2450793, Website: www.tfda.or.tz, Email: info@tfda.or.tz

Table of Contents

Acknowledgements

These guidelines have been developed to outline requirements for monitoring medicines safety in Tanzania. The first draft was developed in January, 2010 with a team of experts and contributors from a number of institutions.. The review of guidelines was based on experiences and knowledge on pharmacovigilance activities, available literature and existing regional and international guidelines to include World Health Organization (WHO) and International Conference on Harmonization (ICH) guidelines (source materials are detailed in the bibliography).

I would like to express my profound gratitude to all those who made their source materials to be available for adaptation as well as the people mentioned below for their time and tireless effort during drafting and writing of the guidelines.

Mr. Dedan Jonas	-	Ministry of Health and Social Welfare
Mr. Robert Mbasa	-	National AIDS Control Programme
Mr. Jerome Ngowi	-	National Tuberculosis and Leprosy Control Programme
Ms. Salama Mwatawala	-	Management Sciences for Health
Mr. Vicent Manyilizu	-	Management Sciences for Health
Ms. Rose Tumbo	-	Muhimbili National Hospital
Mr. Job Batakyanga	-	Bugando Medical Centre
Mr. Francisco Chibunda	-	Bugando Medical Centre
Mr. Kerenge Nyakangara	-	Mbeya Referral Hospital
Mr. Julius Zacharia Marwa	-	Catholic Relief Services/AIDSRelief
Mr. Roman Mallya	-	Catholic Relief Services/IMA World
Mr. Mitangu Adam Fimbo	-	Tanzania Food and Drugs Authority
Mr. Henry Irunde	-	Tanzania Food and Drugs Authority
Ms. Alambo Mssusa	-	Tanzania Food and Drugs Authority
Mr. Florent Laurent Kyombo	-	Tanzania Food and Drugs Authority
Mr. Paul Sonda	-	Tanzania Food and Drugs Authority
Ms. Consolatha Mushumbusi	-	Tanzania Food and Drugs Authority

.
Special thanks are also due to the Management Sciences for Health (MSH), USAID funded project to Strengthening Pharmaceutical Systems (SPS) program for financial support which assisted in the development of these guidelines.

The valuable inputs received from the TFDA Management Team during approval of the guidelines are also greatly acknowledged.

Mitangu A Fimbo
Acting Director – Medicines and Cosmetics
Tanzania Food and Drugs Authority

Abbreviations

ADRs	Adverse Drug Reactions
AEs	Adverse Events
ARs	Adverse Reactions
AMO	Assistant Medical Officer
BMC	Bugando Medical Center
CEM	Cohort Event Monitoring
CHMT	Council Health Management Team
CO	Clinical Officer
CRS	Catholic Relief Services
DG	Director General
EU	European Union
EPI	Expanded Programme on Immunization
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSRs	Individual Case Safety Reports
KCMC	Kilimanjaro Christian Medical Centre
MAH	Marketing Authorization Holder
MNH	Muhimbili National Hospital
MoHSW	Ministry of Health and Social Welfare
NACP	National AIDS Control Programme
NMCP	National Malaria Control Programme
NTLP	National Tuberculosis and Leprosy Programme
OTC	Over-The-Counter
PIL	Package Information Leaflet
PHP	Public Health Programmes
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RHMT	Regional Health Management Team
SAE	Serious Adverse Event
SUSARs	Suspected Unexpected Serious Adverse Reactions
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristics
STG	Standard Treatment Guideline
TC	Therapeutic Committee
TFDA	Tanzania Food and Drugs Authority
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

Foreword

This is the second edition of the *National Guidelines for Monitoring Medicines Safety* in Tanzania which supersedes the first edition entitled "*Guidelines for Monitoring and Reporting Adverse Drug Reactions (ADRs)*". These guidelines have been made under the provisions of Section 5(c) of the Tanzania Food, Drugs and Cosmetics Act, No.1 of 2003.

The former edition did not provide guidance for reporting ADRs by marketing authorization holders (MAH) and patients; it only provided guidance to health care providers. It did not include requirements for reporting medication errors, product quality defects, overdoses and unusual lack of efficacy. The current edition has defined requirements for all these important aspects in pharmacovigilance and also detailing roles and responsibilities of different players in this field taking into account current developments in the field of pharmacovigilance.

The document covers the collection of ADR reports for pharmaceutical products and herbal medicines. Apart from collecting information on safety of medicines, the reporting tools in these guidelines may also be used to collect safety information from use of biological products including vaccines and blood products, medical devices (e.g. dental and medical supplies, contrast media etc), and cosmetics. Adverse drug reactions for marketed products within the scope of this guidance document should be reported to TFDA and other health authorities and/or facilities as defined in these guidelines.

It should be noted that adverse events due to medicines, herbal medicines and medical devices authorized for clinical trials involving human participants pursuant to Sections 61 to 72 of the Tanzania Food, Drugs and Cosmetics Act, No.1 of 2003 are not within the scope of these guidelines.

The guidelines allow for flexibility in approach during implementation. Alternative approaches to the principles and practices delineated in this document may be acceptable provided that they are supported by adequate justification and meet minimum recommended ADR reporting requirements. In connection to this, it is equally important to note that TFDA reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Authority to adequately assess the safety, efficacy or quality of a medicinal product.

Under-reporting of ADRs is still a challenge in the country. In view of this, TFDA will continue to create awareness and organize adequate training in collaboration with other partners. The ultimate goal is to increase the number of ADR reports received per year and henceforth enable the Authority to take the necessary regulatory actions.

Hiiti B. Sillo
Acting Director General
Tanzania Food and Drugs Authority

Introduction

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems. It is an arm of patient care and aims at getting the best outcome of treatment with medicines and other products. The science allows identification of risks including risk factors when medicines are used after marketing authorization and also enables measures to be taken to prevent adverse reactions to patients.

There are two major systems in pharmacovigilance – spontaneous or passive reporting and active surveillance systems. Passive reporting means that no active measures are taken to find adverse effects other than the encouragement of health care providers and others to report safety concerns. Passive reporting is voluntary and depends on the initiative and motivation of the reporter(s). Active (or pro-active) s surveillance means that active measures are taken to find adverse events.

Pharmacovigilance systems are being implemented in Tanzania since 1993. The systems are still being strengthened and coordinated by the Tanzania Food and Drugs Authority (TFDA) together with established zonal Pharmacovigilance Centers located at Kilimanjaro Christian Medical Center (KCMC) - Kilimanjaro, Muhimbili National Hospital (MNH) - Dar-es-Salaam, Bugando Medical Center (BMC) - Mwanza and Mbeya Medical Center (MMC) - Mbeya. The spontaneous reporting system has largely been used. The system uses specially designed forms (Yellow Forms) to collect adverse reaction data from patients.

Since the inception of the pharmacovigilance systems very few reports have been received by TFDA. In response to this, the TFDA has been trying to devise measures to bolster the reporting rate. Amongst the measures include engaging regional and district health systems/authorities as well as private pharmaceutical outlets in the collection of ADR reports, establishing more centers to coordinate collection of ADR reports, integrating pharmacovigilance into public health programmes, conducting training and sensitizing health care providers, manufacturers and patients to report adverse reactions to medicines and other products.

The above measures are viewed as a cornerstone towards a successful pharmacovigilance programme and as a consequence, they have been structured and detailed in these guidelines to put context into perspective.

The guidelines therefore outline the reporting requirements among health care providers, marketing authorization holders and patients. In this respect it defines what needs to be reported, how, by who and when. It further highlights requirements for expedited reporting, reporting of product quality defects, unusual failure in efficacy, medication errors, patient reporting and reporting of overdoses.

The way reports will be assessed by TFDA, management and communication of risk as well as the roles and responsibilities of different players in pharmacovigilance have also been detailed.

In addition, the training requirements as well as monitoring and evaluation (M&E) of pharmacovigilance systems from the national level to the districts have been delineated. Various tools for collection of data including reporting forms have also been appended with the guidelines for easy referencing.

An effective use of these guidelines including the tools which have been developed will significantly improve the detection, understanding and assessment of adverse drug reactions and enable the TFDA and other stakeholders to take appropriate regulatory action and other measures respectively. Possible regulatory actions vary from continuing observation of products to cancelling the marketing authorization. Other possibilities include:

- Conducting post-marketing studies;
- Comprehensive re-assessment of the risk and benefit profile of the product;
- Product labelling changes (including addition of contraindications, warnings,
- precautions or supplementary ADR information in the product information;
- Alteration of the packaging to clearly identify risks and instructions on the use of the product;
- Dissemination of information to health care providers and patients about the risks;
- Issuing public alerts; or
- Withdrawing products from the market.

Glossary of terms

In the context of these guidelines the following words/phrases are defined as follows.

Act
The Tanzania Food, Drugs and Cosmetics Act, 2003 and all regulations relating to pharmacovigilance made under the Act.

Active surveillance
Active measures are taken to find adverse events (e.g. cohort event monitoring).

Adverse Drug Reactions (ADRs)
A response to a medicine which is noxious and unintended, and which occurs at a dose normally used in human for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. The term adverse drug reaction should be considered for harmful or seriously unpleasant effects occurring at doses intended for therapeutic, prophylactic or diagnostic effect and which calls for reduction of dose or withdrawal of the medicine and/or forecast hazard from future administration.

Adverse Event (AE)
Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the product whether or not related to the product.

Case-Control Studies
Studies used to validate signals and to identify risk factors for adverse events (establishing association between medicine and one specific rare adverse event). They compare two groups: those with a condition (event) under study (cases) and a similar group which do not have the condition (controls) by looking backwards in time (retrospectively) to measure the exposure status of the two groups (to the medicine) and compare the relative risk of developing the condition in the two groups.

Cohort Event Monitoring (CEM)
A system created to actively monitor drug events in a population. Health care providers are requested to report all clinical events, regardless of whether they are suspected adverse reactions, for identified patients receiving a specified drug.

Drug Utilization Studies
Studies designed to describe how a medicine is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. They can be used to determine rates and to describe the effect of regulatory actions and media attention on the use of medicines, as well as to develop estimates of the economic burden of the cost of medicines as well as compare recommended and actual clinical practice.

Health care providers

For the purposes of reporting suspected adverse reactions, health care providers are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses, assistant medical officers and clinical officers, pharmaceutical technicians, pharmaceutical assistants and traditional medicine practitioners.

Herbal medicines
Includes herbs (e.g. crude plant materials such as leaves, flowers, fruit, seed etc), herbal materials (e.g. fresh juices, gums, fixed oils, essential oils, dry powders etc), herbal preparations (e.g. comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials) and finished herbal products (e.g. dosage forms preparations made from one or more herbs, may contain excipients etc).

Individual Case Safety Report (ICSR), synonym: Safety report
A document providing the most complete information related to an individual case at a certain point in time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point in time.

Lack of Efficacy
Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

Marketing Authorization Holder (MAH)
An individual or a corporate entity responsible for placing a pharmaceutical product in the market.

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

National Pharmacovigilance Centre (NPC)
A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze and give advise on all information related to drug safety.

Over dosage
A drug overdose is the accidental or intentional use of a drug or medicine in an amount that is higher than is normally used.

Pharmacovigilance (PV)
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems.

Pregnancy Exposure Registry
A prospective observational study that collects information on medicinal product exposure during pregnancy and the associated outcomes.

Periodic Safety Update Report (PSUR)
An update of the world-wide safety experience of a product obtained at defined times post marketing authorization.

Risk-Benefit Balance
An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health

Risk Management System
A risk management system comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

Risks related to use of a medicinal product
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.

Serious Adverse Event (SAE) or Serious Adverse Drug Reactions (Serious ADR)
Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Side effect
Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug.

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

Spontaneous reporting
An unsolicited communication of suspected adverse reactions by a health care provider or consumer to a company, TFDA or other organisation which fulfills the following three conditions:

It describes one or more suspected adverse reactions in a patient
The patient was given one or more medicinal products
It does not derive from a study or any organised data collection scheme.

Summary Product Characteristics (SPC)
Product information as approved by the TFDA. The SPC serves as the basis for production of information for health care providers as well as for consumer information on labels and leaflets of medicinal products.

Toxicity
Cell damage from a direct action of the medicine, often at a high dose, e.g. liver damage from paracetamol overdose.

Unexpected Adverse Drug Reaction
An adverse reaction, the nature, severity or outcome of which is not consistent with domestic labeling, marketing authorization or the Summary of Product Characteristics (SPC). This includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product.

Vigiflow
A web based data management tool used to manage ADR database. All data are stored on a database server in Uppsala, Sweden.

1. National Medicines Policy and Legal Aspect of Pharmacovigilance

The National Medicine Policy clearly states the need for raising awareness on reporting adverse drug reactions (ADRs) at all levels. The policy also recognizes the role of Tanzania Food and Drugs Authority (TFDA) as the leading institution in coordinating activities related to monitoring and reporting of existing and new adverse events associated with the use of medicinal products as stipulated under Section 5 (1) (c) of the Tanzania Food, Drugs and Cosmetics Act, 2003. The activities include detection, assessment, understanding and prevention of ADRs. The success of this exercise necessitates cooperation among all stakeholders including health care providers, drug registrants and manufacturers in the country.

2. Pharmacovigilance Systems in Tanzania

There are different systems for reporting and monitoring adverse events and/or reactions. Amongst them include spontaneous reporting system, active surveillance system (e.g. cohort event monitoring, pregnancy register, case-control studies, drug utilization studies etc.). In Tanzania, both systems are being used.

3. Roles of Various Parties

3.1 Marketing Authorization Holder (MAH)

The Marketing Authorisation Holder (MAH) must ensure that he has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for his products on the market and to ensure that appropriate action can be taken, when necessary. Specifically, the MAH should:

- Provide information to TFDA on all adverse Drug reactions,
- Submit report on adverse reactions occurring outside Tanzania,
- Submit a "null" six monthly report for the first two years and annually for the following three years if there is no ADR report submitted to them,
- Inform TFDA on any significant safety issue(s) or action(s) taken by foreign agency, including the basis for such action(s), and
  Provide periodic safety update report(s) (PSURs) for the marketed product
  Submit risk management plans including risk-benefit assessment reports to TFDA.

3.2 Patients or consumers

Patients or consumers should report any suspected adverse reaction or event associated with the use of a medicinal product immediately to the nearest health facility, health care provider or directly to TFDA

3.3 Health facilities

Health facilities should:

- Receive and distribute ADR reporting forms to health care providers.
  Detect, investigate, manage and report ADRs and take appropriate action to prevent ADRs,
- Conduct preliminary identification of signals and other risk factors,
- Communicate appropriate safety information to health management teams and the community including patients,
- Organize and conduct staff training and sensitization on matters related to pharmacovigilance,
- Set aside a budget for pharmacovigilance activities,
- Identify focal person to coordinate pharmacovigilance activities within their health facilities,
- Integrate pharmacovigilance concept into relevant committees (e.g. hospital therapeutic committees and other health committees), and
- Maintain a register of suspected ADRs including medication errors, drug interactions etc.

3.4 Council Health Management Team (CHMT)

The Council Health Management Team (CHMT) should:

- Appoint a District Pharmacist or any other designated person to become the focal person for pharmacovigilance activities in the respective council,
- Supervise the implementation of pharmacovigilance activities within the council,
- Communicate all relevant safety information to health care providers and patients in the council,
- Conduct further investigation of signals and other risk factors,
- Organize and conduct training and sensitization of health care providers and patients within the council,
- Plan and budget for pharmacovigilance activities within the council, and
- Ensure pharmacovigilance related reports are submitted to TFDA on quarterly basis.

3.5 Regional Health Management Team (RHMT)

The Regional Health Management Team (RHMT) should:

- Appoint a Regional Pharmacist or any other designated person to become the focal person for pharmacovigilance activities in the respective region,
- Supervise the implementation of pharmacovigilance activities within the region,
- Receive summary report of implementation of pharmacovigilance from all districts.
- Communicate all relevant safety information to health care providers and patients in the region,
- Conduct further investigation of signals and other risk factors,
- Organize and conduct training and sensitization of health care providers and patients within the council,
- Provide advice to TFDA on issues pertaining to medicine's safety.

3.6 Zonal Pharmacovigilance Centers

Zonal Pharmacovigilance Centers should

- Work in collaboration with zonal TFDA offices in coordinating pharmacovigilance activities in the respective zones,
- Receive information, respond to queries and provide information related to pharmacovigilance to the council and regions within the respective zones,
- Receive and distribute reporting forms to health facilities,
- Collect reports and provide feedback to health facilities,
- Review AR reports and feed information into the data management tool – *Vigiflow* where accessible or send them to TFDA for further action, and
- Receive safety alerts from TFDA and share them with health care providers and patients in the respective zones.

3.7 TFDA zone offices

Zonal TFDA offices shall:

- Plan and budget for pharmacovigilance activities in the respective zones.
- Work in collaboration with zonal pharmacovigilance centres in coordinating pharmacovigilance activities in the respective zones,
- Receive and distribute ADR forms to zonal pharmacovigilance centres and health facilities,
- Collect, screen and enter ADR reports into *Vigiflow* where possible or send the reports directly to TFDA headquarter offices for further processing,
- Receive safety alerts from TFDA headquarter offices and share them with zonal pharmacovigilance centres, councils, health care providers and patients,
- Respond to queries and provide feedback information related to pharmacovigilance to the council and regions in the respective zones, and
- Monitor and evaluate implementation of pharmacovigilance activities in the respective zones.

3.8 TFDA headquarter office

TFDA headquarters shall:

- Plan and budget for national pharmacovigilance activities,
- Develop, review and distribute ADR forms and collect reports of suspected adverse reactions to medicines and other products from the market,
- Develop, review and distribute reporting tools,
- Acknowledge receipt of ADR reports from health care providers, zonal pharmacovigilance centres and zonal TFDA offices,
- Conduct causality assessment and analyze adverse reactions reports,
- Generate hypotheses or identify signals and take appropriate regulatory action(s) based on signals generated,
- Collect and communicate relevant safety information to all stakeholders,
- Link with WHO program for international drug monitoring and share information on adverse reactions,
- Provide feedback to reporters (e.g. issuing ADR Bulletins/Newsletters etc)

including alerting prescribers, manufactures and the public to new risks of adverse reactions.
- Conduct pharmacovigilance inspection at the manufacturing facilities, where relevant.
- Monitor and evaluate all pharmacovigilance activities in the country.
- Conduct trainings and sensitization of different stakeholders.
- Take regulatory action on a particular medicine with serious adverse reaction.

3.9 Development Partners

Development partners should collaborate with the Ministry of Health and Social Welfare including its institutions and other stakeholders in providing financial and technical support during implementation of pharmacovigilance activities at all levels.

3.10 Public Health Programs (PHPs)

Public health programmes (PHP) in Tanzania include; National AIDS Control Programme (NACP), National Malaria Control Programme (NMCP), National Tuberculosis and Leprosy Programme (NTLP), Expanded Programme for Immunization (EPI) etc. Such programmes should be actively engaged in pharmacovigilance activities. Their specific roles should include:

- Identifying focal persons to coordinate pharmacovigilance activities,
- Planning and budgeting for pharmacovigilance activities,
- Collection of data using existing ADR reporting forms,
- Distribution of ADR forms in programme sites,
- Establishing procedures for data analysis and review,
- Risk management and follow-up of patients,
- Collaborating with TFDA in implementing pharmacovigilance activities,
- Training of health care providers in reporting adverse drug reactions including other aspects of pharmacovigilance,
- Promoting rational and safe use of medicines by health care providers, and
- Educating and informing patients on the importance of reporting adverse drug reactions.
- Assessment and communication of the risks and effectiveness of medicines used in the specific PHP.

3.11 Ministry of Health and Social Welfare (MoHSW)

The MoHSW shall have the following roles:
- Develop and review policies related to pharmacovigilance activities,
- Oversee implementation of pharmacovigilance activities, ensure effective integration of pharmacovigilance activities within public health programs, and
- Mobilize and provide resources for pharmacovigilance activities.

4. Reporting of Adverse Drug Reactions

4.1 Spontaneous reporting

When an adverse reaction to medicine is suspected, one has to complete the ADR reporting form (**Annex 1**). Adverse drug reactions (ADRs) can also be reported electronically using the electronic reporting form which is available online at www.tfda.or.tz or can simply be reported by calling TFDA using numbers printed on the ADR form. All reports submitted will be kept CONFIDENTIAL.

a. Where to obtain and send ADR reporting forms

The ADR reporting form should be obtained, completed and sent to the following offices:

- TFDA headquarter offices
- TFDA website (http://www.tfda.or.tz)
- TFDA zonal offices- These are located in Mwanza (serving Lake Zone) Arusha (serving Northern Zone),Mbeya (serving Southern Highlands Zone) and TF in Dar-es-Salaam (serving Eastern zone).
- Zonal pharmacovigilance centres.
- Regional Medical Officer's office
- District Medical Officer's office
- In-charge of the regional and district hospitals
- In-charge of the health centers
- In-charge of the dispensaries
- Superintendent of the community pharmacies
- Superintendent of the private health facilities

NB: The forms will be provided free of charge by TFDA and as they are already pre-paid, reporters will not be charged for postal mailing.

b. What to report

Report all suspected reactions to pharmaceutical products , herbal medicines, biologicals (e.g. vaccines, blood products etc), medical devices (e.g. dental and medical supplies, contrast media etc) and cosmetics. The following should be reported;-

- All ADRs as a result of prescription and non-prescription;
- All suspected adverse drug reactions regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product;
- Unexpected reactions, regardless of their nature or severity, whether or not consistent with product information or labelling;
- An observed increase in frequency of a given reaction;
- A serious reaction, whether expected or not;
- All suspected ADRs associated with drug-drug, drug-food or drug-food supplement interactions;
- ADRs in special field of interest such as drug abuse and drug use in

pregnancy and during lactation;
- ADRs occurring from overdose or medication errors;
- Unusual lack of efficacy or when suspected quality defects are observed.
- Product quality problems include colour change, separating of composition, caking, change of odour, questionable stability, suspected contamination, poor packaging and labelling, mislabeling, incomplete pack, defective and expired product.

c. Who should report

Submission of a report does not constitute an admission that a health care provider or the drug or the product caused or contributed to the ADR in any way as all reports are termed as suspected.

Reporters should bear in mind that any information related to the reporter and patient identities shall be kept CONFIDENTIAL.

The following should provide reports of any case of suspected ADRs when encountered by the patient:

- Health care providers,
- Marketing Authorization Holders
- Manufacturers,
- Patients and the general public.

It is vital to report an ADR even if you are doubtful about the precise relationship with the given medication or you do not have all the facts. What is required is to report all SUSPECTED ADRs.

Collection of reports from several health care providers in different parts of the country assists in making associations (strengthening of signal) between a particular product and the adverse reaction. Therefore, measures should be taken to ensure that all necessary information for submission of ADR reports are obtained and reported through the reporting forms.

d. When to report

Any suspected ADR should be reported as soon as possible. Delay in reporting will make reporting inaccurate and unreliable. Reporting while the patient is still in the health facility will give the reporter the chance to clear any ambiguity by re-questioning or re-examining the patient.

4.1.1 Completing the ADR reporting form

The ADR reporting form contains key data elements about the patient, the suspected drug, the adverse reaction, the action taken and the outcome (see **Annex 2 – key data elements**). Such elements enhance the quality of an ADR report. Reporters should write legibly and use a separate form for each patient. Attempts should be made to obtain as many information as provided below:

a. The patient's identity - Information about the patient's age, sex, weight, ethnicity and use of substance of abuse should be provided. The patient file number has to be stated as it is useful to get additional information when needed.

b. Information on the suspected drug - This information includes the name of the medicine, source, the dose, route of administration and the impact of withdrawal and re-administration of the suspected medicine on the adverse reaction.

- Use brand name of suspected medicine(s). If generic name is used, specify the manufacturer of the medicine.
- Avoid non-standard abbreviations such as TCL (tetracycline), PCM (Paracetamol), CPZ (Chlorpromazine), etc.
- List any other prescription, non-prescription medicines and/or traditional medicine used concurrently with the suspected medicine with all descriptions i.e. brand name, route, dosage form, strength, frequency, indication, date started and date stopped.
- The dosage form such as tablet, capsule, syrup, suspension, elixir, emulsion, injection, eye drop/ointment, topical crème/ ointment, nasal drop, suppositories rectal/ vaginal etc. should be stated.
- The strength must also be expressed in metric system, e.g. 500mg tab, 250mg/5ml syrup, 1gm rectal suppository etc. Sometimes strength can be expressed in %, e.g. 2% hydrocortisone ointment.
- Frequency of drug administration should be clearly notified using standard abbreviations, e.g. 3 times a day as tid or 8hrly, 2 times a day as bid or 12hrly, 4 times a day as qid or 6 hrly etc.
- Route of administration expressed using standard abbreviation should be used (see also **Annex 3**).
- The date medicine was started and discontinued (if applicable) is important data to assess the cause and effect relationship of the medicine and adverse reaction. Therefore it has to be stated clearly on the reporting form as date/ month/year. If the medicine has not been discontinued at the time of reporting, write continuing.
- Write the reason why the medicine was used or the diagnosis for which the medicine was prescribed for both suspected medicine and other medicines used concurrently.

c. Information on the adverse reaction - A clear and brief description about the nature of adverse reaction, the date of onset, duration, time course and laboratory test results including "negative" and normal results of any relevant test performed should be reported. The severity of the reaction i.e. whether it has necessitated prolonged hospitalization or not, discontinuation of the medicine or not, etc. and the outcome of the de-challenge and re-challenge tests with the suspected medicines have to be reported.

d. Additional information - Any reaction the patient may have experienced previously, particularly similar to the current adverse event, either caused by the same or different medicine has to be reported. Other relevant medical history, such as allergy, chronic disease, pregnancy and other factors, which

may contribute including herbal products, foods and chemicals, should be reported under this heading. You may also add here why you think the adverse effect is due to the particular medicine.

e. **Follow-up report for an ADR that has already been reported -** Any follow-up information for an ADR that has already been reported can be sent on another ADR form, or it can be communicated by telephone, fax or e-mail to TFDA indicating that it is a follow up information. The date of the original report and the report case number must be retrieved from the ADR register so that the follow up information can be matched with the original report. It is very important that follow-up reports are identified and linked to the original report.

4.1.2 Expedited reporting requirements

All serious reactions must be reported on an expedited basis using the same ADR reporting form (**Annex 1**). Expedited reports should be submitted to TFDA immediately and not later than 15 calendar days from receipt of the minimum information required for an adverse reaction report by a health care provider or personnel of the manufacturer.

Serious suspected adverse reactions occurring in all post-marketing studies of which the manufacturer is aware should be reported to the TFDA on an expedited basis.

When additional medically relevant information is received for a previously reported case, the reporting time is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non serious to serious).

4.1.3 Periodic Safety Update Reporting

Periodic Safety Update Reports (PSURs) are important pharmacovigilance documents. They provide an opportunity for Marketing Authorization Holders (MAHs) to review the safety profile of their products and ensure that the Summary of Product Characteristics (SPC) and Package Leaflets are up to date. They also provide a valuable source of pharmacovigilance data.

MAHs should submit PSURs to TFDA. PSURs should as a minimum contain the following information:

- Information on the product (i.e. brand name, dosage form, strength, manufacturer and country of origin),
- The scope of drug safety data and the surveillance period,
- Collection of adverse drug reaction (ADR) information (i.e. local serious ADRs, local non-serious ADRs, foreign serious ADRs, foreign non-serious ADRs, case reports published on international or local literatures including academic conferences).

4.1.4 Reporting unusual failure in efficacy

Reports of unusual failure in efficacy must be reported to TFDA using ADR reporting form (**Annex 1**). The underlying principle is that if a product fails to exert the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the product is being used.

Possible reasons for lack of efficacy include:

- Did not retain the medication because of vomiting or severe diarrhea,
- Lack of adherence to treatment schedule,
- Inadequate dose,
- Poor quality medication,
- Counterfeit medication,
- Incorrect diagnosis,
- Interactions reducing blood levels,
- Drug resistance.

Clinical judgement should be exercised by the health care provider to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription.

Lack of efficacy of medicines used for the treatment of life-threatening diseases, vaccines and contraceptives should be considered as requiring **expedited reporting**.

4.1.5 Reporting medication errors

a. By health care providers

Medication errors can occur when prescribing, repacking, dispensing, or administering a product. Common causes of medication errors include poor communication, patient misunderstanding, and ambiguities in product names or directions for use.

Errors, or hazardous conditions including administering the wrong drug, strength, or dose of medications; confusion over look-alike/sound-alike medicines; incorrect route of administration; calculation or preparation errors; misuse of medical equipment; and errors in prescribing, transcribing, dispensing, and monitoring of medications should be reported to TFDA using the ADR reporting form (**Annex 1**).

Medication errors reporters are encouraged to submit associated materials such as product photographs, containers, labels, prescription order scans, etc, that would support the information being submitted. TFDA guarantees CONFIDENTIALITY of information received and respects reporters' wishes as to the level of detail included in the report.

When reporting errors, include the following:

- Describe the error or preventable adverse medicine reaction. What went wrong?

- Was this an actual medication error (reached the patient) or are you expressing concern about a potential error or writing about an error that was discovered before it reached the patient?
- Patient outcome.
- Type of health facility (hospital, dispensary, retail pharmacy, ADDO, drug outlets, health centres, home-based services, etc).
- The generic name (INN or official name) of all products involved.
- The brand name of all products involved.
- The dosage form, concentration or strength, etc.
- How was the error discovered/intercepted?
- State your recommendations for error prevention.

NB. Do not submit any patient identifiable information when reporting medication errors.

b. By Marketing Authorization Holders

The Marketing Authorization Holders or product registrants should report cases of medication errors that are associated with serious adverse reactions on an expedited basis. Cases not associated with adverse reactions and near misses should only be reported in Periodic Safety Update Reports (PSURs). Cumulative information on medication errors, resulting in adverse reaction or not, should be discussed in the section of the PSUR on the overall safety evaluation. The potential for medication errors and their prevention should be addressed in the Risk Management Plan.

4.1.6 Reporting suspected ADRs to herbal medicines

Health professionals, providers of herbal medicines, patients/consumers and manufacturers should report any suspected adverse reactions to herbal medicines. Details of the suspected herbal product to include species name and/or brand name or ingredients, country of origin, batch number, expiry date and name of provider should be provided. The precise Latin binomial botanical name (genus, species, author as well as name of family) of the medicinal plants concerned should be used whenever possible together with the plant parts used and extraction and preparation methods employed. Suspected adverse reaction to herbal medicines should be reported using ADR reporting form (**Annex 1**).

4.1.7 Reporting product quality defects

Medicines quality concerns include a number of hazards, which may be due to improper formulation, packaging, or labelling. Some product quality defects may occasionally pose a threat. Problems of quality defect that occur during the manufacturing, shipping, or storage of prescription or over-the-counter products shall be reported to the Marketing Authorization Holder and direct to TFDA using the form for reporting poor quality products **(Annex 4).**

On receipt of the report of medicine quality defect that are associated with serious adverse reactions, MAH should assess the situation and take immediate action within reasonable time. Simultaneously, MAH should report such product quality defects and measures taken to TFDA in writing within 15 calendar days after becoming aware of the defect.

4.1.8 Patient reporting

A simplified reporting form (**Annex 5**) should be used by patients to report information on suspected adverse drug reactions. Patients should be encouraged to report adverse events and seek medical attention through their health care providers. Further information on the report can be sought from the health care provider for serious and/or unknown reaction reported directly from patients.

Patients who experienced serious adverse drug reaction should be given special cards (i.e. **Patient ADR Alert Card** appended as **Annex 6**) by the health care provider who diagnosed and managed the reaction. The Alert Card will be prepared and distributed to health facilities by TFDA.

The card will alert all health care providers that the bearer of the card had experienced serious reaction(s) (e.g. hypersensitivity reactions) or had experienced a serious adverse reaction to a particular medicine.

The card will be carried by the patient at all times and be presented to health care provider at the time of consultation. This will help the health care provider to identify the patient's medicines-related co-morbidity and prevent similar reactions.

4.1.9 Reporting of Overdoses

The health care provider should report cases of overdose (accidental or intentional) that lead to suspected serious adverse reactions on an expedited basis. This should include reports that indicate that the taking of the suspected drug led to suicidal intention and a subsequent overdose of the suspected drug or other medications.

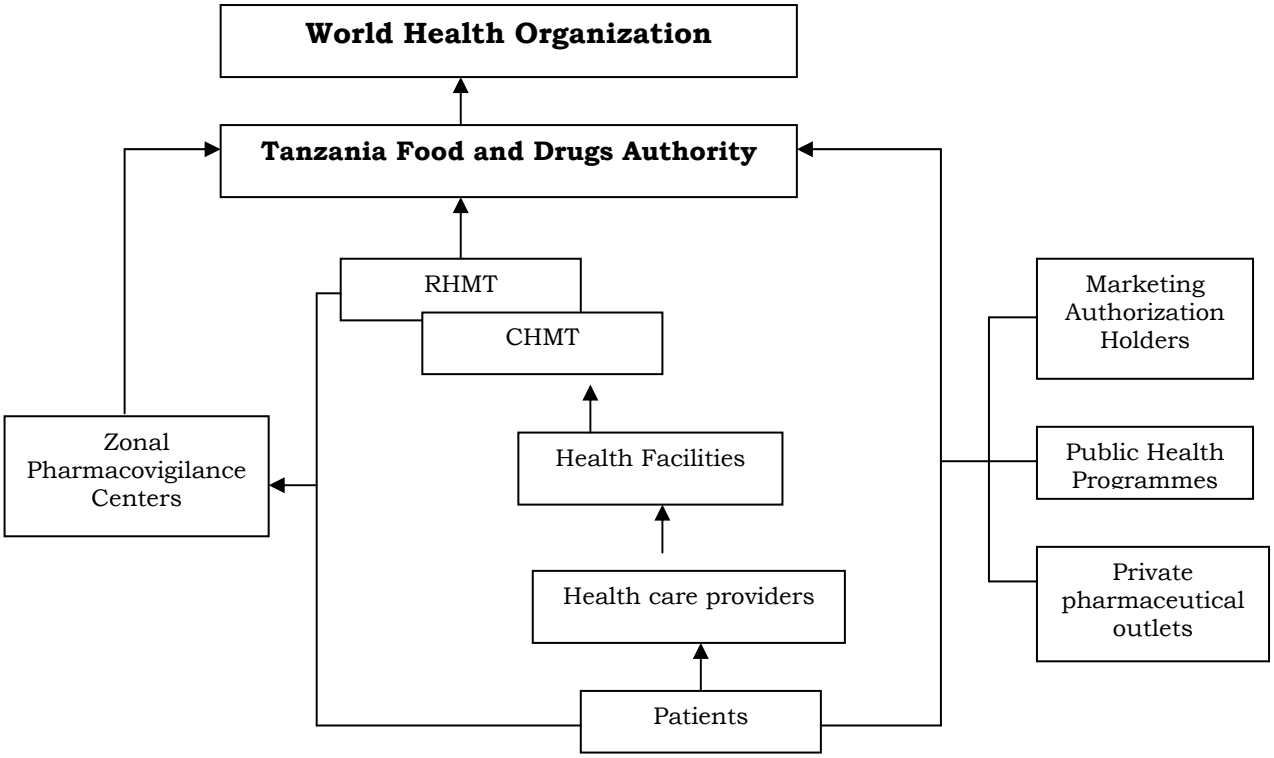
Reports of overdose with no associated adverse reactions should not be reported as adverse reactions. They should be routinely followed up by the health care providers to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome of an overdose.

Patients are encouraged to immediately report to health care providers in case of overdosage.

4.10 Flow of ADR information

The flow of ADR information is summarized in Fig. 1 below.

Fig.1: Flow of ADR information



4.2 Active surveillance

Various approaches of active surveillance exist, including cohort event monitoring (CEM), case-control studies, registries, drug utilization studies etc. Such studies may be conducted for the purpose of identifying previously unrecognized safety concerns (hypothesis-generation), investigating potential and identified risks (hypothesis-testing in order to substantiate a causal association), or confirming the known safety profile of a medicinal product under normal conditions of use. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Data collection tools to be used in active surveillance studies may be designed or adapted depending on the disease or medicines under investigation.

Reports on active surveillance studies should be submitted to TFDA for evaluation and appropriate regulatory action where applicable.

5. Assessment of ADR reports

Assessment of ADR reports (i.e. individual case safety reports (ICSRs)) should be carried out to determine the seriousness and expectedness of the suspected adverse reaction(s). Reaction(s) to new medical entities and unexpected or serious reactions should receive priority.

The World Health Organization (WHO) causality assessment criteria (**Annex 7**) together with the World Health Organization - Adverse Reaction Terminologies (WHO-ART) should be used for signal detection. When a signal is identified, the possibility of a causal relationship should be established and in these circumstances, all relevant adverse reaction data should be further analyzed. All ICSRs fulfilling the minimum information requirements should be included in the overall analysis. Additional information may be requested from manufacturer or reporter if needed.

The TFDA together with other parties, where applicable, should carry out the assessment. Data on adverse reactions should also be shared with the WHO through the data management tool – Vigiflow.

6. Communicating with reporters and other stakeholders

Adverse reaction reports sent to TFDA and other parties should be acknowledged after receipt. Acknowledgement letters should be sent within one (1) week, where possible. This will motivate and encourage reporters to keep sending reports and as a result improve the reporting rate.

Signals generated by running queries on Vigiflow should be communicated to health care providers and all other stakeholders.

Results from the literature scan, statistics and regulatory measures taken should be communicated to health care providers and other stakeholders through the TFDA - Drug Safety Newsletter, TFDA website (www.tfda.or.tz), press releases, media and all other possible means.

7. Risk-Benefit Assessment by MAH

MAH should submit risk management plan(s) and immediately notify the TFDA of any change in the balance of risks and benefits of their products.

Overall risk-benefit assessment should take into account and balance all the benefits and risks. Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

Whenever possible, both risks and benefits should be considered in absolute terms and in comparison to alternative treatments. The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product. The populations being treated must also be taken into account.

7.1 Assessment of Risks

Assessment of risks involves a stepwise process requiring identification, confirmation, characterization (including identification of risk factors), and quantification of the risk in the exposed population. Overall assessment of risks should consider all available sources of information, including:

- Spontaneous adverse reaction reports;
- Adverse reaction data from studies which may or may not be company-sponsored;
- In-vitro and in-vivo laboratory experiments;
- Epidemiological data;
- Registries, for example of congenital anomalies/birth defects;
- Data published in the scientific literature;
- Investigations on product quality; and
- Data on sales and product usage.

Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures. The quality and degree of evidence of risks should be taken into account.

In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance. Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.

When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the MAH should propose appropriate studies to further investigate the nature and frequency of the adverse reactions. A new or updated Risk Management Plan should be proposed accordingly.

7.2 Assessment of Benefits

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of many parameters including: the extent to which the medicinal product cures or improves the underlying condition or relieves the symptoms; the response rate and duration and quality of life.

In the case of prophylactic medicinal products, the benefit may be considered as the reduction of the expected severity or incidence of the disease. With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates.

Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality and degree of the evidence of benefit should be taken

into account. Benefit should, as far as possible, be expressed in quantitative terms in a way that makes it comparable to the risks.

7.3 Improving the Risk-Benefit Balance

The MAH should aim to optimize the safe use and the risk-benefit balance of an individual product and ensure that the adverse effects of a medicinal product do not exceed the benefits within the population treated. The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks using risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings and, if appropriate, pre-treatment tests to identify patients at risk, monitoring during treatment for early diagnosis of adverse reactions).

When proposing measures to improve the risk-benefit balance of a product, their feasibility in normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimization, the impact of dose reduction on efficacy should be carefully evaluated.

If there are important new safety concerns requiring urgent action, the MAH, should initiate urgent safety restrictions. These measures should be immediately communicated to TFDA. The following types of actions may be necessary and may be initiated by the MAH:

- Variation of marketing authorization(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the Summary of Product Characteristics (SPC) and the Package Information Leaflet (PIL);
- Direct provision of important safety information to health care providers, patients and the general public;
- Withdrawal of the product from the market.

8. Pharmacovigilance Inspections

The MAH should establish pharmacovigilance systems.
Such systems will be inspected by TFDA to ensure compliance with pharmacovigilance requirements. Inspections will be routine as well as targeted to MAHs suspected of being non-compliant. The reports of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action.

The focus of inspections will be to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations.

These inspections will be prioritized based on the potential risk to public health, the nature of the products, extent of use, number of products that the MAH has on the market and other risk factors.

Where an inspection reveals non-compliances the MAH will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence.

The MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

In addition, in the event of non-compliance, regulatory actions may be taken by TFDA which might include the following:

- Education and facilitation – MAHs may be informed of non-compliance and advised on how this can be remedied,
- Re-inspection - Non-compliant MAHs may be re-inspected to ensure compliance is achieved,
- Warning - A formal warning letter may be issued to remind MAHs of their pharmacovigilance regulatory obligations,
- Naming non-compliant MAHs - TFDA will make public a list of MAHs found to be seriously or persistently non-compliant,
- Urgent safety restriction,
- Variation, suspension or revocation of the Marketing Authorisation in accordance with the Tanzania Food, Drugs and Cosmetics Act, No.1, 2003.

9. Training and Capacity Building

Training and capacity building in pharmacovigilance are required for health care providers working at all health facilities to detect, understand, assess and prevent adverse drug reactions. Health care providers therefore need to be made aware that ADR monitoring is a part of good professional practice.

Training and capacity building are required to ensure that health care providers understand prescribing practices for medicines, the correct dosage regimens and how treatment failures are defined. In conjunction, they need to be taught the reaction profile of the medicines used, how to identify ADRs, how to manage them, when to refer patients, the basic data elements required in an ADR report, how to report, to whom and when.

Common concerns and barriers to reporting by health care providers will need to be addressed during training activities. Communication issues also need to be addressed in training courses. Health care providers in peripheral health facilities in rural and remote areas should also be included in training schemes.

The training manual developed by TFDA should be used during training. The MoHSW should also incorporate pharmacovigilance concept in the training curricula of health training institutions.

10. Monitoring and Evaluation

The TFDA, RHMT, CHMT, health facilities and PHPs should respectively establish a monitoring and evaluation (M&E) system to periodically monitor and evaluate the performance of the pharmacovigilance system. The M&E system should essentially evaluate whether, or to what extent:

- The reporting is complete, timely and accurate;
- Response has been quick enough;
- Case management has been appropriate; and
- Action has been appropriate to avoid system error.

A set of indicators (**Annex 8**) should be used when evaluating the pharmacovigilance system. The indicators amongst other things will evaluate the following:

- Distribution of reporting by health care provider category, specialization or patient reporting;
- Reporting quality, e.g. completeness of information, precision of description,
- contributory value to decision-making;
- Proportion of reports, describing reactions that are serious or previously unknown;
- Promptness of reporting;
- Reporting rate, e.g. the number of case reports per unit of population or number of health care providers; and
- Evaluation of the impact of adverse reactions on morbidity, mortality and health care costs (often done by analysing hospital admissions due to ADRs).

Annex 1: Adverse Drug Reaction Reporting Form

TANZANIA FOOD AND DRUGS AUTHORITY

REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES

Note: Identities of reporter, patient and institution will remain confidential

I. PARTICULARS OF PATIENT

Patient Initials or Record No.: - _____	Sex: - Male ❑ Female ❑
Date of Birth (dd-mm-yyyy) or age:-_____	Weight in kg:-_____

II. DETAILS OF ADVERSE REACTION

Description of reaction: …… …… ……....…….... ……	Date Reaction Started ___/___/___ Date Reaction Stopped (if known) ___/___/___ Onset latency…….

Health related information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc. ***Please write any relevant medical and laboratory results including dates (if done)*** ....
.....

III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED

Name of suspected medicine(s)/ vaccine(s) (Specify brand name or manufacturer if known).	Dosage	Frequency	Route	Therapy Date		Batch. No & Expiry date (If known)	Reason for use
				Start	Stop		
1.							
2.							
3.							
Other medicines used at the same time and or one month before (including herbal medicines)							
1.							
2.							
3.							

IV. MANAGEMENT OF ADVERSE REACTION

Reaction subsided after stopping the suspected drug/reducing the dose:	❑ Yes	❑ No	❑Unknown
Reaction reappeared after reintroducing drug:	❑ Yes	❑ No	❑ Not applicable

Seriousness of the Reaction **(please tick all that apply):**

❑ Discomfort but able to work	❑ Caused persistent disability or incapacity

❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died
❑ Life threatening	❑ Others, please give details……...…….
Treatment of adverse reaction ❑ No	❑ Yes **(if yes please specify)**:……...
……	
Outcome of the reaction Not yet recovered ❑	Recovered (Date):__/__/__ ❑ Died (Date):__/__/ Unknown ❑
Cause of death……...……..	

V. THERAPEUTIC FAILURE

PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW : (Continue at the back)

VI. MEDICATION ERRORS AND OVERDOSAGE

PLEASE WRITE DETAILS OF MEDICATION ERRORS AND OVERDOSAGE BELOW:

PLEASE WRITE ANY OTHER RELEVANT ADDITIONAL INFORMATION BELOW :

VII. PARTICULARS OF REPORTER /HEALTH CARE PROVIDER

Name: _____ Profession: _____ Name and Address of the health facility:

Contact phone No: _____ E-mail: _____

Signature: _____ Date of this report: ___/___/_____

❑ *Please tick if you wish to receive information about other local reports associated with the suspected drug(s)*

Thank you for your cooperation	*Submission of an ADR case report does not discredit the competence of the reporter.*	*Ref No. (for official use)*

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Use a separate form for each patient
- Report direct to TFDA through the following addresses:-

Mail : Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

Phone: 22-2450512 / 2450751

Internet; http://www.tfda.or.tz
E-mail: adr@tfda.or.tz

Moisten gum and f

The ADR reporting form and the guidelines are also available for downloading at http://www.tfda.or.tz

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable patient effect suspected to be associated with drugs, cosmetics or medical devices use.

Report even if:

- You're not sure that the product caused the event
- You don't have all the details

When to report?

As soon as possible

Submission of follow-up reports:

Any follow-up information for an ADR that has already been reported can be sent on another ADR form or it can be communicated directly to TFDA by telephone, fax or e-mail. Please indicate that it is a follow-up report.. It is very important that follow-up reports are identified and linked to the original report.

Second Fold

POSTAGE WILL BE PAID BY LICENCEE

No postage stamp required
If posted in Tanzania

BUSINESS REPLY SERVICE
LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORITY
P. O. BOX 77150
DAR ES SALAAM

Annex 2: Key Data Elements

Some data elements might not be relevant, depending on the circumstances. Attempts should be made to obtain follow-up information on as many other listed items as are applicable to the case.

1. Patient Details

Initials
Other relevant identifier (patient number, for example)
Gender
Age, age category (e.g., adolescent, adult, elderly), or date of birth
Concomitant or Pre-existing conditions
Medical history
Relevant family history

2. Suspected Medicinal Product(s)

- Brand name as reported
- Common Name, e.g., International Nonproprietary Name (INN)
- For herbal products, it is important to include the Latin binomial, author reference, family, type of extract (e.g., aqueous versus alcoholic, including percent of solvent), part of the plant used, ingredients and quantity of each (for combination products - the suspected ingredient)
- Batch/lot number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose (specify units, e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, and duration of treatment

3. Other Treatment(s)

The same information as in item 2 should be provided for the following:

- Concomitant medicinal products (including non-prescription, OTC products, herbal products, complementary and alternative therapies, etc.)
- Relevant medical devices and cosmetics

4. Details of Adverse Drug Reaction(s)

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious if reported as such

- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, health center, dispensary)
- Outcome (recovery and any sequelae)
- For a fatal outcome, stated cause of death
- Relevant autopsy or post-mortem findings
- Relatedness of product to reaction(s)/event(s)

5. Details of Reporter of an Adverse Reaction

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, health care professional, etc.)
- Profession (specialty)

6. Administrative and Market Authorization Holder Details

- Source of report (e.g., spontaneous, literature etc)
- Date the event report was first received by MAH
- Country in which the reaction occurred
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to TFDA
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile number of contact person of MAH
- MAH's identification number for the case (the same number should be used for the initial and follow-up reports on the same case)

Annex 3: Route of Administration – Standard Abbreviations

ROUTE	CODE
Buccal	BU
Conjuctival	CO
Dental	DE
Implant	MP
Inhalation	IH
Insufflation	IS
Intra-arterial	IA
Intra-articular	IR
Intra-cardiac	IC
Intradermal	ID
Intramuscular	IM
Intranasal	IN
Intraperitoneal	IP
Intrapleural	IL
Intrathecal	IT
Intratracheal	TR
Intrauterine	IU
Intravenous	IV
Intravesical	IB
Per oral	PO
Per rectal	PR
Subcutaneous	SC
Sublingual	SL
Systemic (if route is not Specified)	SY
Topical (external)	TO
Transmammary transfer	TM
Urethral	UR
Vaginal	VA

Annex 4: Quality Defects Reporting Form

TANZANIA FOOD AND DRUGS AUTHORITY

FORM FOR REPORTING POOR QUALITY PRODUCTS

Note: Identities of reporter(s) will remain confidential

PRODUCT IDENTITY	
Brand Name:…….	Name and Address of Distributor/Supplier:
Generic Name:……..	……...
Batch/Lot Number:…….....	…….
Date of Manufacture:……	…….
Expiry Date:…….	…….
Country of Origin:…….	

PRODUCT FORMULATION (Tick appropriate box)	COMPLAINT (Tick appropriate box(es))
❑ Tablets/Capsules	❑ Colour change
❑ Oral Suspension/Syrup	❑ Turbid Solution
❑ Injection	❑ Change of Odour
❑ Cream/Ointment/Liniment/Paste	❑ Caking
❑ Powder for reconstitution of suspension	❑ Moulding
❑ Powder for reconstitution of injection	❑ Separating
❑ Eye drops	❑ Powdering/Crumbling
❑ Ear drops	❑ Incomplete Pack
❑ Nebulizer solution	❑ Mislabeling
❑ Diluent	❑ Other, please specify:
❑ Other, please specify:	

Describe the complaint in detail:

STORAGE CONDITIONS			
Does the product require refrigeration?	❑ Yes	❑ No	Other details (if necessary)
Was the product available at the facility?	❑ Yes	❑ No	
Was the product dispensed and returned by client?	❑ Yes	❑ No	
Was the product stored according to manufacturer's recommendations?	❑ Yes	❑ No	

Comments (if any)

REPORTER NAME AND CONTACT ADDRESS	
Name of Reporter:	Contact Address:
Contact Phone No: _____	
E-mail: (if available) _____	
Date of this report: _____	
Thank you for your cooperation	*Ref No. (for official use)*

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Report direct to TFDA through the following addresses:-

Mail : Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

Phone: 22-2450512 / 2450751

Internet; http://www.tfda.or.tz
E-mail: adr@tfda.or.tz

The poor quality reporting form and guidelines are also available for downloading at http://www.tfda.or.tz

What to report?

Please report all product defects suspected to be associated with drugs, vaccines, cosmetics or medical devices use.

When to report?

As soon as possible

MAH should report product quality defects and measures taken to TFDA in writing within 15 calendar days after becoming aware of the defect.

.

Moisten gum and fold. For maximum adhesion, press down for few seconds

Second Fold

POSTAGE WILL BE PAID BY LICENCEE

No postage stamp required
If posted in Tanzania

BUSINESS REPLY SERVICE
LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORITY
P. O. BOX 77150
DAR ES SALAAM

Annex 5: Patient ADR Reporting Form

TANZANIA FOOD AND DRUGS AUTHORITY

ADVERSE REACTION PATIENTS' REPORTING FORM

(For reporting adverse reactions and product problems by non-health care providers)

Note: Identities of patient will remain confidential

I. PERSON REPORTING

Patient ❑ Community health worker ❑ Mother ❑ Relative ❑

Other ❑ Specify: _____

Name of the health facility the medicine was obtained from:

_____

Sex: - Male ❑ Female ❑

Age of the patient_____

II. BRIEF DESCRIPTION OF THE REACTION/EVENT

……

……

……..……..

Date Reaction Started ___/___/___

Date Reaction Stopped (if known) ___/___/___

Date reported……

III. DETAILS OF SUSPECTED MEDICINE USED

Name of suspected medicine(s)	Dosage	Frequency	Route	Therapy Date	
				Start	Stop
1.					
2.					
3.					

IV. DESCRIPTION OF ANY HERBAL MEDICINE THE PATIENT WAS TAKING

V. SERIOUSNESS OF THE ADVERSE REACTION

❑ Discomfort but able to work	❑ Caused persistent disability or incapacity
❑ Discomfort could not work	❑ Caused a congenital anomaly
❑ Required or prolonged hospitalization	❑ Patient Died: Date of death _____
❑ Life threatening	❑ Others, please give details……..…...

VI. SOURCE OF THE MEDICINE

❑ Hospital Pharmacy	❑ Traditional Healer
❑ Retail Pharmacy	❑ Supermarket/Open Market
❑ Wholesale Pharmacy	❑ Family/Neighbour
❑ ADDO Shop	❑ Others, please specify……..…...

VII. REPORTER NAME AND CONTACT ADDRESS

Name: (Optional):

Contact Address:

Contact Phone No: _____

E-mail: (if available) _____

Date of this report: _____

Thank you for your cooperation

Ref No. (for official use)

First Fold

Guide to filling the form

How to report?

- Dully fill in the form as required
- Report direct to TFDA through the following addresses:-

Mail : Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam

Fax:: 22- 2450793

Phone: 22-2450512 / 2450751

Internet; http://www.tfda.or.tz
E-mail: adr@tfda.or.tz

The ADR reporting form and the guidelines are also available for downloading at http://www.tfda.or.tz

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable effects suspected to be associated with drugs, cosmetics or medical devices use.

Report even if:

- You're not sure that the product caused the event
- You don't have all the details

When to report?

As soon as possible

Moisten gum and fold. For maximum adhesion, press down for few seconds

Second Fold

POSTAGE WILL BE PAID BY LICENCEE

No postage stamp required
If posted in Tanzania

BUSINESS REPLY SERVICE
LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORITY
P. O. BOX 77150
DAR ES SALAAM

Annex 6: Patient ADR Alert Card

TANZANIA FOOD AND DRUGS AUTHORITY *Front side*

ADVERSE DRUG REACTION ALERT CARD

PATIENT NAME: .....
AGE: ..... GENDER: .....
DATE ISSUED: .....ADDRESS: .....
SUSPECTED DRUG(S): .....
DESCRIPTION OF REACTION: .....
Other comments (if any): .....
.....

Please carry this card with you at all times and remember to show it to your health care provider at each time of consultation	***Tafadhali hakikisha umebeba kadi hii kila wakati na kumbuka kumwonyesha mhudumu wa afya unapo pata matibabu***

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tel: +255-22-2450512/2450751/ 2452108, Fax: +255-22-2450793, Website: **www.tfda.or.tz**, Email: info@tfda.or.tz, adr@tfda.or.tz

CRITERIA FOR ISSUE OF A PATIENT ALERT CARD *Rear side*

The alert card is to be given to:

Patients who are hypersensitive/allergic/intolerant to a particular drug,
Patients who developed a 'near-fatal' reaction to any particular drug,
Patients who had a drug-induced morbidity to any drug,
Patients who had hospital admission due to an AR to any drug.

Annex 7: Causality Assessment Criteria for Suspected ADRs

Term	Description	Comments
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
Probable / Likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.	This definition has less stringent wording than for "certain" and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no re-challenge information is needed, but confounding drug administration underlying disease must be absent.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence	This is the definition to be used when drug causality is one of other possible causes for the described

	to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	clinical event.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
Conditional / Unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.	
Unassessable / Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Annex 8: Pharmacovigilance Indicators

1. Definition

Indicators are specific objective measures that allow the evaluation of baseline situation and progress in healthcare services and interventions. In essence the pharmacovigilance (PV) performance indicators are measures of inputs, processes, outputs, outcomes, and impacts for PV programs or strategies. They are measures that describe how well a PV program is achieving its objectives. The set of PV indicators include a background information and three other categories of indicators – structural, process and outcome/impact

2. Background indicators

They define and describe the environment where the pharmacovigilance activities are taking place and other factors likely to impact on pharmacovigilance. The information will include those on demographics, economics, health care system and pharmaceutical situation. They provide the denominator for calculating most of the indicator values. They include the following:

S/N	BACKGROUND INDICATORS	
1.	Total population of the setting (region or facility)	
2.	Gender and age structure of the population: a. Male: b. Female: c. Life expectancy:	
3.	Total number of drug manufacturing facilities in the country:	
4.	Total number of pharmaceutical outlets in the country:	
5.	Total number of pharmacies and drug outlets in the country:	
6.	Total number of registered drugs (incl. all brand names): a. Prescription only: b. Pharmacy sale only: c. General sale:	
7.	Total number of medicines in the National Essential Medicines List:	
8.	What proportion of drugs are sold/obtained in the informal sector:	
9.	Total number of hospitals, health centers and dispensaries: a. Public: b. Private:	
10.	Total no. of different categories of health care providers: a. Doctors (incl. AMOs, COs etc): b. Dentists: c. Pharmacists (incl. technicians and assistants): d. Nurses: e. Others:	

3. Structural Indicators

The structural indicators assess the existence of key PV structures, systems and mechanisms in the setting. The availability of basic infrastructure is required to enable pharmacovigilance operations. They assess the elements which give visibility to PV. They also assess the existence of a policy and regulatory framework which enable PV to operate. The responses are essentially qualitative.

S/N	STRUCTURAL INDICATORS	
1.	Is there legislative provision for pharmacovigilance activities?	Yes❑ No❑
2.	Is there a national policy document on PV?	Yes❑ No❑
3.	Is there any financial arrangement or statutory budget for the PV center/health facility?	Yes❑ No❑
4.	Is the personnel (full time equivalents) disposition in the PV centre/health facility adequate?	Yes❑ No❑
5.	Is there a computer processing facility in the PV center/health facility?	Yes❑ No❑
6.	Is there provision for consumption & prescription data of medicines?	Yes❑ No❑
7.	Are there communication facilities in the PV centre/health facility (telephone, facsimile, e-mail, internet etc)?	Yes❑ No❑
8.	Is there a library with drug safety information sources (primary–tertiary)?	Yes❑ No❑
9.	Is there a Vigiflow data management system?	Yes❑ No❑
10.	Is there a program (incl. a laboratory) for monitoring the quality of pharmaceutical products?	Yes❑ No❑
11.	Is there a newsletter/information bulletin/website as a tool for PV information dissemination?	Yes❑ No❑
12.	Is there a national essential medicines list in use?	Yes❑ No❑
13.	Is there a national standard treatment guideline in use?	Yes❑ No❑
14.	Is PV incorporated into the curriculum of the various health care providers? a. Doctors b. Dentists c. Pharmacists d. Nurses e. Others (specify_____)	 Yes❑ No❑ Yes❑ No❑ Yes❑ No❑ Yes❑ No❑ Yes❑ No❑
15.	Are there ADR reporting forms in the facilities?	Yes❑ No❑
16.	Number of products voluntarily withdrawn by MAH because of safety concerns	

4. Process Indicators

The process indicators assess the entire mechanisms and degree of PV activities. These are measures that assess directly or indirectly the extent to which the system is operating.

S/N	PROCESS INDICATORS	
1.	Total number of ADR reports received in the last year? (also express as no. per 100,000 persons in population	
2.	Number of facilities with a functional PV unit (submitting ≥ 10 reports annually) to TFDA:	
3.	Percentage of total reports sent by the different categories of health care providers? a. Doctors b. Dentists c. Pharmacists d. Nurses e. Patients f. Manufacturers g. Others	
	National Center (TFDA)	
4.	Total number of reports in the national database:	
5.	Total number of reports received per million population per year:	
6.	Average no. of reports per health care provider per year:	
7.	Percentage of health care providers aware and knowledgeable of ADRs per facility:	
8.	Percentage of patients leaving a health facility aware of ADRs in general (and on specific therapy):	
9.	Percentage of health care providers sending reports to the TFDA:	
10.	Percentage of reports issued informative feedback:	
11.	Percentage of satisfactorily completed reports submitted to TFDA:	
12.	Percentage of reports subjected to causality assessment in the preceding year:	
13.	Percentage of reports submitted to TFDA that was committed to UMC database:	
14.	Total number of reports received by the centre in the preceding year:	
15.	No. of trainings conducted on PV during the last 12 months:	
16.	Percentage of health personnel trained on PV during the last 12 months:	
	Manufacturers	
17.	Percentage of registered companies which submitted a comprehensive PSUR to TFDA as stipulated in the guidelines:	
18.	Percentage (& number) of registered products with a well outlined PV plan / risk management plan from manufacturers/MAHs	
19.	Average number of reports per pharmaceutical company per year:	
20.	Percentage of MAHs submitting PSURs:	
21	Percentage of registered manufacturing industries with a functional pharmacovigilance unit	
22	Is there any requirement mandating Marketing Authorization Holders (MAH) to submit PSURs	
	Counterfeit or substandard drugs	
23.	Percentage of medicines that are counterfeit/substandard in the market:	

2.	Number of facilities with a functional PV unit (submitting ≥ 10 reports annually) to TFDA:	
3.	Percentage of total reports sent by the different categories of health care providers? a. Doctors b. Dentists c. Pharmacists d. Nurses e. Patients f. Manufacturers g. Others	
	National Center (TFDA)	
4.	Total number of reports in the national database:	
5.	Total number of reports received per million population per year:	
6.	Average no. of reports per health care provider per year:	
7.	Percentage of health care providers aware and knowledgeable of ADRs per facility:	
8.	Percentage of patients leaving a health facility aware of ADRs in general (and on specific therapy):	
9.	Percentage of health care providers sending reports to the TFDA:	
10.	Percentage of reports issued informative feedback:	
11.	Percentage of satisfactorily completed reports submitted to TFDA:	
12.	Percentage of reports subjected to causality assessment in the preceding year:	
13.	Percentage of reports submitted to TFDA that was committed to UMC database:	
14.	Total number of reports received by the centre in the preceding year:	
15.	No. of trainings conducted on PV during the last 12 months:	
16.	Percentage of health personnel trained on PV during the last 12 months:	
	Manufacturers	
17.	Percentage of registered companies which submitted a comprehensive PSUR to TFDA as stipulated in the guidelines:	
18.	Percentage (& number) of registered products with a well outlined PV plan / risk management plan from manufacturers/MAHs	
19.	Average number of reports per pharmaceutical company per year:	
20.	Percentage of MAHs submitting PSURs:	
21	Percentage of registered manufacturing industries with a functional pharmacovigilance unit	
22	Is there any requirement mandating Marketing Authorization Holders (MAH) to submit PSURs	
	Counterfeit or substandard drugs	
23.	Percentage of medicines that are counterfeit/substandard in the market:	

24.	Percentage reduction of counterfeit/substandard medicines attributed to PV activity:	
	Medication errors	
25.	Number of medication errors reported in the preceding year:	

5. Outcome/Impact Indicators

The outcome and impact indicators measure the effects (results and changes) of PV activities. It measures the extent of realization of the PV objective which in essence is ensuring patient safety. The focus of the impact of PV is definitely on efficient and safe use of medicines.

S/N	**OUTCOME/IMPACT INDICATORS**	
1.	No. of signals generated in last 5 years:	
2.	Percentage of avoidable/preventable adverse reactions reported in the preceding year:	
3.	Number of drug related hospital admissions per 1,000 admissions:	
4.	Number of drug related deaths per 100,000 persons in the population:	
5.	Medicines related deaths per 1,000 persons admitted into hospital (annual):	
6.	Medicines related congenital malformations per 100,000 births (annual):	
7.	Medicines related congenital malformations per 100,000 population (annual):	
8.	Number of medicines associated with congenital malformations (annual):	
9.	Percentage reduction of identified signature diseases:	
10.	Number of regulatory actions taken in the preceding year consequent on pharmacovigilance activities? a. Label changes (variation): b. Safety warnings: c. Drug withdrawals:	
11.	Average cost of treatment of medicines related illness:	
12.	Mean duration of medicines-related hospital stay:	
13.	Average cost of medicines related hospitalization:	
14.	Average work/school days lost due to drug related problems:	
15.	Cost offset attributed to PV activities:	
16.	Health budget impact (annual and serial) attributed to PV activity:	
	Rational use of drugs	
17.	Average no. of medicines per prescription:	
18.	Average no. of prescriptions with medicines exceeding recommended dose:	
19.	Average no. of prescriptions containing medicines with potential for interaction:	

Bibliography

European Union, (2007). *The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use*, Vol. 9A. Brussels.

KPPB, (2009), *Guidelines for the National Pharmacovigilance System in Kenya,* 2nd edition, Kenya Pharmacy and Poisons Board, Ministry of Medical Services and Ministry of Public Health and Sanitation, Nairobi, Kenya.

MoHSS, (2009). *Draft National Guidelines for Medicine Safety Surveillance,* Ministry of Health and Social Services, Windhoek, Namibia

TFDA, (2006). *Guidelines for Monitoring and Reporting Adverse Drug Reactions (ADRs)*, 1st edition, Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania.

TFDA, (2006). *Pharmacovigilance: Training Manual for Health Professionals*, Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania.

TFDA, (2003). *The Tanzania Food, Drugs and Cosmetics Act, No.1, 2003*, Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania.

WHO, (2009), *A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines*, World Health Organization, Geneva, Switzerland.

WHO, (2008), *A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines*, World Health Organization, Geneva, Switzerland.

WHO, (2006), *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool*, the Uppsala Monitoring Center, World Health Organization, Uppsala, Sweden.

WHO, (2004), WHO *Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*, World Health Organization, Geneva, Switzerland.

WHO, (2004). *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for Drug Regulatory Authorities,* WHO/DMP/RGS/98.5, World Health Organization, Geneva, Switzerland.