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Communication to Healthcare Professionals **28 March 2020**

GUIDELINE FOR ADVERSE DRUG REACTIONS (ADRs) REPORTING FOR HEALTHCARE PROFESSIONALS

This document has been prepared to serve as a guideline to healthcare professionals, reporting adverse drug reactions and product quality problems. It represents South African Health Products Regulatory Authority's (SAHPRA's) current thinking on the safety, quality and efficacy of medicines (including vaccines, complementary medicines and old medicines), medical devices and in-vitro diagnostics (IVDs). It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of medicines including vaccines complementary medicines and old medicines and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

Guidelines and ADR Reporting form are available from the SAHPRA website. The ADR reporting form is also available as Appendix B of this document.

First publication released for comment Comments to be send to pvqueries@sahpra.org.za	v1 01 April – 30 June 2020 (commenting period)

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CHIEF EXECUTIVE OFFICER

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ABBREVIATIONS AND ACRONYMS

ADRs	Adverse Drug Reactions
AEFI	Adverse Events Following Immunisation
AIDS	Acquired Immune Deficiency Syndrome
DHCPLs	Dear Healthcare Professional Letters
DoH-PvPHP	Department of Health Pharmacovigilance Centre for Public Health Programmes
DRC	Directorate of Radiation Control
DTC	Drug and Therapeutic Committee
EML	Essential Medicines List
EPI	Extended Programme for Immunisation
HCP	HealthCare Professional
HIV	Human Immunodeficiency virus
ICSR	Individual Case Safety Report
IVD	In vitro diagnostics
NADEMC	National Adverse Drug Event Monitoring Centre
MCC	Medicines Control Council
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OTC	Over the counter
PIDM	Programme for International Drug Monitoring
PHP	Public Health Programmes
SAHPRA	South African Health Products Regulatory Authority
SOP	Standard Operating Procedure
TB	Tuberculosis
UMC	Uppsala Monitoring Centre
WHO	World Health Organisation

1 INTRODUCTION

This guideline is intended to assist healthcare professionals in the participation of very important process of continuous surveillance of safety and efficacy of the health products which are used in their clinical practice. Continuous evaluation of medicines' benefit and harm help to achieve the ultimate goal of safe and effective treatments available to patients.

The guideline is intended to assist healthcare professionals in the reporting of suspected adverse drug reactions (ADRs) associated with the use of all registered health products, including medicines, old medicines, medical devices and in-vitro diagnostics (IVDs).

For the purpose of this guideline:

- the terms "holder of certificate of registration" and "applicant" are used interchangeably;
- the terms "medicine", "drug", "therapeutic agent" and "causative agent" are also used interchangeably;
- the terms "pharmaceutical products", "health product" and "product" are also used interchangeably;
- the terms "adverse drug reaction" and "reaction".

1.1 The South African Health Products Regulatory (SAHPRA)

SAHPRA is an entity of the National Department of Health, created by the South African Government to ensure that the health and well-being of human and animal health is at its core. SAHPRA assumed the roles of both the Medicines Control Council (MCC) as well as the Directorate of Radiation Control (DRC) which were housed at the National Department of Health (NDoH). Subsequently, SAHPRA was constituted as an independent entity that reports to the National Minister of Health through its Board.

SAHPRA is mandated by the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965) as amended, to regulate (i.e. monitor, evaluate, investigate, inspect, register and review) all health products and their use in South Africa.

SAHPRA has also been delegated the task of overseeing radiation control in South Africa. This function is governed by the Hazardous Substances Act (Act 15 of 1973) which aims to protect the public (workers, patients, etc.) against radiation used in both health settings and in industry.

SAHPRA's function is therefore to promote public health and safety by ensuring that all medicines, medical devices and IVDs that are available and used in the South Africa are safe, effective and of good quality and acceptable performance.

1.2 The Pharmacovigilance obligation of the healthcare professional

According to Regulation 40 of Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended:
A healthcare professional, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any:

a) suspected ADRs; or
b) new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.

2 DEFINITIONS

These terms may have other meaning under different context but the meaning that will be used in this guideline will be as defined in this document.

2.1 Abuse of medicine

Abuse of medicine refers to the persistent or sporadic, international excessive use of medicines which is accompanied by harmful physical or psychological effects.

2.2 Adverse Drug Reaction (ADR) or Adverse Reaction

An adverse drug reaction (ADR) means a noxious and unintended response to a medicine, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse or abuse of a medicine. The reaction may be a known side effect of the medicine or vaccine or it may be new and previously unrecognized. ADR can be caused by any therapeutic agent, including prescribed and over the counter (OTC) medicines, vaccines, and complementary medicines, and all of these should be reported.

A reaction, contrary to an event, is characterised by the occurrence of a suspected causal relationship between the medicine and the reaction, as determined by the reporter or a reviewing healthcare professional. The fact that the healthcare professional is making a report serves as an indication that the observed event may be caused by the medicine.

2.3 Adverse Event

Adverse event is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicine, whether considered related to the medicine, or not.

2.4 Causality assessment

Causality assessment is defined as the evaluation of the likelihood that a medicine was the causative agent of an observed adverse drug reaction.

2.5 Complementary medicine

Complementary medicine means any substance or mixture of substances that:

a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by the Authority;
b) is used or purporting to be suitable for use or manufactured or sold for use
   i. in maintaining, complementing or assisting the physical or mental state; or
   ii. to diagnose, treat, mitigate, modify, alleviate, or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state of a human being or animal; and
c) is used:
   i. as a health supplement; or
   ii. in accordance with those disciplines as determined by the Authority.

Complementary medicines include western herbal medicines, traditional Chinese medicines, minerals, vitamins, probiotics, aromatherapy medicines, homeopathy medicines, etc. SAHPRA regulates complementary medicines but there are still medicines that are available on the market that have not as yet been registered.

2.6 Congenital Anomalies

Congenital anomalies are defined as structural and/or functional abnormalities, usually irreversible, that develop/occur during the period of conception and/or embryo-foetal development during one or more trimesters of pregnancy, affecting one or more of the following domains: genetic material, histology, anatomy, organ system, development, growth, differentiation, physiological function and/or metabolic function and/or homeostatic mechanisms which may be identifiable either prenatally and/or at birth or later in life. Congenital anomalies are also known as birth defects, congenital disorders, congenital defects or congenital malformations.

2.7 Consumer

Consumer in relation to healthcare, means a person who uses or is a potential user of health services, as well as their family and caregivers.

2.8 Counterfeit medicine

Counterfeit medicine means a medicine in respect of which a false representation has been made about its contents, identity or source by any means including its labelling and packaging.

2.9 Clinical Trial

A study performed to investigate the safety or efficacy of a medicine. For human medicines, these studies are carried out in human participants.

2.10 Dechallenge

Dechallenge means withdrawal of a medicine from the patient's therapeutic regimen.

- **Negative dechallenge** means continued presence of an adverse experience after withdrawal of the medicine.
- **Positive dechallenge** means partial or complete disappearance of an adverse event after withdrawal of the medicine.

2.11 eReporting

eReporting is a module for VigiFlow® system, that allows for seamless electronic reporting of Individual Case Safety Report (ICSR) directly from the source into VigiFlow® system. It reduces the workload of manual data entry from ADR paper forms into VigiFlow® system.

2.12 Essential Medicines List (EML) Clinical Guide

The EML Clinical Guide is a National Department of Health Mobile Application which contains the Primary Health Care Standard Treatment Guidelines, Hospital Level Adult Guidelines, Tertiary and Quaternary Level EML Recommendations and Essential Medicines List for 2015. It includes an ADR reporting module which is used to report ADRs.

2.13 Healthcare Professional/Provider

Healthcare professional or health care provider means a person providing health services in terms of any law, including in terms of the:

- Allied Health Professions Act, 1982 (Act No. 63 of 1982)
- Health Professions Act, 1982 (Act No. 56 of 1982)
- Nursing Act, 1978 (Act No. 50 of 1978);
- Pharmacy Act, 1974 (Act No. 53 of 1974)
- Dental Technicians Act, 1979 (Act No. 19 of 1979)

2.14 Hypothesis

A hypothesis is an idea which is suggested as a possible explanation for a particular situation or condition, but which has not yet been proved to be correct.

2.15 Holder of a certificate of registration/applicant

Holder of a certificate of registration means a person/company in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality, safety, effectiveness and compliance with the conditions of registration.

2.16 Individual Case Safety Report (ICSR)

Individual Case Safety Report (ICSR) is a document providing the most complete information related to an individual case at a certain point of time. ICSRs are used for reporting suspected adverse reactions to a medicine that occur in a single patient at a specific point in time.

An individual case is the information provided by a primary source to describe suspected adverse reactions related to the administration of one or more medicine to an individual patient at a particular point of time.

2.17 Individual Case Safety Report (ICSR)

Lack of efficacy is defined as failure to produce the expected outcome of which the medicine was indicated for. Lack of efficacy applies to registered medicines, including when used for an unapproved indication.

2.18 Medication error

Medication error is defined as failure in the treatment process that leads to, or has the potential to lead to, harm to the patient and includes:

- prescribing errors;
- dispensing errors;
- medicine preparation error;
- administration error and
- monitoring error.

2.19 Minimum information required for a report

It is information required for a case to be deemed valid for data capturing and it includes the following:

- information about the patient,
- which medicine is suspected to have caused the reaction,
- the reaction that has occurred, and
- information about the reporter. A report may be nullified if it lacks the minimum information.

For further information, required to ensure that the report is clinically meaningful, see point 5.4.1.

2.20 Pharmacovigilance

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (i.e. ADRs). The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health.

2.21 Post marketing surveillance

Post marketing surveillance is the practice of monitoring the safety of a medicine, medical device or IVD after it has been released on the market and is an important part of the science of pharmacovigilance. Medicines are approved/authorized to be used by the public on the basis of clinical trials, which involve relatively small numbers of participants who have been selected for such purpose. Post-marketing surveillance is used to confirm or deny the safety of a medicine after it is used in the general population by large numbers of people who have a wide variety of medical conditions by using approaches such as spontaneous ADR reporting procedures, pregnancy registries, etc.

2.22 Product Quality Problem

Product quality problems include concerns about the quality, authenticity, performance, or safety of any medicine or medical device. Problems with product quality may occur during manufacturing, distribution, or storage and include suspect counterfeit product; product contamination; defective components; poor packaging or product mix-up; questionable stability; medical device malfunctions and labelling concerns.

2.23 Rechallenge

Rechallenge means reintroduction of a product suspected of having caused an adverse event following a positive dechallenge.

- **Negative rechallenge** means failure of the medicine, when reintroduced, to produce signs or symptoms similar to those observed when the medicine was previously introduced.
- **Positive rechallenge** means reoccurrence of similar signs and symptoms upon reintroduction of a medicine.

2.24 Serious Adverse Drug Event or Adverse Drug Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires patient hospitalisation or prolongation of existing hospitalisation;
- results in an abortion, premature delivery, congenital anomaly/birth defects;
- results in persistent or significant disability/incapability; or
- is a medically significant/ important event or reaction.

The term “life-threatening” in the definition of “serious” refers to a reaction/event in which the patient was at risk of death at the time of the reaction/event; it does not refer to an event which, hypothetically, might have caused death if it were more severe. Medical and scientific judgement should be exercised when deciding whether other situations are serious or not. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse. The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious’, which is based on patient/event outcome or action criteria.

2.25 Signal

A signal refers to ‘reported information on a possible causal relationship between an adverse event and a medicine, 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.

2.26 Spontaneous ADR report

A spontaneous report is a communication to a pharmaceutical company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicines, and which does not derive from a study.

2.27 Teratogen

A teratogen is any substance/agent (e.g. medicine) that can harm/damage the sperm, ovum, the conceptus, developing embryo and/or foetus during one or more trimesters of pregnancy, affecting structure and/or function across one or more of the following domains: genetic material, histology, anatomy, organ system development, growth and differentiation, physiological function and/or metabolic function and/or homeostatic mechanisms which may be detectable prenatally, at birth or later in life.

2.28 Unexpected adverse drug reaction

An unexpected adverse drug reaction is one in which the nature, specificity, severity and outcome is not consistent with domestic labelling or holder of registration of certificate or expected from the characteristics of the medicine.

2.29 VigiAccess®

VigiAccess® is a web application that allows the public to access VigiBase® database and retrieve statistical data on the suspected adverse drug reactions of medicines reported to the World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM).

2.30 VigiBase®

VigiBase® is the WHO global database of individual case safety reports (ICSRs). It is developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of WHO and its member countries. It consists of reports of adverse drug reactions to medicines and vaccines received from member countries since 1968. It is updated with incoming case reports on a continuous basis. The purpose is to ensure that early signs of previously unknown medicines-related safety problems are identified as rapidly as possible. Contrary to VigiAccess®, consumers and healthcare professionals do not have access to VigiBase® database.

2.31 VigiFlow®

VigiFlow® is a web-based ICSR management system that is available for use by national pharmacovigilance centres e.g. SAHPRA, of the WHO Programme for International Drug Monitoring. VigiFlow® supports the collection, processing and sharing of data of ICSRs to facilitate effective data analysis.

2.32 Vigilance

Vigilance in relation to a medicine, medical device or IVD, means the continuous monitoring and evaluation of its safety, efficacy and performance profile and the management of any risk throughout its life-cycle.

2.33 VigiLyze®

VigiLyze® is the search and analysis tool used to retrieve global ICSR data from VigiBase® database.

2.34 Uppsala Monitoring Centre (UMC)

UMC is located in Uppsala, Sweden and it is the field name for the WHO Collaborating Centre for International Drug Monitoring. UMC works by collecting, assessing and communicating information from member countries' national pharmacovigilance centres in regard to the benefits, harm, effectiveness and risks of medicines. UMC is responsible for:

- the co-ordination of WHO Programme for International Drug Monitoring and its member countries;
- the collection, assessment and communication of information from member countries about the benefits, harms and risks of medicines and other substances used in medicines to improve patient therapy and public health worldwide;
- collaborating with member countries in the development and practice of the science of pharmacovigilance.

2.35 World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM)

The PIDM was established in 1968, to ensure that evidence about harm to patients was collected from as many sources as possible. This would enable individual countries to be alerted to patterns of harm that were emerging across the world and which might not be evident from their local data alone. The PIDM consists of a group of more than 150 member countries (South Africa became a member in 1992) that share the vision of safer and more effective use of medicines. They work nationally and collaborate internationally to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems. UMC has been responsible for the technical and operational aspects of the programme since 1978.

3 PHARMACOVIGILANCE

3.1 Why is pharmacovigilance and reporting of ADRs important?

When a health product is first registered and made available in South Africa, information about its safety and effectiveness is usually only available from clinical trials. Clinical trials, through different test phases (see Appendix A), provide information about many of the possible adverse events associated with a health product, but do not detect all possible adverse events because they:

- usually do not continue for long enough to detect adverse events that take a long time to develop,
- do not include enough patients to detect adverse events that occur rarely and
- do not include all of the different types of people who might eventually use the product and who might be more vulnerable to some adverse events, such as older people, children, pregnant women or people with other medical conditions.

Rare ADRs, occurring in only a small percentage of cases, after a long period of use or when a medicine interacts with a particular combination of other medicines or conditions, may not be detected during clinical trials. For ADRs that were not discovered during clinical trials to be detected, investigated and communicated, and the appropriate action taken, it is therefore vital that post-marketing pharmacovigilance of all medicines is comprehensive. Effective pharmacovigilance should take into account trends in use, as well as the occurrence of ADRs, enabling more effective advice to be given to those prescribing and using medicines and should ensure better standards of safety and efficacy.

SAHPRA, like other Regulatory Authorities around the world, monitors the safety of health products to contribute to a better understanding of their possible adverse events when they are used outside the controlled conditions of clinical trials. Continuous reporting by health professionals and consumers provide important information for the pharmacovigilance system in South Africa.

3.2 Pharmacovigilance System in South African

In order to prevent undesirable effects in patients due to sub-standard health products and inappropriate or unsafe use of health products, an Adverse Drug Reaction (ADR) monitoring system was established in South Africa in 1987. This system is coordinated by the Regulatory Pharmacovigilance unit of SAHPRA, which consists of the main office in Pretoria and a satellite office, National Adverse Event Drug Monitoring Centre (NADEMC), situated in Cape Town's Groote-Schuur Hospital and attached to University of Cape Town's Clinical Pharmacology Division.

The regulatory pharmacovigilance unit work in collaboration with programmatic units based at NDoH head office in Pretoria. The programmatic units are:

- the Extended Programme for Immunisation (EPI) unit
- the Department of Health Pharmacovigilance Centre for Public Health Programmes (DoH-PvPHP)

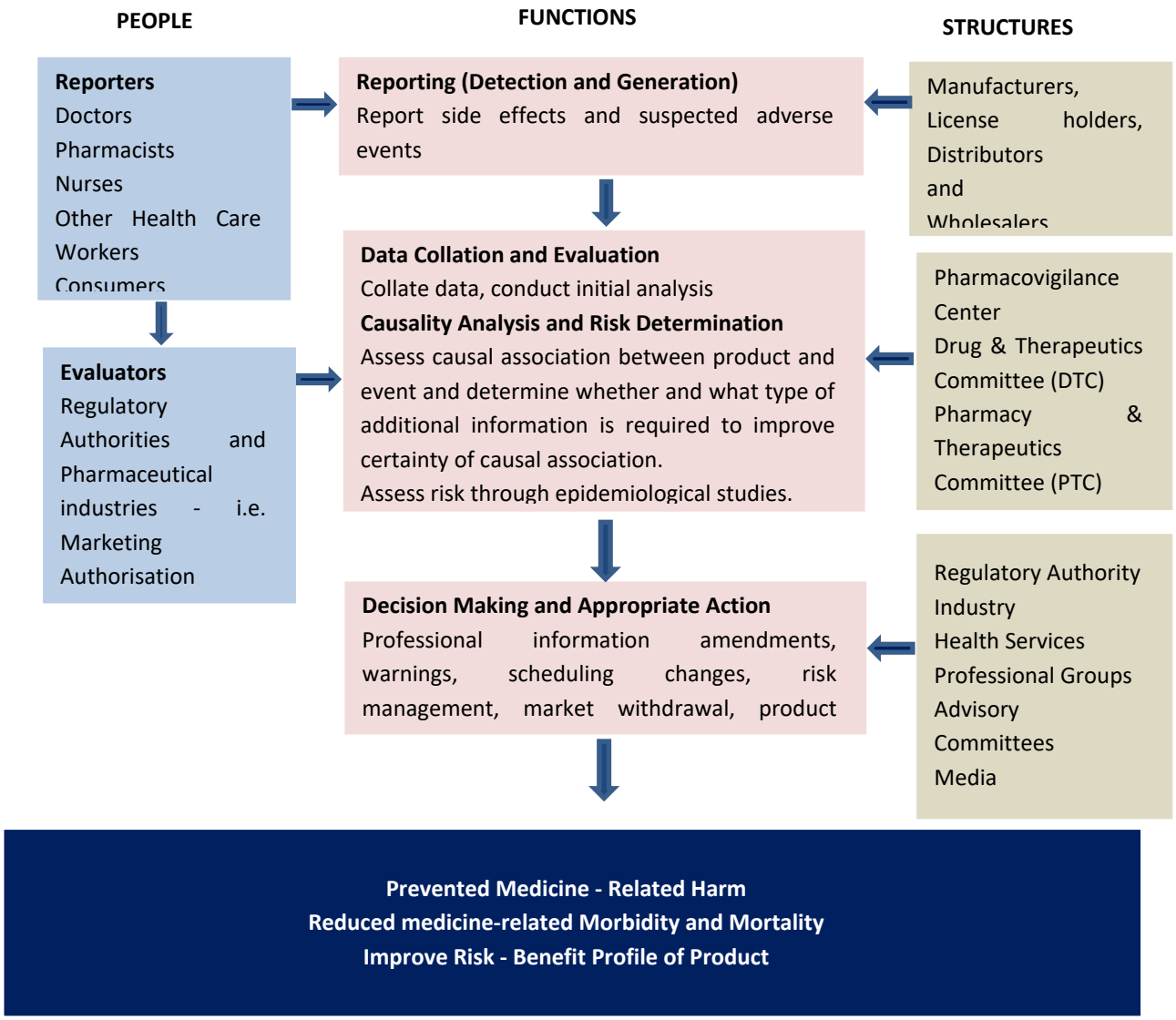
Table 1: Overarching Pharmacovigilance Bodies

Characteristic	**Regulatory**	**Public Health Programmes (PHP)**	
Focal Point	SAHPRA and National Adverse Drug Event Monitoring Centre (NADEMC)	DoH-PvPHP	EPI
Medicines under focus	All medicines available in the country	HIV/AIDS and TB medicines	Vaccines
Objectives	Ensure marketed medicines are safe, effective and of good quality in the interest of the public	Minimise preventable harm and maintain public trust in the programmes and the medicines it employs	
Communication of results and corrective actions	Through regulatory decision-making, market withdrawal, labeling changes, Public Health Advisories, dear healthcare professional letters (DHCPLs), Press Statements and safety alerts	Epidemiological newsletters, press statements, guidelines, training and educational materials, local or international publications, infrastructural changes and changes in conditions of drug use	

The regulatory pharmacovigilance unit's key role is safety-monitoring of all health products available in the South African market. Its core activity is the collection and evaluation of ADR reports submitted by healthcare professionals, consumers and pharmaceutical companies in the country. The ultimate goal of this activity is to contribute to the rational and safe use of medicines and to continuously monitor the risks and benefits of all medicines available at every level of healthcare. Ensuring safety of medicines is the responsibility of all stakeholders involved in medicines chain.

The diagram below indicates different stakeholders involved in pharmacovigilance and their key responsibilities.

Diagram 1: Professional groups/associations and their functions



4. PROCEDURES FOR REPORTING

4.1 How do healthcare professionals identify ADRs?

4.1.1 Obtain patient history and do a proper examination

i. Take a proper history

- A full medical history should be done properly.
- Can this ADR be explained by other causes e.g. patient's underlying disease, other prescription medicine/s, OTC medicines or complementary medicines; toxins or foods?
- It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is. A medicine related cause should be considered, especially when other causes do not explain the patient's condition.

ii. Where necessary, do a thorough physical examination with appropriate laboratory, imaging and other relevant investigations

- Few medicines produce distinctive physical signs (exceptions include fixed drug eruptions, steroid-induced dermal atrophy, acute extrapyramidal reactions);
- Laboratory tests are especially important if the medicine is considered essential in improving patient care or if the laboratory test results will improve management of the patient;
- Try to describe the reaction as clearly as possible and where possible provide an accurate diagnosis or pictures.

4.1.2 Obtain patient history and do a proper examination

- Some reactions occur immediately after being given a medicine while other reactions take time to develop;
- The time from the start of therapy to the time of onset of the suspected reaction must be logical.

4.1.3 Effect of dechallenge and rechallenge should be determined (when necessary)

- Positive dechallenge (partial or complete disappearance of a reaction when dechallenge occurs) is a strong, although not conclusive indication of a medicine induced reaction.
- Rechallenge (reintroducing the medicine after a dechallenge) is justifiable when the benefit of re-introducing the medicine to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases, the reaction may be more severe on repeat exposure.

4.1.4 Where possible, check the known pharmacology of the medicine

- Is the reaction known to occur with the particular medicine as stated in the professional information (previously known as package insert) or other reference?
- If the reaction is not documented in the professional information, it does not mean that the reaction cannot occur with that particular medicine.

4.2 What to report?

ADRs resulting from prescription medicines, (OTC) medicines, complementary medicines and vaccines should be reported. Ideally serious, undocumented and unexpected ADRs are to be reported. If there is any doubt about whether or not an ADR has occurred and should be reported, it is always best practice to submit a report as causality does not need to have been established.

i. ADRs in children

All suspected ADRs occurring in children under the age of 18, should be reported regardless of whether the medicine is registered for use in children.

ii. ADRs in the elderly

Healthcare professionals should be particularly aware that the elderly may be more susceptible to adverse drug reactions and it is therefore important to monitor drug safety in this age group. Many elderly patients are more likely to be taking multiple medicines and may also metabolise them less effectively or be more sensitive to their effects.

iii. ADR reports on lack of efficacy

Lack of efficacy with medicines used for the treatment of life-threatening diseases (e.g. antimicrobial agents), vaccines or contraceptives or other classes of medicines where lack of efficacy could result in serious consequences, require reporting. Normal progression of disease does not imply lack of efficacy. The batch/lot number of the suspected medicine for a report of lack of efficacy must be included in the report.

iv. Complementary medicines

The 'natural' content of complementary medicines means they are often considered to be 'safe' by the public who, along with many professionals, fail to recognise the potential potency of many such products. Patients and healthcare professionals should also be aware that interactions between complementary and other, prescribed or OTC, medicines can also cause unexpected reactions. It is therefore important that any suspected ADR which occurs from a complementary medicine is reported and that as much information about the ingredients and the source of the remedy are included.

v. Delayed drug effects

Some reactions may become manifest months or years after exposure. Any suspicion of such an association should always be reported. Examples of delayed reactions that might need to be reported include:

- kidney disease from long term usage of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs);
- disabling and potentially permanent side effects which involve tendons, muscles, joints, nerves and central nervous system (i.e. tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell) following the use of fluoroquinolone antibiotics.

vi. Interactions

If an adverse effect is suspected to be related to an interaction between two or more medicines, it should be reported as an adverse reaction.

vii. Medication errors

Medication errors, whether resulting in an adverse drug reaction or not, must be reported.

viii. Overdose

Suspected ADRs, associated with an overdose, should be reported, as well as other reactions that may have occurred due to the overdose.

ix. Reports relating to pregnancy and breastfeeding

The healthcare professional must report suspected ADRs related to pregnancy or breastfeeding regardless of whether the medicine is contra-indicated in pregnancy and/or lactation.

x. Serious adverse drug reactions

All serious suspected reactions must be reported. The side effects of an established medicine may be well known but if a serious reaction occurs it should always be reported regardless of whether it is expected or not.

xi. Product quality problem

Healthcare professionals are encouraged to report product quality problems, whether resulting in an adverse drug reaction or not. The batch/lot number of the suspected medicines must be included in the report.

xii. Teratogenicity and congenital anomalies

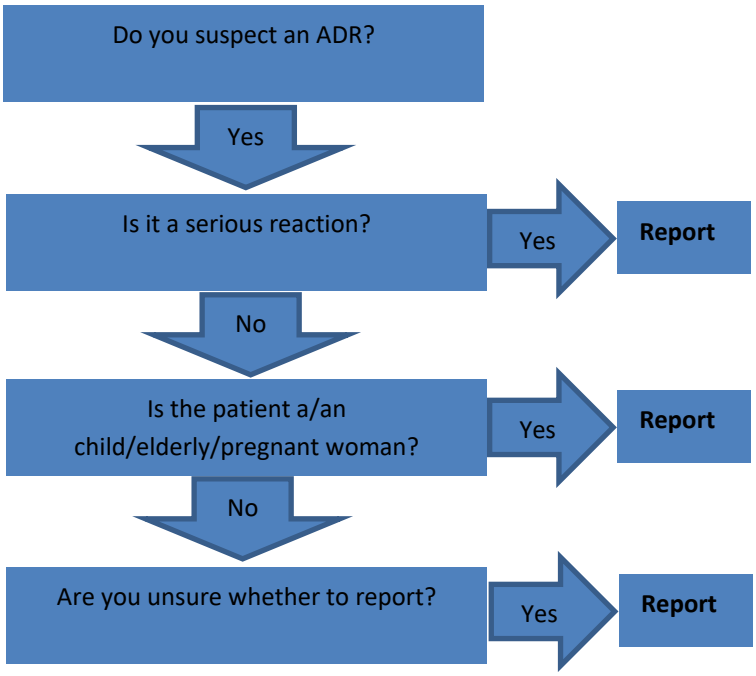
The following information should be provided for reports on congenital anomalies or teratogenicity:

- age and sex of the infant;
- the birth date or the date on which the pregnancy was ended; (duration of pregnancy/gestational age of foetus/baby);
- date and/or duration of exposure to teratogen/substance/medicine in preconception period, and/or any or all trimesters of pregnancy;
- the teratogen/substance(s) or medicine(s) exposed to and the dose in case of a medicine and reason(s) for exposure or treatment with the medicine(s)

- the type of congenital anomaly/malformation/adverse event/ reaction noticed at or after birth, and the seriousness thereof
- whether the congenital anomaly/malformation/adverse event/reaction resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, was a medically significant/important reaction/event or would have persistent and/or significant disability/incapability consequences
- any adverse reactions experienced by the mother must be considered a new initial case report and should be reported separately.

Suspected ADRs should also be reported in cases where a baby is born with a congenital abnormality or where a pregnancy results in a malformed or aborted foetus and the report should include information of all medicines taken during pregnancy.

Diagram 2: Flow diagram to show when an ADR must be reported.



4.3 When to report an ADR?

A healthcare professional must report when they have identified an ADR suspected to have been caused by a medicine(including vaccines and complementary medicines), medical devices and IVDs. Healthcare professionals are encouraged to report suspected ADRs even when they **do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction. However, healthcare professionals should note that even if all the facts are not available at the time of reporting, the minimum information required for a valid case (i.e. information about the patient, suspected medicine, the reaction and information about the reporter) should always be included in the report.**

4.4 How to report?

4.4.1 How to report an ADR?

Reporting of suspected ADRs can be done via the eReporting link available on the SAHPRA website. Alternatively, complete the Adverse Drug Reaction (ADR)/Product Quality Problem Report Form (see Appendix B) available from the SAHPRA website (https://www.sahpra.org.za) and email it to adr@sahpra.org.za. When completing the form, the healthcare professional should include the minimum information required for a case to be deemed valid, which is as follows:

- information about the patient:
  - patient's initials,
  - local identification/ reference number [any number or code that identifies the patient to the reporter, but not to SAHPRA (e.g. hospital number; file number)],
  - gender,
  - age at time of the ADR or date of birth and
  - weight (if known),
- which medicine is suspected to have caused the reaction,
  - name (preferably proprietary name),
  - dose, frequency and route used,
  - therapy date,
  - indication for use,
  - batch/lot number,
  - expiration date,
- the reaction that has occurred,
  - description of the reaction,
  - onset date of the reaction,
  - outcome of the reaction after use of the medicine was stopped or reduced,
  - information about the reaction, in instances where there is repeat exposure of the medicine,
- information about the reporter,
  - name or initials, email address and telephone number,
  - occupation,
  - health institution/facility.

Further information that is required to ensure that the report is clinically meaningful is as follows, but is not limited to:

- concomitant medicines, therapy dates,
- other relevant patient information/ history,
- date of the report and
- relevant tests/laboratory data (if available).

These are important points to consider when reporting an ADR:

- It should be noted that by supplying these anonymised details a healthcare professional will not breach the confidentiality agreement they have with the patient. Although explicit consent from the patient is not required, it is best practice to inform the patient if a report will be submitted.
- Healthcare professionals should submit ALL the relevant information available at the time of initial identification of an ADR, not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data, is encouraged.
- Additional information, not available at the time of the initial report, should be provided when available, as a follow-up report (using the same reference number as the initial report)
- The healthcare professional who initially reported the suspected ADR is required to submit their names or

initials, institution, email address, telephone number and qualifications.

4.4.2 How to report an ADR?

Please refer to the EPI SOP (see Appendix C).

4.4.3 Follow-up reports

Any follow-up information from the healthcare professional relating to an initial ADR report submitted to SAHPRA, must be cross-referenced to the reference number (if applicable) on the initial report. The follow-up report which follows a previous (first) communication to SAHPRA must be clearly marked that it is a follow up. This is the only reliable way to minimise duplication of reports, submitted by reporters, in the VigiFlow® system.

4.5 Who should report ADRs?

All healthcare professionals, including doctors, dentists, pharmacists, nurses and other healthcare professionals are requested to report all suspected adverse reactions to medicines (including vaccines, complementary medicines) particularly serious ADRs and those related to new medicines. Consumers should be encouraged to report all suspected adverse drug reactions to their healthcare provider. It is vital to report an adverse drug reaction to the SAHPRA's Pharmacovigilance unit.

4.6 Where to report?

All healthcare professionals, including doctors, dentists, pharmacists, nurses and other healthcare professionals are requested to report all suspected adverse reactions to medicines (including vaccines, complementary medicines) particularly serious ADRs and those related to new medicines. Consumers should be encouraged to report all suspected adverse drug reactions. It is vital to report an adverse drug reaction to the SAHPRA's Pharmacovigilance unit.

- ADR reports should be sent to SAHPRA, Pretoria office by email: adr@sahpra.org.za; or NADEMC (satellite office of SAHPRA Pharmacovigilance unit) on fax: 021 448 6181 or relevant pharmaceutical company (contact details found on the outer package of the health product).
- Using the mobile app

  How to download the EML Clinical Guide

  - Go to Google Play or App Store
  - Open search function
  - Type EML Clinical Guide and click install

  How to report ADRs using the Mobile App

  - After downloading the EML Clinical Guide
  - Select the tools tab
  - Select report Adverse Drug Reaction tab
  - Report the Adverse Drug Reaction tab has a drop down menu and selection criteria where possible
  - On successful completion, a copy of the report will be sent to the reporter and adr@sahpra.org.za
  - All safety notifications and pharmacovigilance related queries must be sent to pvqueriessahpra.org.za
- Using eReporting link to VigiFlow®
  - Healthcare professionals (and consumers) can report ADR reports through eReporting module (accessible from SAHPRA website) directly into VigiFlow®.
  - eReporting allows for seamless electronic reporting of ADR reports, thus reducing the workload of manual data entry from ADR paper forms into VigiFlow®.

- Pharmacovigilance unit personnel need only to enter a small amount of data, this allows more time for the pharmacovigilance team to verify the coding and to conduct causality assessment of cases of interest.

4.7 What happens next?

Once an ADR report has been received:

- SAHPRA (pharmacovigilance unit) staff capture the anonymised information on to the VigiFlow® system in a structured format;
- VigiFlow® system assigns a unique identification number;
- An acknowledgement letter (which quotes the unique identification number assigned to the report and the local/reference number) is sent to the reporter (provided they submitted their email address).
- The captured information for each report is checked for quality and completeness, before being sent to the global database known as VigiBase®, where it is confidentially stored.

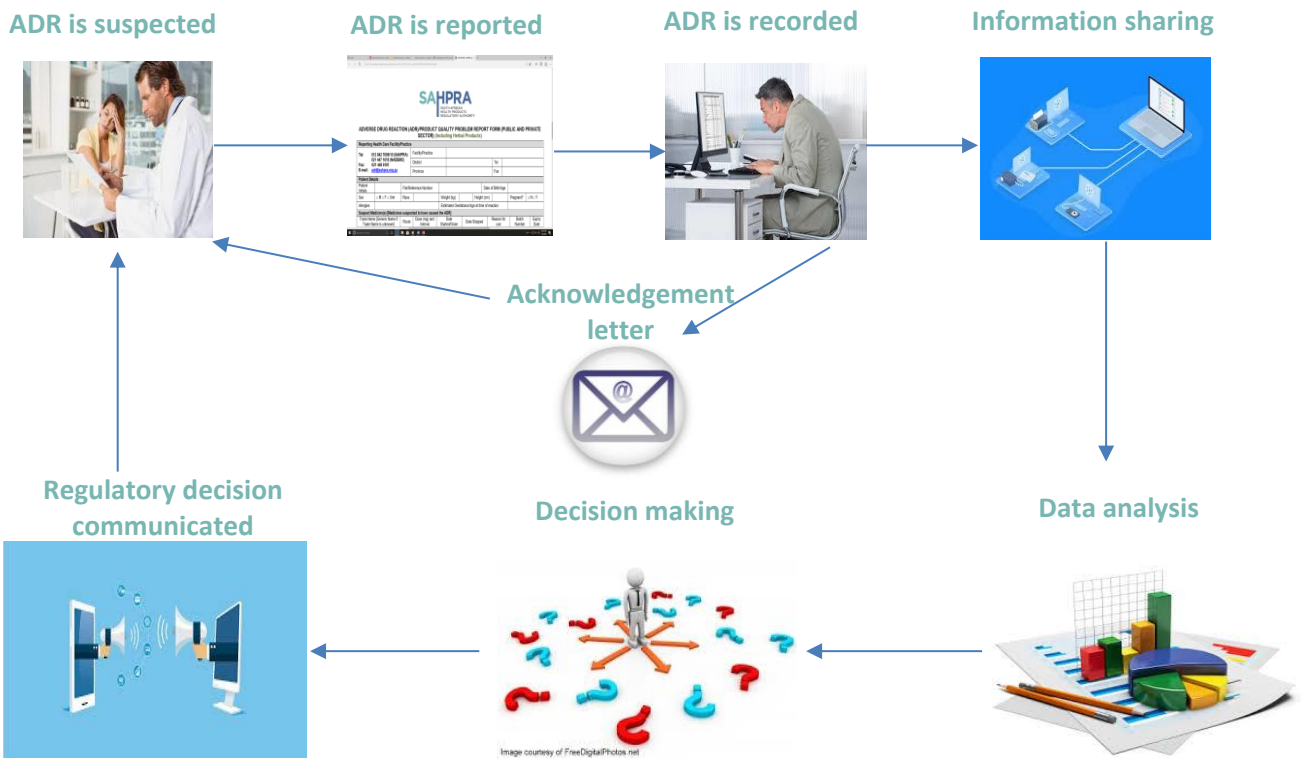
At any point during this process the reporter may be asked by the SAHPRA pharmacovigilance unit to provide clarification or further information about the ADR report. The SAHPRA pharmacovigilance unit personnel, using referenced data from other sources (e.g. case reports in the literature; pre- and post-marketing clinical trials; epidemiological studies; record-linkage databases; data from other drug regulatory authorities), conduct preliminary causality assessment and prepare reports on ADR cases with emerging drug safety problems. The report reviews are then presented to the Pharmacovigilance Advisory Committee (an advisory committee of the Authority) for:

- signal detection;
- causality assessment between medicines and reported reactions and
- identification of possible risk factors contributing to the reaction.

When safety concerns are identified, the overall ADR profile for the medicine is compared with the relevant therapeutic alternatives, and its benefits in terms of efficacy, the therapeutic indication and target patient population(s). The Pharmacovigilance Advisory Committee advise the Authority on drug safety so that regulatory decisions can be made on whether changes in the use of a medicine are needed. Regulatory changes may include:

- product label change;
- product withdrawal/ suspension;
- dear healthcare professional letters (DHCPLs);
- press statements;
- medicines safety alerts;
- product restrictions (up-scheduling, limited packaging, limited prescribers) and
- educational programme.

Diagram 3: Flow diagram: ADR Form Life cycle



5. WHAT HAPPENS TO THE REPORTER?

5.1 Will reporting have any negative consequences on the healthcare profession or the patient?

The adverse drug reaction report does not constitute an admission that the reporter or any other healthcare professional contributed to the adverse drug reaction in any way. The details of the report will be stored confidentially in VigiBase® database. The names of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information obtained from the report will not be used for commercial purposes. The information is only meant to improve our understanding of safety in relation to the use of medicines in South Africa.

5.2 Confidentiality

Strict confidentiality will be maintained by SAHPRA regarding the identities of the patient and the reporter.

6. REFERENCES

1. Board of Science of the British Medical Association. 2006. Reporting Adverse Drug Reactions. A Guide for Healthcare Professionals. BMA Report.
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7. Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa. Version 6
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7. APPENDICES

APPENDIX A: CLINICAL TRIALS PROCESS FOR MEDICINES

Clinical trials for pharmaceutical products are carried out in four phases, only moving from one phase to the next if the previous phase has shown promising results. The four 'ideal' phases are as follows:

- Phase I – the drug is tested on a small number of healthy volunteers to test how it is metabolised, whether it is safe for humans and to find the best way of administering the treatment.
- Phase II – a small number of patients are given the drug to test for side effects, activity and optimum dose, and to start comparing it to the current treatment or a placebo.
- Phase III – the drug is given to a larger group of patients for continued testing of safety and efficacy and to compare it with the current treatment or a placebo. These trials are nearly always randomised.
- Phase IV – this phase occurs once the drug has been licensed and checks for possible long-term side effects of the drug. It is also known as post-marketing surveillance.

APPENDIX B: ADR REPORTING FORM

APPENDIX C: EPI SOP