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Communication to Healthcare Professionals **May 2021**

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, adverse event following immunisations 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. 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 and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

Guidelines and ADR Reporting & Quality Problem Forms are available from the SAHPRA website. The ADR Reporting Form is also available as an Appendix A of this document.

Other guidelines for collecting adverse events relating to medical devices and in vitro diagnostics (IVDs) will be developed at a later stage.

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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
HCR	Holder of Certificate of Registration
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
WEB-RADR	WEB-Recognising Adverse Drug Reactions
WHO	World Health Organisation

1 INTRODUCTION

This guideline is intended to assist healthcare professionals/providers in the participation of very important process of continuous surveillance of safety and efficacy of the medicines, 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/providers in the reporting of suspected adverse drug reactions (ADRs), adverse events following immunisations (AEFIs) and product quality issues associated with the use of medicines.

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 product", "health product" and "product" are also used interchangeably;
- the terms "adverse drug reaction", "reaction" and "adverse event" are used interchangeably;
- the terms "Authority" and "South African Health Products Regulatory Authority" are used interchangeably.

1.1 The South African Health Products Regulatory Authority (SAHPRA)

SAHPRA is a Section 3A public entity that was formed by the South African government to oversee the regulation of all health products, which include medicines, medical devices, in vitro diagnostics (IVDs) and radiation-emitting products used in healthcare and industry. SAHPRA replaced the Medicines Control Council (MCC) as well as the Directorate of Radiation Control (DRC).

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

a) suspected ADRs/AEFIs; 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 definitions below are applicable to the context of this document.

2.1 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 it may be new and previously unrecognized. An ADR can be caused by any therapeutic agent, including prescribed and over the counter (OTC) medicines. All such adverse effects 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/provider. The fact that the healthcare professional/provider is making a report serves as an indication that the observed event may be caused by the medicine.

2.2 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.

2.3 Adverse Event Following Immunisation (AEFI)

An AEFI is defined as any untoward medical occurrence which follows immunisation; does not necessarily have a causal relationship with the usage of the vaccine; may be any unfavourable symptom about which a vaccine recipient complains; and may be an abnormal laboratory finding, sign or disease found by medical staff.

2.4 Adverse Effect

An adverse effect is a negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

2.5 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.

2.6 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

A 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 Drug overdose

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

2.11 Dechallenge

Dechallenge means a withdrawal /reduction in dose 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.

2.12 eReporting

eReporting is a module of the VigiFlow® system that allows for seamless electronic reporting of an individual case safety report (ICSR) directly from the source into the VigiFlow® system. It reduces the workload of manual data entry from ADR paper forms into VigiFlow® system.

2.13 Essential Medicines List (EML) Clinical Guide

The EML Clinical Guide is a National Department of Health Mobile Application (App) which contains the Primary Healthcare 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.

2.14 Healthcare Professional/Provider

Healthcare professional or healthcare 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)

2.15 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.

2.16 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.

2.17 Individual Case Safety Report (ICSR)

ICSR is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.
An individual case safety report is the information provided by a primary source to describe suspected adverse reactions or adverse events following immunisations related to the administration of one or more medicine to an individual patient at a particular point of time.

2.18 In vitro diagnostic (IVD)

IVD means a medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

2.19 Lack of efficacy

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

2.20 Medical device

Medical device means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, including Group III and IV Hazardous Substances contemplated in the Hazardous Substances Act, 1973 (Act 15 of 1973) -

a. intended by the manufacturer to be used, alone or in combination, for humans or animals, for one or more of the following:
   i. diagnosis, prevention, monitoring, treatment or alleviation of disease;
   ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
   iii. investigation, replacement, modification or support of the anatomy or of a physiological process;
   iv. supporting or sustaining life;
   v. control of conception;
   vi. disinfection of medical devices; or
   vii. providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body; and
b. which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on human or animal body, but which may be assisted in its intended function by such means.

2.21 Medication error

Medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including:

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

Medication errors and medicines-related adverse events have important implications – from increased length of hospitalisation and costs to undue discomfort and disability or increased mortality. Thus, minimizing of medication errors, through early detection and clinical audit, is of paramount importance in healthcare by promoting compliance, adherence, recovery and the general well-being of patients.

2.22 Medicine

a. means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in -
   i. the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or
   ii. restoring, correcting or modifying any somatic or psychic or organic function in humans; and

b. includes any veterinary medicine.

2.23 Med Safety App

The Med Safety App is a free smart phone app for reporting of suspected ADRs/AEFIs to Regulatory Authorities and it is developed by the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK MHRA) as part of the Innovative Medicines Initiative WEB-Recognising Adverse Drug Reactions (WEB-RADR) project.

2.24 Misuse of medicine

Misuse of medicine is defined as the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner. This includes patients using a drug for a different condition than that for which the drug is prescribed, patients taking more drug than prescribed or at different dosing intervals, and individuals using a drug not prescribed for them although for therapeutic purposes.

2.25 Minimum information required for a report

It is information required for a case to be deemed meaningful 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 4.4.1.

2.26 Pharmacovigilance

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

2.27 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. It 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 disprove 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.

2.28 Product Quality Problem

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

2.29 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.

2.30 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.

2.31 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.

2.32 Spontaneous ADR report

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

2.33 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.

2.34 Unlisted adverse reaction

An adverse reaction that is not specifically included as a suspected adverse effect in the professional information (previously known as package insert) or other scientific reference. This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the professional information or other scientific reference.

2.35 Uppsala Monitoring Centre (UMC)

UMC is the WHO Collaborating Centre for International Drug Monitoring. UMC works by collecting, assessing and communicating information from member countries' national pharmacovigilance centres concerning the benefits, harm, effectiveness and risks of medicines. UMC is responsible for:

- co-ordination of WHO Programme for International Drug Monitoring and its member countries;
- 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.

2.36 Vaccine

A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease. Vaccines are usually administered through needle injections, but can also be administered by mouth or sprayed into the nose.

2.37 VigiAccess®

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

2.38 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 ADRs/AEFIs to medicines/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/providers do not have access to VigiBase® database.

2.39 VigiFlow®

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

2.40 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.

2.41 VigiLyze®

VigiLyze® is the search and analysis tool used to retrieve global ICSR data from VigiBase® database. Consumers and healthcare professionals/providers do not have access to this tool.

2.42 Web-Recognising Adverse Drug Reactions (WEB-RAIDR) project

Web-RAIDR project, launched in September 2014, sought to utilise the powers of social media and new technologies for pharmacovigilance purposes. The project developed mobile applications (apps) enabling patients, caregivers, and healthcare professionals/providers to report ADRs/AEFIs and receive up-to-date information and news alerts.

2.43 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/AEFIs 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 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/AEFIs, 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/AEFIs 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/AEFIs, 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/providers and consumers provides important information for the pharmacovigilance system in South Africa.

3.2 Pharmacovigilance System in South Africa

In order to prevent undesirable effects in patients due to sub-standard health products and inappropriate or unsafe use of health products, an ADR/AEFI 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 the University of Cape Town's Clinical Pharmacology Division.

The regulatory pharmacovigilance unit works 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

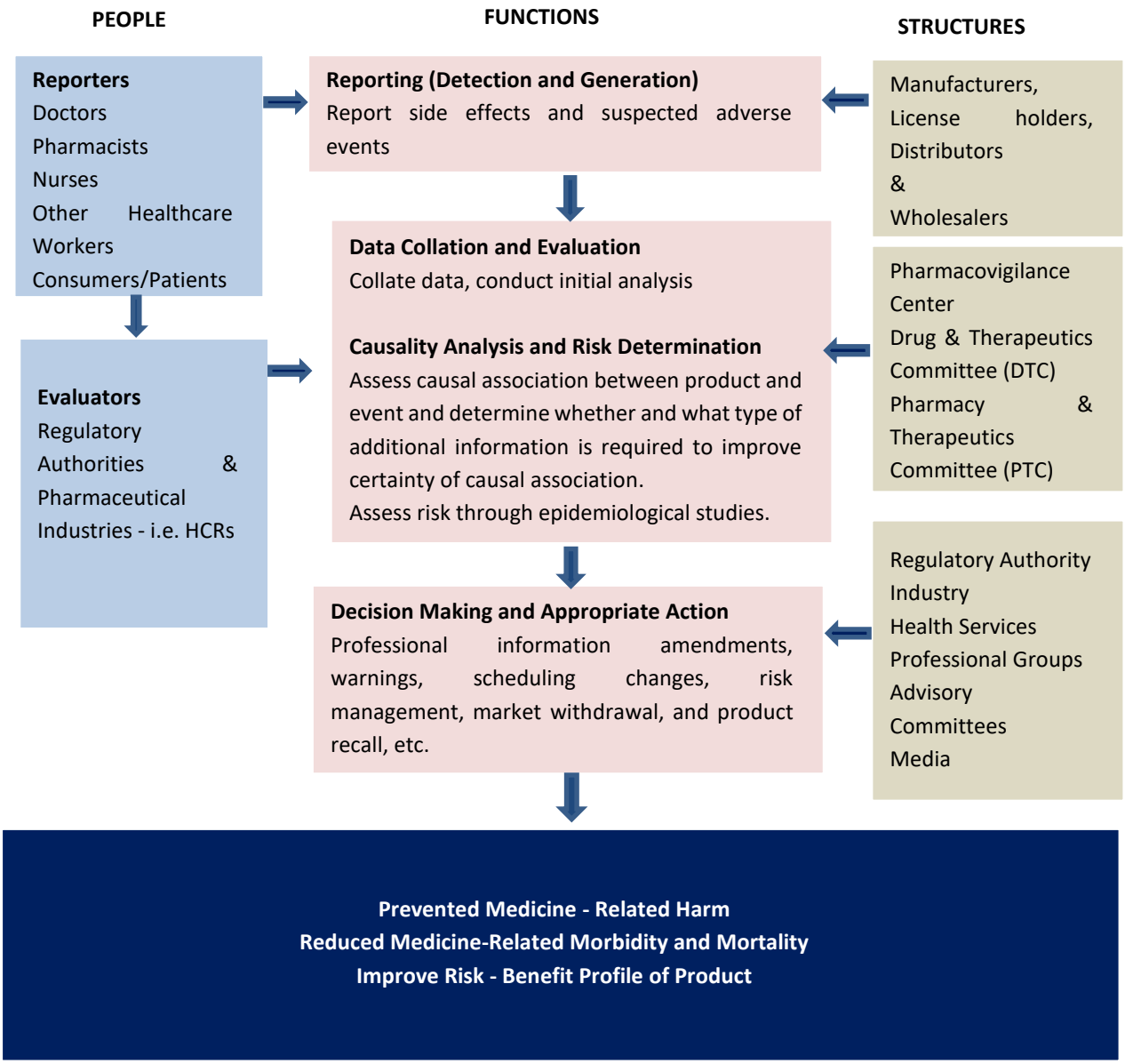
Characteristic	Regulatory	Public Health Programmes (PHP)		Manufacturer/HCR
Focal Point	SAHPRA and National Adverse Drug Event Monitoring Centre (NADEMC)	DoH-PvPHP	EPI	Company Pharmacovigilance Programme
Medicines under focus	All medicines available in the country	HIV/AIDS and TB medicines	Vaccines	All medicines registered or authorised for marketing by the particular company.
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		Ensure marketed medicines are safe, effective and of good quality as per product conditions of registration. Minimise preventable harm and maintain public safety with the medicines marketed.
Communication of results and corrective actions	Through regulatory decision-making, market withdrawal, labelling changes, Public Health Advisories, dear healthcare professional letters (DHCPLs), Press Statements and medicines safety alerts	Epidemiological newsletters, press statements, guidelines, training and educational materials, local or international publications, infrastructural changes and changes in conditions of drug use		Through reporting to the Authority, decision-making, labelling and professional information changes, market withdrawal, dear healthcare professional letters (DHCPLs), guidelines, training and educational materials, local or international publications.

Developed by Dr Ushma Mehta

The regulatory pharmacovigilance unit's key role is safety-monitoring of all medicines available in the South African market. Its core activity is the collection and evaluation of ADR/AEFI reports submitted by HCRs, healthcare professionals/providers and consumers 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 the 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/providers identify ADRs/AEFIs?

4.1.1 Obtain patient history and perform an appropriate examination

i. Take a proper history

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

ii. Where necessary, perform 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;
- Describe the reaction as clearly as possible. Where possible provide an accurate diagnosis and/or supply pictures.

4.1.2 Obtain patient history and perform an appropriate examination

- Some reactions occur immediately after a medicine is administered 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 is instituted) 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 or other scientific 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 or OTC medicines should be reported. All ADRs/AEFIs should be reported. Most importantly serious, undocumented and unexpected ADRs/AEFIs are to be reported. If there is any doubt about whether the ADR/AEFI 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/AEFIs occurring in children under the age of 18, should be reported regardless of whether the medicine is registered for use in children.

ii. ADRs/AEFIs in the elderly

Healthcare professionals/providers should be particularly aware that the elderly may be more susceptible to ADRs/AEFIs. It is therefore important to monitor drug safety in this age group. 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 for medicines used in 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. 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.

v. 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.

vi. Medication errors

Medication errors, whether resulting in an adverse drug reaction, adverse event following immunisation or not, should be reported.

vii. Overdose

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

viii. Reports relating to pregnancy and breastfeeding

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

ix. Serious adverse drug reactions

All serious suspected reactions should 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.

x. Product quality problem

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

xi. 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. The report should include details of all medicines taken during pregnancy.

4.3 When to report an ADR/AEFI?

A healthcare professional/provider should report when they have identified an ADR/AEFI suspected to have been caused by a medicine. Healthcare professionals/providers are encouraged to report suspected ADRs/AEFIs even when they **do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction. Healthcare professionals should note that even if all the facts are not available at the time of reporting, the minimum information required for a meaningful case (i.e. information about the patient, suspected medicine, the reaction and information about the reporter) should always be included in the report. However, it is important that healthcare professionals/providers make every effort to ensure that all facts are included in the report to provide a meaningful assessment of the report.**

4.4 Information to consider when reporting?

4.4.1 What to consider?

When completing the form, the healthcare professional/provider should include the minimum information required for a case to be deemed meaningful, 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/AEFI 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 note when reporting an ADR/AEFI:

- It should be noted that by supplying these anonymised details a healthcare professional/provider 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/providers should submit ALL the relevant information available at the time of initial identification of an ADR/AEFI, 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/provider 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 AEFI?

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

4.4.3 Follow-up reports

Any follow-up information from the healthcare professional/provider relating to an initial ADR report submitted to SAHPRA, should 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 should 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/AEFIs?

All healthcare professionals/providers, including doctors, dentists, pharmacists, nurses and other healthcare professionals/providers are requested to report all suspected adverse reactions/adverse event following immunisation particularly serious ADRs/AEFIs and those related to new medicines. Consumers should be encouraged to report all suspected ADRs/AEFIs preferably via their healthcare professionals/providers.

4.6 How to report?

All ADRs should be reported to SAHPRA's Pharmacovigilance unit through one of the channels stipulated below:

4.6.1 Med Safety App:

It is the preferred tool for reporting suspected ADRs

WHERE TO FIND MED SAFETY APP?

The Med Safety App is available for download from:

- App store (For iOS devices)
- Google Play (For Android devices).

HOW TO DOWNLOAD THE MED SAFETY APP:

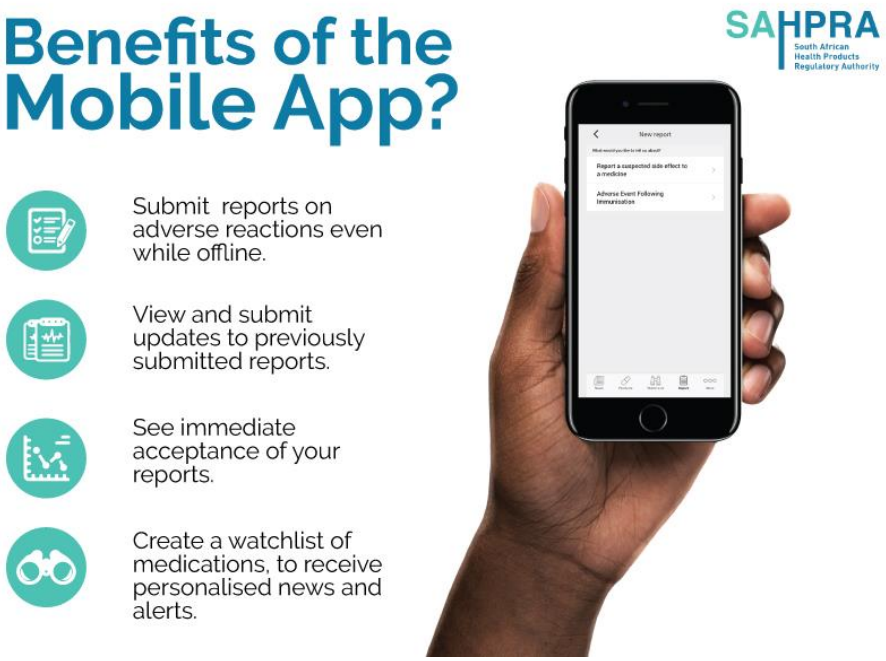
- Open the Play Store (Android) or the App Store (IOS)
- Search for *Med Safety* icon
- Tap the *Med Safety* icon
- Tap to *install* to the download the App
- Tap *Open*
- Select a region, in this case South Africa. Sometimes it selects automatically depending on the settings you already have on your phone
- Click *continue as guest* or *create an account*
- Report ADRs and/or product quality problems

Upon successful submission of the report, a message is displayed on the app to confirm submission and an email acknowledgement is sent to the reporter. For more information about the Med Safety App, please visit the WEB-RADR website at https://web-radr.eu/.

WHY USE MED SAFETY APP?

The WEB-RADR App provides a number of benefits:

- The App facilitate reporting of ADRs by the **public** and **healthcare practitioners.**
- The app provides feedback to reporters on a platform that is readily available to reporters.
- Users are able to create watch list which enables users to view information that is relevant to them by following products of interest.
- The user can change the language within the app, and the language is automatically adapted to that to which the device is configured
- The WEB-RADR app is compatible with the latest iOS and Android operating systems.



4.6.2 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.

4.6.3 Using the EML Clinical Guide mobile app

HOW TO DOWNLOAD THE EML CLINICAL GUIDE MOBILE APP

- 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
- Confirm that 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

4.6.4 Adverse Drug Reactions & Quality Problem Reporting Form

ADR reports should be sent to SAHPRA, Pretoria office by email: adr@sahpra.org.za; or to relevant pharmaceutical company (contact details found on the outer package of the health product).

4.7 What happens after reporting?

Once an ADR/AEFI report has been received:

- SAHPRA (Pharmacovigilance unit) staff capture the information on to the VigiFlow® system in a structured

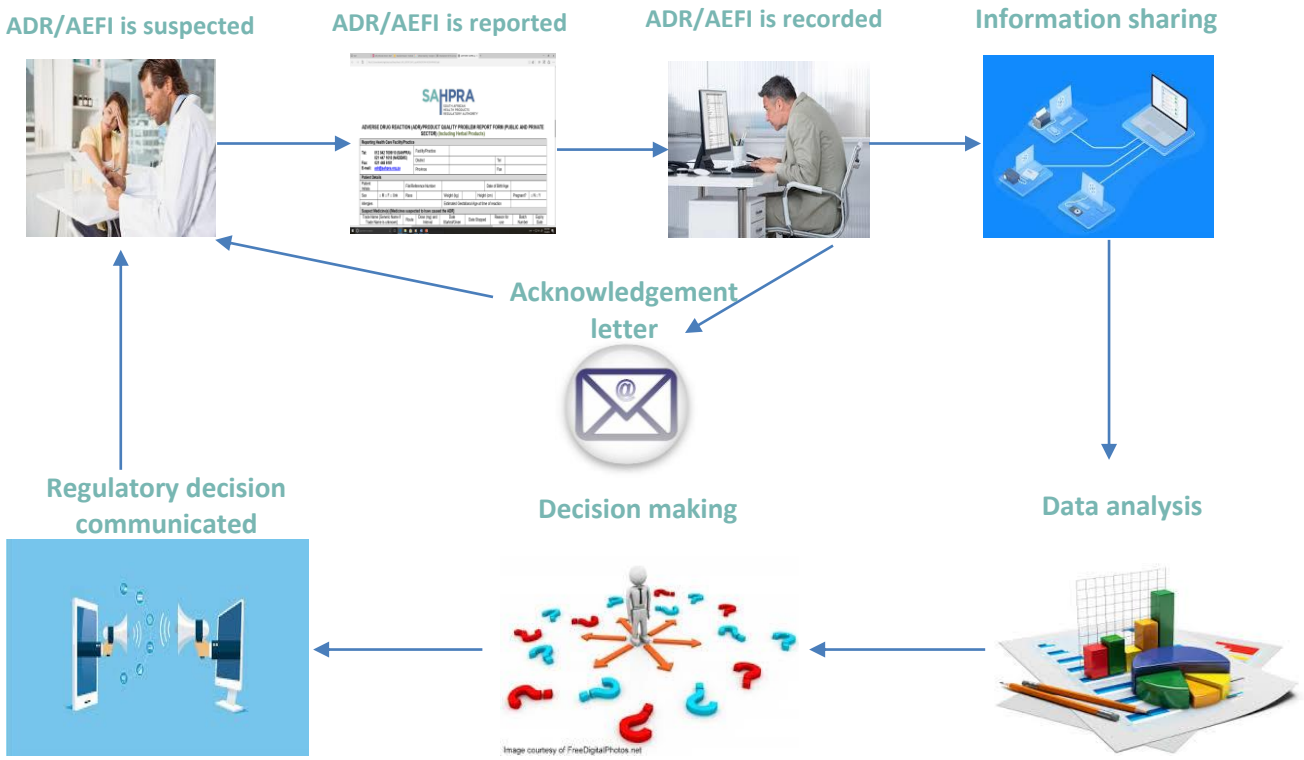
format;
- VigiFlow® system assigns a unique identification number;
- An acknowledgement letter (which quotes the unique identification number assigned to the report and the local/reference number) is sent to the reporter (provided they submitted their email address).
- The captured information for each 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 SAHPRA Pharmacovigilance unit to provide clarification or further information about the ADR report. 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
- an educational programme.

Following consideration of the advice provided by the Pharmacovigilance Advisory Committee, the Authority engage with industry to alert the HCRs about safety concerns related to their products and communicate regulatory decisions related to products implicated as suspect medicines to ADRs.

Diagram 2: Flow diagram: ADR Form Life cycle



5. WHAT HAPPENS TO THE REPORTER?

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

The ADR report does not constitute an admission that the reporter or any other healthcare professional contributed to the ADR 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 ADR 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

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7. APPENDICES

APPENDIX A: ADR REPORTING FORM

Adverse drug reaction ***ARF 1***

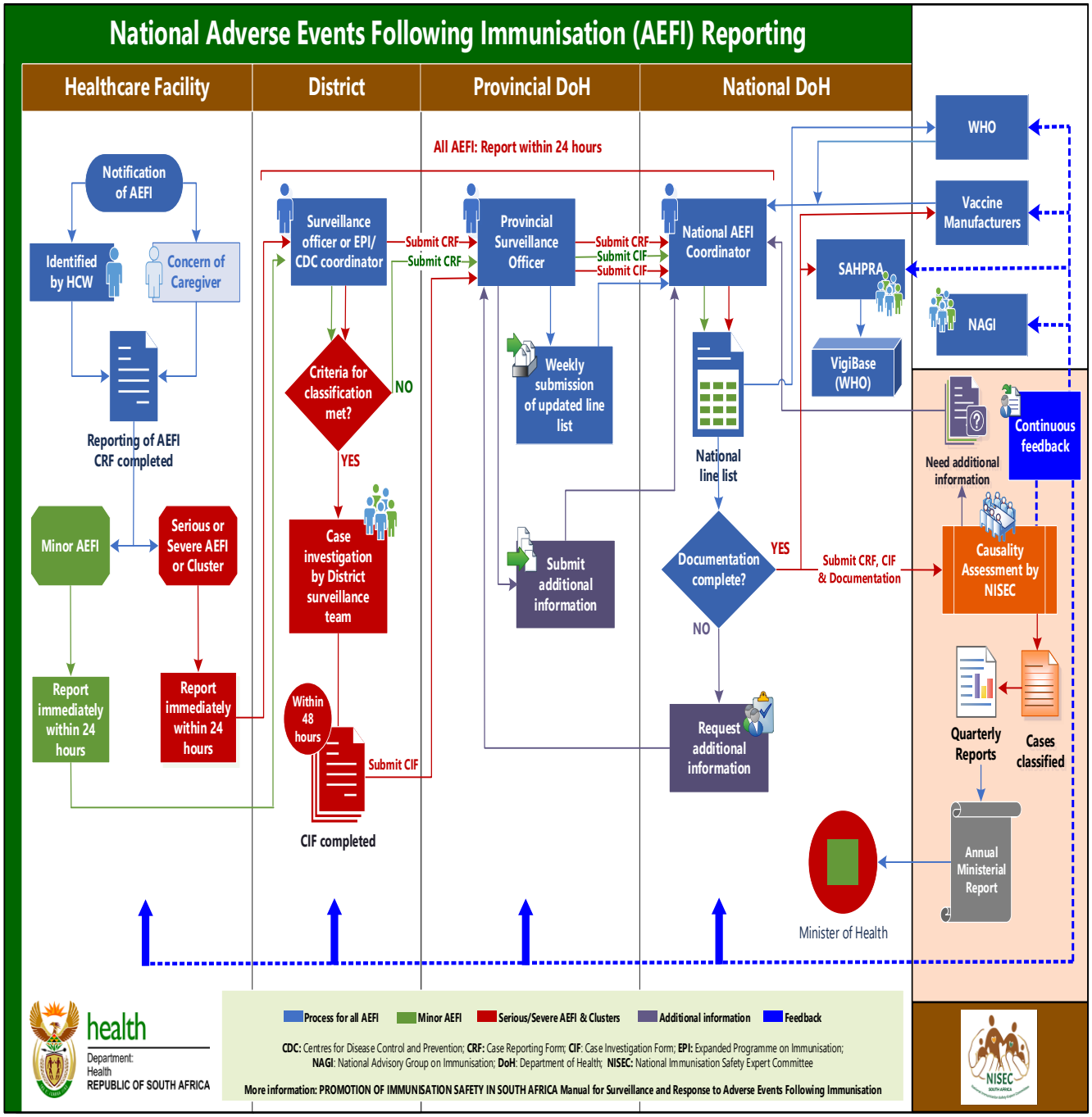
SAHPRA South African Health Products Regulatory Authority

ADVERSE DRUG REACTIONS & QUALITY PROBLEM REPORTING FORM

Version 1: Released for implementation	May 2003
Version 2: Released for implementation	November 2004
Version 3: Updated contact details	April 2011
Version 4: New form	April 2017
Version 5:Updated contact details and SAHPRA logo	May 2019
Version 5.1: Updated SAHPRA logo	January 2020
Version 5.2: Updated contact details	January 2021
Version 5.3: Alternative reporting tool (Med Safety App)	April 2021

The ADR & quality problem reporting form is available on the SAHPRA website at:

https://www.sahpra.org.za/wp-content/uploads/2021/04/6.04_ARF1_v5.3_April2021-addition_of_Med_Safety_App.pdf

APPENDIX B:

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