THE NATIONAL VIGILANCE POLICY FOR HEALTH TECHNOLOGIES IN SOUTH AFRICA

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# ABBREVIATIONS AND ACRONYMS

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ADRI</td>
<td>Adverse Drug Reaction Information System</td>
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<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>CEM</td>
<td>Cohort Event Monitoring</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>DAIDS</td>
<td>Division of AIDS Causality Assessment</td>
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<tr>
<td>DHCP</td>
<td>Dear Health Care Professional</td>
</tr>
<tr>
<td>DUS</td>
<td>Drug Utilisation Study</td>
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<tr>
<td>EML</td>
<td>Essential Medicines List</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunisation</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>HCR</td>
<td>Holder of Certificate of Registration</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
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<tr>
<td>ICSR</td>
<td>Individual Case Safety Report</td>
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<tr>
<td>IVD</td>
<td><em>In Vitro</em> Diagnostics</td>
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<tr>
<td>MAH</td>
<td>Market Authorisation Holder</td>
</tr>
<tr>
<td>MCC</td>
<td>Medicines Control Council</td>
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<tr>
<td>NADEMTC</td>
<td>National Adverse Drug Event Monitoring Centre</td>
</tr>
<tr>
<td>NDoH</td>
<td>National Department of Health</td>
</tr>
<tr>
<td>NISEC</td>
<td>National Immunisation Safety Expert Committee</td>
</tr>
<tr>
<td>OHSC</td>
<td>Office of Health Standards Compliance</td>
</tr>
<tr>
<td>PBRER</td>
<td>Periodic Benefit Risk Evaluation Report</td>
</tr>
<tr>
<td>PEM</td>
<td>Prescription Event Monitoring</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>PVC</td>
<td>Pharmacovigilance Committee</td>
</tr>
<tr>
<td>RA</td>
<td>Regulatory Authority</td>
</tr>
</tbody>
</table>
RMP  Risk Management Plan
SAE  Serious Adverse Event
SAHPRA  South African Health Products Regulatory Authority
SSFFC  Substandard, Spurious, Falsely Labelled, Falsified and Counterfeit
TSR  Targeted Spontaneous Reporting
UMC  Uppsala Monitoring Centre
WHO  World Health Organisation
WHO-PIDM  WHO Programme for International Drug Monitoring
GLOSSARY / DEFINITION OF TERMS

The definitions given below apply to the terms used in this policy. They may have different meanings in other contexts.

**Adverse Event:** Any untoward medical occurrence that may present during treatment with a health product, but which does not necessarily have a causal relationship with this treatment.

**Adverse event following immunization (AEFI):** Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding symptom or disease.

**Adverse Drug Reaction (ADR):** A response to a medicine which is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

**Applicant:** The person by, or on whose behalf, an application for regulatory review of a health product is made to the Authority.

**Causal Relationship:** A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance: a medicine causing an adverse reaction.

**Causality Assessment:** The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction.

**CIOMS:** Council for International Organizations of Medical Sciences. CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. CIOMS represents a substantial proportion of the biomedical scientific community through its member organizations, which include many of the biomedical disciplines, national academies of sciences and medical research councils.

**Cohort Event Monitoring (CEM):** A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time.

**Counterfeit Medicine:** Medicines that are deliberately and fraudulently mislabeled with respect to identity and/or source.

**DAIDS Causality Assessment:** The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events consists of parameters, or Adverse Events (AEs), with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs.
Data Mining: A general term for computerized extraction of potentially interesting patterns from large data sets, often based on statistical algorithms.

Dechallenge: The withdrawal of a medicine from a patient; the point at which the continuation, reduction or disappearance of adverse effects may be observed.

Incident: A health event which is believed to be incidental to the taking of a particular medicine.

Individual Case Safety Report (ICSR): A report that contains information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient.

Information Component (IC): A measure of the disproportionality in the reporting of a medicine–ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the medicine and the ADR. Positive IC values indicate higher reporting than expected.

Marketing Authorization Holders (MAHs): The holder of a marketing authorization to market a medicinal product.

Medical Dictionary for Regulatory Activities (MedDRA): Medical terminology developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with an emphasis on ease of use for data entry, retrieval, analysis and display.

Medication Error: An error which occurs during the prescribing, dispensing and/or use of a medication.

Medicine: Any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in the diagnosis, treatment, mitigation or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or restoring, correcting or modifying any physical, mental or organic function in man or in animals.

Periodic Safety Update Report (PSUR): A periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined times post marketing authorization applicable.

Periodic Benefit Risk Evaluation Reports (PBRERs): PBRERs are to be submitted to the competent authority as part of the new chemical entity application for registration in line with its risk management plan where applicable.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem.

National Pharmacovigilance Centre: Refers to the Pharmacovigilance unit of SAHPRA.
Post-Marketing Surveillance (PMS): The practice of monitoring safety and effectiveness of pharmaceutical products or other consumable medical products after it has been released on the market with the objectives to decrease mortality and morbidity associated with adverse events and improving understanding of effectiveness in real-world situations.

Rechallenge: To try a therapeutic pharmaceutical drug, suspected allergen, or medical treatment on a patient a second or subsequent time, to see if the suspected effects of the treatment occur again. This is typically performed to confirm allergic or adverse reactions to allergens or medications, but may also be used to confirm beneficial treatments or to retry a probable beneficial treatment which did not appear to be effective previously.

Reporter: Any person, patient or healthcare professional or institute who describes a suspected adverse effect on an ADR or ICSR form for submission to the National Pharmacovigilance Centre or any other relevant organisation for further consideration.

Serious Adverse Event: A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is life-threatening.

Side Effect: Any unintended effect of a medicine occurring at normal dosage which is related to the pharmacological properties of the medicine.

Signal: 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 on the seriousness of the event and the quality of the information.
PART 1

VIGILANCE POLICY AND LEGAL FRAMEWORK FOR VIGILANCE OF HEALTH TECHNOLOGIES IN SOUTH AFRICA
1.1 INTRODUCTION

The South African National Vigilance Policy for Health Technologies framework serves as a guidance for health technology-related vigilance activities in the country. Vigilance activities are centrally coordinated by the South African Health Products Regulatory Authority (SAHPRA), in collaboration with National Department of Health (NDoH), and all key stakeholders both in the public and private health sector, including the pharmaceutical industry. This document also serves as a tool for providing an enabling environment for effective planning, implementation, monitoring and evaluation of the vigilance system by all key stakeholders. Issues related to the systems and structures required for post-authorization monitoring of safety and effectiveness of all health products in South Africa (SA) are also addressed in this document.

If successfully implemented, the SA vigilance system will lead to early detection of health technology-related adverse reactions, interactions and other medicine-related problems, as well as detection of previously unknown adverse reactions (signals). Furthermore, the system ensures communication of changes in risk/benefit balance of health products to stakeholders with a view of promoting patient safety including rational and safe use of medicines, vaccines, medical devices, *In Vitro* Diagnostics (IVDs) and complementary medicines.

1.1.1 Purpose

The National Vigilance Policy for health technologies in SA guides healthcare providers and patients in the operations of the Republic’s vigilance system. The primary purpose of this document is to provide guidance to healthcare providers and patients in the post-marketing surveillance of medicines and other health technologies, both in the private and public sectors, thereby contributing to the regulatory objective of ensuring that health products used in clinical practice and domestic settings are safe, effective and of acceptable quality and performance.

The document gives an overview of what health technology vigilance is, how to detect and classify adverse drug reactions (ADRs) and the structural organization of the vigilance system in SA. It also describes the reporting procedures and protocols to SAHPRA, as mandated by the Medicines and Related Substances Act 101 of 1965 (as amended) to oversee the safety, efficacy, quality and performance of health products in SA and the expected post-reporting outcomes.

The document also encourages all healthcare providers and patients to participate in vigilance-related activities and to report all suspected ADRs and other health technology-related events to help safeguard the health of all South Africans.

1.1.2 Legal framework of Vigilance in South Africa

SAHPRA was established following the promulgation of the Medicines and Related Substance Amendment Act No. 72 of 2008 and Act 14 of 2015. SAHPRA replaced the Medicines Control Council (MCC), and has the broad legislative mandate of monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, scheduled substances, clinical trials, medical devices and related matters in the public interest.
In order to achieve its objectives the Authority must, among other and equally important objectives:

- Ensure that evidence of existing and new adverse events and reactions, interactions, and signals emerging from post-marketing surveillance and vigilance activities are investigated, monitored, analyzed and acted upon through an effective vigilance system.

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

According to Regulation 40 of the Medicines and Related Substances Act 101 of 1965, as amended:

(1) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C(1)(b) must inform the Authority, in the manner and within the time frame as determined by the Authority, of any –

- (a) new or existing quality, safety or effectiveness concerns related to any medicine or scheduled substance, including but not limited to adverse drug reactions; and
- (b) risk management activities associated with paragraph (a).

(2) A person who has applied for registration of a medicine in terms of section 15 of the Act, a holder of a certificate of registration in respect of a medicine or Scheduled substance, or a holder of a licence in terms of section 22C(1)(b) must maintain or have access to records of the reports and case reports referred to in subregulation (1) above.

(3) A healthcare provider, veterinarian or any other person should inform the Authority, in the manner as determined by the Authority, of any-

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

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

- Allied Health Professions Act 63 of 1982
- Health Professions Act 56 of 1982
- Nursing Act 50 of 1978
- Pharmacy Act 53 of 1974
- Dental Technicians Act 19 of 1979
1.1.3 Background of vigilance in South Africa

Pharmacovigilance started formally in 1987 at University of Cape Town as the National Adverse Drug Events Monitoring Centre (NADEMC). The unit was later adopted by NDoH, which resulted with the start of pharmacovigilance activities at a national level in SA. Due to the existing sanctions placed on SA to its then apartheid policies, membership to the World Health Organisation Programme for International Drug Monitoring (WHO-PIDM) was denied at that time. Following the release of Nelson Mandela in 1990 and the first lifting of sanctions in 1991, a way was paved for membership to the WHO PIDM.

In 1992, SA became the first African country to be a full member of the WHO PIDM. In accordance with an agreement between the WHO and the Government of Sweden, the WHO Headquarters maintains responsibility for policy issues on drug monitoring, while the operational responsibility rests with the Uppsala Monitoring Centre (UMC). The UMC is an independent organisation, established in 1978, that operates under WHO principles to detect and analyse ADR signals in case reports submitted by member countries, facilitate information exchange between the WHO and national ADR centres such as SAHPRA, conduct pharmacovigilance research, develop training tools and software and publish pharmacovigilance information.

In 1998, the adverse event following immunization (AEFI) targeted spontaneous reporting (TSR) system for the expanded programme for immunization (EPI) was established. The AEFI unit started having working relations with NADEMC until to date.

In 2003, the Pharmacovigilance Committee (PVC), an advisory committee to SAHPRA; then Medicines Control Council (MCC) was established. The main responsibility of the PVC is to advise SAHPRA on post-marketing safety issues related to medicines. Following the establishment of the Committee, the ADR reporting guidelines for the pharmaceutical industry was developed. The guidelines aimed to improve the quality and quantity of reports.

In the same year, the national antiretroviral (ARV) treatment programme was launched. With the ARV, strengthening of the national spontaneous reporting system became vital and resulted with the implementation of Targeted Spontaneous reporting system for ADRs associated with ARV use.

In 2011, the South African National department of Health’s programmatic pharmacovigilance unit reported on its decentralized system, a TSR system for ARVs and TB medicines aimed at improving ARV and TB medicine use.

In 2012, Nevirapine (NVP)-induced ADRs resulted in maternal deaths, which led to the change of first-line ARVs in pregnant women from NVP to efavirenz (EFV)-based regimens. Safety of ARVs in pregnancy raised serious concerns, which prompted the national pregnancy exposure registry and birth defect surveillance system to be piloted in Kwa-Zulu-Natal province. The intension of this registry was to monitor the safety all medicines used during pregnancy.

In 2017, the National Immunisation Safety Expert Committee (NISEC) was established following the recommendation by the PVC. NISEC is a Ministerial Advisory Committee with a critical role in confirming the causality assessments of
selected AEFI investigations and in determining causality when this has not been established with confidence by the investigator.

1.2. GUIDING PRINCIPLES OF THE NATIONAL VIGILANCE POLICY

The policy is based on the following guiding principles:

- Good quality healthcare is assured through application of vigilance principles and practice in private and public healthcare systems at all levels in order to ensure patient safety.
- Patients' access to safe and rational use of medicines, biologicals, vaccines and medical devices.
- Healthcare providers are to consider vigilance practice as a professional responsibility.
- Integration of vigilance into the overall health system for both public and private.
- Existence of consistent and effective partnerships and collaboration with all stakeholders involved in vigilance.
- Existence of financial commitment at all levels for sustained safety monitoring of medicines, medical devices, and other medicine related issues.
- Use of current WHO and International Council for Harmonisation (ICH) guidelines for different types of methods of vigilance activities including causality assessment and pharmacovigilance training tools.
- The vigilance unit of the Authority is working in close collaboration with the WHO-PIDM including submitting Individual Case Safety Reports (ICSR) to the VigiBase® database.
- The vigilance unit of the Authority collect patient ADRs in an ethical and confidential manner, analyse and communicate the information in a way that improves therapeutics and patient safety through the use of bulletins, media releases, circulars, dear healthcare providers’ letters, and publications of medicines safety alerts in medical journals.
- Inclusion of vigilance training curriculum and modules at academic institutions for both undergraduate and postgraduate biomedical degrees, medicine, pharmacy, nursing, physiotherapy and occupational health training programs using the WHO vigilance toolkit.

1.3 VIGILANCE SYSTEM IN SOUTH AFRICA

1.3 1 Structure of the vigilance system in South Africa

- The South African vigilance system incorporates activities and resources at the facility, district, provincial, national and international levels and strives to foster collaboration among all partners to contribute to ensuring medicine safety.
- The figure below illustrates the components of the South African vigilance system with different functions for monitoring, detecting, reporting, evaluating and documenting medicine safety data as well as intervening and gathering information from and providing feedback to reporters, i.e. healthcare providers and consumers.
- When the information has been collected, evaluators analyze it to determine the adverse event’s severity, probable causality and preventability.
- Significant data and findings are communicated to a structure or entity that has the authority to take appropriate action. The entity may be a hospital’s drugs and therapeutics committee, national pharmacovigilance center (SAHPRA), etc.
- The final function in the framework is appropriate action.
- The risk reduction action may be regulatory (e.g. withdrawing marketing authorisation, recalling a medication) managerial (revising a hospital formulary, instituting distribution controls), or educational (teaching prescribers about medicine-medicine interactions or proper product handling).

Fig.1: The South African Pharmacovigilance Framework

Prevented medicine-related problems & Reduced morbidity and mortality
Fig 2: Flow of vigilance data in the public health services

- Monitoring & reporting of MEs & ADRs
- Data capturing into the VigiFlow system
- Data analysis and signal detection

Fig 3: Vigilance activities including responsible structures that are involved in decision-making processes

<table>
<thead>
<tr>
<th>Structure Level</th>
<th>Activities</th>
<th>Responsible Structure</th>
<th>Safety Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility Level</td>
<td>Monitoring &amp; reporting of MEs &amp; ADRs</td>
<td>Drugs &amp; Therapeutic Committee</td>
<td>Managerial &amp; Educational</td>
</tr>
<tr>
<td>Provincial Level</td>
<td>Discussion of MEs &amp; ADRs affecting the province</td>
<td>Provincial Drugs and Therapeutics Committee</td>
<td>Managerial &amp; Educational</td>
</tr>
<tr>
<td>National Level (Regulatory)</td>
<td>Promoting, collecting, collating, analyzing and evaluating patterns of ADRs, MEs, PQ</td>
<td>SAHPRA Pharmacovigilance unit</td>
<td>Regulatory e.g. withdrawing MA, Recall, label amendment</td>
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1.4. ISSUES ADDRESSED BY THE POLICY

1.4.1 Coordination of vigilance related activities in South Africa

Currently, there are non-regulatory pharmacovigilance programmes ran by the government, academia and other non-governmental institutions. These include the pharmacovigilance systems related to:

- Programmatic Immunization
- Programmatic HIV and TB
- Non-governmental organizations
- Academia e.g. The Medicines Information Centre based at the University of Cape Town Pharmacology Department/Groote Schuur Academic Hospital
- Poison centres

Current challenges to vigilance co-ordination:

- While these programmes are generating potentially useful information, there is little or no collaboration between them and the Authority, even when the same medicines and patient populations are targeted.
- Due to this lack of collaboration among vigilance stakeholders, data cannot be meaningfully pooled and analyzed.
- Outputs from the existing parallel systems are limited to local academic/operational research needs and are rarely used in public health policy making.
- To ensure complementarity between the different vigilance programmes, initiatives and the Authority, lines of data and communication flow need to be clearly defined.
- There need to be greater collaboration between the programmes, local vigilance initiatives and the Authority in order to facilitate the sharing of expertise, experience and resources and also standardize data collection methods and reporting tools to enable pooling of similar data structures for ease of comparison and analysis.
PART 2

FUNCTIONS OF SAHPRA’S VIGILANCE UNIT AND VIGILANCE SYSTEMS IN SOUTH AFRICA
2.1 FUNCTIONS OF THE VIGILANCE UNIT OF THE AUTHORITY

The functions of the vigilance unit of the Authority include:

- To promote vigilance in the Republic, collect and manage ICSRs, which includes reports of adverse events, medication errors and suspected counterfeit/substandard medicines,
- To collaborate and harmonize with other ICSRs collection activities within the country (e.g. medicine information centres, poison control centres, public health programmes, etc.) and international ICSRs monitoring programmes.
- To identify signals of medicines safety such as unknown or poorly characterized adverse events in relation to a health product.
- To undertake assessment of risk and options for risk management.
- To identify if there are quality problems in medicines resulting in ICSRs and more generally, support the identification of medicine quality issues.
- To provide effective communication and feedback on aspects related to medicines safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines.
- To apply information from vigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines.
- To set up and collaborate with regional/sentinel centers country wide, in line with the terms of reference, vigilance indicators including current legislation and guidelines.
- To encourage the conduct of medicines utilization studies.
- To be an active participating member of the WHO PIDM through the WHO Collaborating Centre for International Drug Monitoring, the UMC in Uppsala, Sweden.
- Reporting ICSRs to the WHO medicines safety database; VigiBase® and sharing safety data for analysis and signal detection.
- Conducting surveillance of AEFIs in collaboration with the EPI.

2.2 ADR REPORTING TOOLS

2.2.1 ADR reporting form

- The ADR reporting form is the tool for reporting all suspected adverse reactions by healthcare providers and consumers.
- The form can be used to report suspected adverse reactions for medicines, biologicals and complementary medicines.
- The current ADR reporting form was updated in 2017 and 2019 to be in-line with the VigiFlow® requirements and to accommodate the requirements of programmatic pharmacovigilance.
- An electronic version of the form can be found on the SAHPRA website in the following link.
- There are a number of other ADR reporting forms circulating in healthcare facilities, besides the one recommended by the Authority. These use of these forms is not encouraged, since they might capture all the clinically relevant
information required by the Authority. The Authority therefore encourages the use of the recommended ADR reporting form available on the SAHPRA website.

- The currently updated form is also available in the latest version of the South African Medicine Formulary (SAMF 13th ed.).

### 2.2.2 Council for International Organizations of Medical Sciences (CIOMS) Reporting Form

- In 1986 CIOMS set up its first working group on pharmacovigilance (Working Group on International Reporting of Adverse Drug Reactions), to explore a means of coordinating and standardizing international adverse drug reporting by pharmaceutical manufacturers to regulatory authorities (RAs).

- The Working Group devised a method for reporting by manufacturers, which included standardized definitions, procedures and format.

- The CIOMS reporting form, for the first time set the standard for reporting and was later the basis for establishing many of the national reporting forms.

- The CIOMS form, together with the ICH E2B guideline, can be found on the CIOMS website.
2.2.3 Reporting ADRs using the Essential Medicines List (EML) Clinical Guide Mobile Application

- The EML Clinical Guide Application can be downloaded from Google Play or the Apple Store. ADRs can be reported by selecting the “Tools” tab and then selecting the “Report Adverse Drug Reaction” tab.
- The ADR form can then be completed electronically and, on successful completion, a copy of the ADR report will be emailed automatically to the reporter and to SAHPRA on adr@sahpra.org.za

2.2.4 VigiFlow®

- Since the start of a formal pharmacovigilance system in SA in 1987, reported data was managed through the WHO Medical Adverse Drug Reactions Information System (ADRI) database.
- The ADRI database would not allow electronic exchange of data to the VigiBase® and was not compliant with the E2B standard.
- The ADRI database was also not web-based and therefore was MSOffice-based.
- In October 2016, the Authority acquired VigiFlow® system, the WHO ICSR management system following the use of the ADRIS database.
- VigiFlow® is a web-based ICSR management system that is available for use by national pharmacovigilance centres (e.g. SAHPRA) of the WHO PIDM.
- VigiFlow® supports the collection, processing and sharing of ICSR data to facilitate effective data analysis.
- ICSR data can be shared and exchanged, by both electronic importation and exportation in a harmonised format as ICH E2B XML-files, with external stakeholders, such as pharmaceutical companies, public health programmes, provincial offices, and with VigiBase®, the WHO global database of ICSRs.
- VigiFlow® is compliant with the international ICH E2B standard and maintained by the Uppsala Monitoring Center (UMC) in Uppsala, Sweden.
- Since VigiFlow® is a web-based system, no local installations, back-ups or maintenance are necessary. However, it means that internet access is required because no off-line functionality is available. Internet access is encrypted and all data stored in VigiFlow® is accessible only by authorised users.

2.2.5 eReporting

- In 2020, following the activation of the new SAHPRA website, the Authority activated the eReporting link to the VigiFlow® on its website.
- eReporting is a module for VigiFlow®, the web-based ICSR management system used in the WHO PIDM maintained by UMC.
- eReporting allows national pharmacovigilance centres to capture ICSRs directly from patients and healthcare providers into VigiFlow®.
- The eReporting module allows for seamless electronic reporting from patients and healthcare providers and therefore reduces the workload of manual data entry from ADR paper forms into VigiFlow®.
• With eReporting, national vigilance centre personnel need only enter a small amount of data. This gives vigilance teams more time for verifying the coding and assessing the results.
• eReporting can only be used by healthcare providers and patients or care givers.

2.3 DATA INPUT INTO VIGIFLOW®

VigiFlow® supports data input in the following ways:

• Receiving ADR reports from the Marketing Authorization Holder (MAH) or Holder of the Certificate of Registration (HCR) via E2B systems
• Online reporting from healthcare providers or patients
• Manual data entry from paper forms by Regulators

2.4 DECENTRALIZING DATA ENTRY / CASE ASSESSMENT USING VIGIFLOW®

• To decrease the workload at national pharmacovigilance centres (SAHPRA), data entry and / or case assessment can be done by other organisations, which include regional pharmacovigilance centres, hospitals, public health programmes, medicine information centres, poison centres or provincial offices.
• The national pharmacovigilance centre will however always have full oversight of all reports in the database, and all reports will be able to be edited.
• Only the national pharmacovigilance centre can send reports to the WHO global database, VigiBase®.
• VigiFlow® allows for the setup of a hierarchical structure of up to three levels to decentralize data entry. By default, each centre will only be able to view / edit the ICSRs created by itself and all centres below it.
• The following diagram can be used as an example to outline the hierarchical structure of the decentralized system:
2.5 VIGIBASE®

- VigiBase® is the unique WHO global database of ICSRs.
- It is the largest database of its kind in the world, with over 20 million reports of suspected adverse effects of medicines, submitted, since 1968, by member countries of the WHO Programme for International Drug Monitoring.
- It is continuously updated with incoming reports.

2.6 TOOLS TO HARMONISE MEDICINE SAFETY PRACTICES

The following are the tools adopted by SAHPRA for information sharing and harmonization with both local and international stakeholders:

2.6.1 E2B

E2B is an international standard for transmitting medicine adverse events reports specified and developed by the ICH of Technical Requirements for Pharmaceuticals for Human Use, current version is E2B (R3).

2.6.2 WHODrug

- WHODrug Global is the international reference for medicinal product information and it is maintained by the UMC.
- With its unique drug code hierarchy and extensive coverage, it provides a consistent drug dictionary with exact terminology when coding concomitant medications.
- The dictionary is used to identify drug names and evaluate medicinal product information, including active ingredients and products’ anatomical and therapeutic classifications, from nearly 150 countries.
- WHODrug Global's standardised data makes it easier to identify drug-related problems in clinical trials and pharmacovigilance, helping us to develop safer medicines.
- This is because using WHODrug to code data supports more effective analysis, thereby speeding up the regulatory submission process.

2.6.3 MedDRA

- MedDRA is a highly specific and standardised medical terminology dictionary to facilitate sharing of regulatory information internationally for medical products used by humans.
- It was developed by the ICH in the late 1990s.
- MedDRA is available to all for use in the registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale.
- Products covered by the scope of MedDRA include pharmaceuticals, biologics, vaccines and drug-device combination products.
- Today, its growing use worldwide by RAs, pharmaceutical companies, clinical research organisations and healthcare professionals allows better global protection of patient health.
2.7 VIGILANCE AWARENESS, TRAINING AND CAPACITY BUILDING

South African healthcare providers and consumers need to be trained on vigilance and the reporting system in the country. Priority needs to be given to healthcare providers since this is in-line with their professional responsibilities to ensure rational drug use and appropriate pharmaceutical care. ADR identification and reporting are not well understood and are seldom reported, therefore signals are hardly detected in the country. Attention to monitoring may also be neglected, and thus healthcare personnel need to be made aware that ADR monitoring is an integral part of good clinical practice (GCP).

Training and capacity-building is required to ensure that healthcare personnel understand good prescribing practices for new drugs, the correct dosage regimen, and how treatment failures are defined. Alongside this, they need to know where to refer patients in the event of ADRs and related safety events, and also accurately complete the ADR reporting form. Clinical guidance for improved recognition of adverse reactions is required.

Healthcare personnel need to feel confident in reporting and assisting provincial investigations. Common concerns and barriers to reporting by healthcare providers will need to be addressed and clarified in such training activities (e.g. fear of blame etc).

In the initial stage, the training is planned as:

a. A rapid cascade followed by a continuous training (with other training programs) to reach out to all pharmacists, clinicians and nurses.

b. SAHPRA will achieve this in collaboration with other various programs such as:
   i. Programmatic Pharmacovigilance Directorate of the National Department of Health, where SAHPRA training initiatives will be integrated with on-going training in the sector
   ii. Internship service training programmes of all healthcare providers, by inclusion of vigilance training.
   iii. Undergraduate pharmacy and medical curricula, by inclusion of vigilance training.
   iv. Office of Health Standards Compliance (OHSC), by including vigilance infrastructure in facility assessment tools for both clinics and hospitals of all levels.
PART 3

METHODS USED TO COLLECT SAFETY INFORMATION IN VIGILANCE
3.1 METHODS USED TO COLLECT SAFETY INFORMATION IN VIGILANCE

Several methods can be used to collect safety information in vigilance. In all pharmacovigilance systems, spontaneous reporting forms the backbone of the system despite its well-known limitation of under-reporting and lack of baseline data. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other methods including active patient follow-up e.g. Cohort Event Monitoring (CEM). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2B Guidelines. The full document can be downloaded from the ICH website using this link http://www.ich.org/products/guidelines/efficacy/efficacysingle/article/pharmacovigilanceplanning.html

Pharmacoepidemiology studies provide valuable information about the health effects of healthcare products, Guidelines for Good Pharmacoepidemiology Practice, 2015.

3.1.1 Spontaneous Reporting
Spontaneous reports are those adverse drug events/reactions that are voluntarily reported to either the pharmaceutical manufacturers, or provincial pharmacovigilance centers, or to national regulatory authorities by healthcare professionals, patients or consumers. Spontaneous reporting is also referred to as passive reporting. A spontaneous report is an unsolicited communication by health-care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (WHO definition). It is designed to detect ADRs not previously observed in preclinical or clinical studies, to improve understanding of the potential risks, including reactions resulting from medicines interactions or effects of medicines in particular populations, and to help provide a basis for effective medicines regulation, education and consequent changes in practices by prescribers and consumers.

Spontaneous reporting is the most common method of surveillance worldwide. It has played a major role in the identification of safety signals throughout the marketed lifetime of medicines in general. It is the easiest system to establish and the cheapest to run. However, reporting is generally very low and subject to strong biases; and there is no database of all users or information on overall medicine utilization. It is possible to identify risk factors with spontaneous reports, however it is not possible to calculate incidences and compare safety profiles of different medicines.

A new term has been introduced that will replace “spontaneous reports”: this is individual case safety reports (ICSRs). ICSRs play a major role in the identification of signals of risk once a medicine is marketed. ICSRs can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

3.1.2 Case Series of Spontaneous Reports
Series of case reports can provide evidence of an association between a medicine and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between medicine exposure and outcome. There are certain distinct adverse events known to be associated frequently with drug therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore, when events
such as these are spontaneously reported, it is important that pharmacovigilance centres place emphasis on these reports for details and rapid follow-up.

### 3.1.3 Stimulated Reporting
Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings), for new products or for limited periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete documentation.

### 3.1.4 Targeted Spontaneous Reporting (TSR)
Targeted spontaneous reporting is a variant of spontaneous reporting. It focuses on detecting ADRs in a well-defined group of patients on treatment. Targeted spontaneous reporting (TSR) builds on the principles of both spontaneous reporting (described above) and cohort event monitoring (CEM, [described below]). Health professionals in charge of a well-defined group of patients would be sensitized to report specific safety concerns suspected to be medicine related. It provides a comprehensive monitoring method which is affordable, feasible and sustainable in settings with limited financial and human resources and promotes the role of pharmacovigilance as a best practice that improves quality of care.

This focused approach has the same objectives and flow of information as spontaneous reporting. The reporting requires no active measures to look for particular syndromes. TSR may be adapted either to measure all adverse reactions in the defined population or to focus only on specific reactions of particular concern. It is suitable for monitoring of patients on ARVs, anti-TB and other essential medicines. The monitoring of ADRs can be integrated as a standard of care, to accompany the routine practice of monitoring success, death, default or failure of treatment within the cohort. One benefit of monitoring for safety within a treatment cohort is that the number and profiles of the exposed patients are known. To measure the burden of medicine related problems accurately, recording and reporting of observed events needs to be as complete as possible.

### 3.1.5 Active Surveillance
Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is achieved by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as “hot pursuit”. The most comprehensive method is the cohort event monitoring (CEM). It is an adaptable and powerful method of getting good comprehensive data. Other methods of active monitoring include the use of registers, record linkage and screening of laboratory results in medical laboratories.

### 3.1.6 Cohort Event Monitoring (CEM)
CEM is a prospective, observational, cohort study of adverse events associated with one or more medicines. An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which
does not necessarily have a causal relationship with the treatment. CEM is sometimes referred to as prescription event monitoring (PEM), but this term is inappropriate when individual prescription with subsequent dispensing by pharmacists is not part of the process of supplying medicines to patients. In most resource limited countries, the treatment of TB and other important diseases is not provided on a prescription basis. A CEM programme is essentially an observational study in normal clinical practice of a new medicine in the early post-marketing phase, but it can be used for older medicines. Its basic function is to act as an early warning system of problems with new medicines, although it will provide much more information.

CEM records all clinical events and not just suspected ADRs. It involves actively and systematically asking for reports of any and all events and provides a method that facilitates reporting. An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgment on its causality. Favorable events may be recorded as an indication of an unexpected therapeutic effect.

3.1.7 Prescription Event Monitoring (PEM)
Prescription event monitoring is a method of active pharmacovigilance surveillance. In prescription event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events and reasons for discontinuation can be included in the questionnaire.

Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

3.1.8 Sentinel Sites
Active surveillance can also be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups that would not be available in a spontaneous reporting system. Further, information on the use of a medicine, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.

3.1.9 Registries
A patient registry is a list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry), a specific exposure (medicines registry) and death (death registry). In each type of registry, information can be collected through a battery of standardized questionnaires in a prospective fashion.
3.1.10 Comparative Observational Studies
Traditional epidemiologic methods are a key component in the evaluation of adverse events. A number of observational study designs are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

3.1.11 Cross-Sectional Study
Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly linked. These studies are best used to examine the prevalence of a disease at one-time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

3.1.12 Case-Control Study
In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups.

3.1.13 Cohort Study
In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicine at one time during follow up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving medicines exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a medicine of interest or to study very rare outcomes.

3.1.14 Targeted Clinical Investigation
When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicine in general
practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

3.1.15 Descriptive Studies
Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with medicine exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

3.1.16 Natural History of Disease
The science of epidemiology originally focused on the natural history of disease, including the characteristics of ill patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events.

Studies that examine specific aspects of adverse events, such as the background incidence rate or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

3.1.17 Drug Utilization Study
Drug utilization studies (DUS) describe how a medicine is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.
PART 4

REPORTING OF ADVERSE DRUG REACTIONS (ADRS) BY HEALTHCARE PROFESSIONALS, PATIENTS AND CONSUMERS
4.1 REPORTING OF ADRs BY HEALTHCARE PROFESSIONALS, PATIENTS AND CONSUMERS

4.1.1 Who should report ADRs?
- Anyone can report an ADR.
- All healthcare workers, including doctors, dentists, pharmacists, nurses, and other healthcare professionals;
- Patients, consumers and community workers should be encouraged to report ADRs to their healthcare providers, preferably to the clinician who prescribed the treatment, or directly to the Authority.
- Reporters may be from either the public or private health sector.
- Other reporters may include professionals in medical laboratories and pathology departments.

4.1.2 What should be reported?
- All suspected adverse drug reactions regardless of severity
- Medication errors
- Interactions of medicines
- Misuse/overdose
- Substandard, Spurious, Falsely Labelled, Falsified Counterfeits (SSFFCs), and
- Lack of effect
- All product quality issues e.g.:
  - Suspected contamination
  - Questionable stability
  - Defective components
  - Poor packaging or labeling
  - Therapeutic failures

4.1.3 Which events should I report?
You don't need to be certain, just suspicious!

Every report counts. While an individual report may not be enough to determine whether a particular health product caused an adverse event, all reports help to build a picture of the safety profile of a product and assist with SAHPRA’s safety monitoring program.

The work of SAHPRA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines, medical devices and other health products.

SAHPRA particularly needs to know:
- all suspected adverse events to new health products
• all suspected medicine and/or vaccine interactions
• unexpected adverse events (that is, adverse events that do not appear in the professional information and patient information leaflet)
• serious adverse events, such as those suspected to:
  o cause death
  o cause admission to hospital /prolongation of hospitalization
  o cause birth defects
  o be life-threatening
  o result in significant disability or incapacitation

4.1.4 When to Report Suspected ADRs and ADR reporting tools
• An ADR report should be submitted to the Authority, as soon as possible after the reaction has been identified.

4.1.5 Why report adverse events to SAHPRA?
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 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 number of patients to detect adverse events that occur rarely
• 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.

SAHPRA, like other Regulatory Agencies 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. Reports by consumers and health professionals provide important information for SAHPRA's safety monitoring program.

4.1.6 What are the benefits of these reports for my patients and me?
• Improvement on the quality of care offered to patients
• Reduction of drug related problems leading to better treatment outcome
• Improved patient confidence in professional practice, hence professional growth
• Improved knowledge for both the patient and the healthcare professional
• Access to feedback information on drug related problems reported within the country and internationally
• Satisfaction for the fulfillment of a moral and professional obligation
4.1.7 Will reporting have any negative consequences on me?
- Adverse drug reaction reports do not constitute an admission that a health professional contributed to the event in any way.
- The outcome of the report, together with any important or relevant information relating to the reaction that has been reported, will be sent back to the reporter as appropriate.
- The details of the report will be stored in a confidential database.
- The name of the reporter or any other healthcare 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 understanding of the medicines used in South Africa and worldwide.

4.1.8 Why are health professionals in the best position to detect and report on ADRs?
- The effectiveness of a National Pharmacovigilance Program is directly dependent on the active participation of health professionals.
- They are in the best position to report suspected ADRs observed in their everyday patient care, because they are the people who diagnose, prescribe, dispense and monitor patients' response to the medicines.
- All healthcare providers should report ADRs as part of their professional responsibility, even if doubtful about the precise relationship with the given medication.
- You can reduce suffering and Save thousands of patients' lives by doing just one thing: REPORTING ALL SUSPECTED ADVERSE DRUG REACTIONS

4.1.9 How do I recognize ADRs in my patient?
ADRs are difficult and sometimes impossible to distinguish from the disease being treated since they may act through the same physiological and pathological pathways. However, the following approach is helpful in assessing possible drug-related ADRs:

a) Obtain Patient History and do a proper examination
- Take full medicine and medical history.
- An ADR should be your first differential diagnosis at all TIMES!
- Determine if the adverse reaction can be explained by other causes e.g. patient's underlying disease, other medicine/s, over-the-counter medicines or complementary medicines; toxins or foods
- The patient should be 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.
- Few medicines produce distinctive physical signs. Exceptions include fixed medicine eruptions, steroid-induced dermal atrophy, acute extra pyramidal 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 and where possible provide an accurate diagnosis.

b) Establish time relationships
- Some reactions occur immediately after taking 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.

c) Dechallenge and Rechallenge (when necessary)
- Resolution of suspected ADR when the medicine is withdrawn is a strong, although not conclusive, indication of medicine-induced reaction.
- In cases where a withdrawal reaction is experienced, a rechallenge is when the medicine is reintroduced to the patient. Rechallenge is only 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.
- “Positive” dechallenge is resolution of an ADR after withdrawing the medicine.

d) 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 reference?
- If the reaction is not documented in the professional information, it does not mean that the reaction cannot occur with that particular medicine.

4.1.10 Minimization of occurrence of Suspected ADRs
Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines that are described as follows:

- Use few medicines, whenever possible
- Use medicines that you know well
- Do not change therapy from known medicines to unfamiliar one without good reasons.
- Use text books and other reference materials providing information on medicine reactions and interactions.
- Take extra care when you prescribe medicines known to exhibit a large variety of interactions and adverse reactions (anticoagulants, hypoglycemic, and medicines affecting the CNS) with careful monitoring of patients with such reactions.
- Beware of the interaction of medicines with certain food stuffs, alcohol and even with house hold chemicals. Review all the medicines being used by your patients regularly, taking special notice with those bought without prescription (over the counter, complementary).
- Be particularly careful when prescribing to children, the elderly, pregnant and lactating women, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is also essential in these patients.
- If the patient shows signs and/or symptoms not clearly explained by the course of their illness, think of adverse drug reaction.
• Counsel patients on the correct use and storage of medicines to ensure the integrity of the medicinal product as well as to avoid accidental ingestion of medicines by children.

• If you suspect an adverse reaction, consider stopping the medicine or reduce the dosage as soon as possible and please report the adverse drug reaction to the Authority.

### 4.1.11 What information do I need to report?

In order for an ICSR to be valid for reporting, the following four data elements are mandatory and should be available:

- Identifiable patient with initials, please note patient full name is not required for confidentiality reasons.
- Suspected adverse reaction
- Suspected medicine
- Details of the reporter including contact details. Please note that contact details are required for purposes of follow-up should more information be required and for provision of an acknowledgment letter.

By providing all information relevant to a specific adverse event, you can help SAHPRA’s pharmacovigilance unit assess the possible role of the medicine in causing the adverse event. Providing as much information as possible will reduce the need for SAHPRA to follow up. However, it is important not to delay reporting an adverse event if some information is not available. If we need more information, we will contact you. Any information identifying the reporter or patient is kept confidential.

There is also essential clinical information to be included on an ADR form which is important in causality assessment. It is therefore important that the form is as complete as possible in order for the report to add value.

### 4.1.12 Characteristics of a Complete Case Report

Complete case reports include the following elements:

- Description of the adverse events or disease experience, including time to onset of signs or symptoms;
- Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
- Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
- Documentation of the diagnosis of the events, including methods used to make the diagnosis;
- Clinical course of the event and patient outcomes (e.g., hospitalization or death)
- Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
- Information about response to dechallenge and rechallenge; if available
- Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).
- Contact details of the person reporting the reaction, particularly for follow-up purposes.
For reports of medication errors, a complete case report also includes full descriptions of the following, when such information is available:

- Products involved (including the trade (proprietary) and generic name, manufacturer, dosage form, strength, concentration, and type and size of container);
- Sequence of events leading up to the error;
- Work environment in which the error occurred; and
- Types of personnel involved with the error, type(s) of error, and any other contributing factors.

### 4.1.13 How to report an ADR?

- It is better not to wait until final results and information such as hospital letters are received, because the report may be forgotten. These additional details can be sent to the Authority later as a follow-up.

### 4.1.14 Follow-Up

- All reports of serious events will be followed up if details are incomplete.
- This may require the involvement of health professionals in a clinical setting who have been trained and appointed for this type of work.
- Occasionally follow-up information is required to fully assess reports of non-serious events.
- Follow-up requests will be kept to a minimum as they can discourage further reporting, however provision of comprehensive clinical information is encouraged with the initial report.
- Examples of follow-up information might be: essential missing details, information on the final outcome, the result of re-challenge, the results of laboratory tests, and post-mortem results from health facilities where an autopsy is undertaken.

### 4.1.15 What happens to reports

- Received reports are screened and checked for validity, duplication and eligibility.
- A valid report must contain four minimum data elements, which are suspect drug, ADR, patient and a reporter.
- In order to check for duplicate reports, certain characteristics of an ADR report may be used to identify duplicate reporting or follow up reports, for example, patient name, sex, date of birth or age, suspected drug name, dates of drug exposure, source of reported information (e.g. same journal and different sender) etc.
- Reports are then captured into the individual case safety report management system, called VigiFlow® by senior admin officers.
- Each report is allocated a unique report ID number by the system, which is written on each report.
• Quality verification of the captured information follows. This is conducted by technical officers, who are pharmacists by profession.

• Reports are then assessed for causality before submitting to the UMC VigiBase®

• All adverse events are risk assessed and entered into the appropriate database for future reference. The information is used by SAHPRA to help identify safety signals. A safety signal is a ‘flag’ for a possible safety concern. When SAHPRA identifies a signal, it undertakes a detailed evaluation to establish the possible role of the health product in causing the adverse event.

4.1.16 What can SAHPRA do in response to a safety concern?

• If SAHPRA identifies a safety concern relating to a health product, it can take regulatory action to ensure that the medicines continue to have acceptable safety, efficacy/performance and quality for its intended use.

• SAHPRA also seeks to ensure that health professionals and the public are aware of the safety concerns and any changes to the availability and recommended use of the medicines.

Actions SAHPRA can take in response to a safety concern include:

• informing health professionals through medicine safety alerts published in Medical journals and “Dear Healthcare Professional” letters distributed to individual healthcare professionals

• informing consumers through press releases,

• requiring changes to product labelling, or adding warnings, precautions and adverse event information to the Professional Information and Patient Information Leaflet

• cancelling the registration of the product, or limiting the population in which the health product can be used

• changing the scheduling status of a medicine to restrict access to the medicine

• requiring the Holder of Certificate of Registration to undertake post-marketing studies to investigate the safety concern if more information is needed before a judgment can be made about the need for further action.

4.1.17 Feedback to Reporters

• The pharmacovigilance unit of the Authority provide an acknowledgment letter as a form of feedback to anyone who reports an ADR and provide contact details of the reporter.

• Furthermore, feedback is also provided in a form of DHCP letter, press releases, medicine safety alerts and news bulletin

• Individualized feedback is also provided in specific cases.
PART 5

DATA ANALYSIS & MANAGEMENT OF INDIVIDUAL CASE SAFETY REPORTS (ICSRS), CAUSALITY ASSESSMENT AND SIGNAL DETECTION
5.1 DATA ANALYSIS & MANAGEMENT OF ICSRs (ADRs, SAEs, AEFIs)

- Once an ICSR is received and captured on the VigiFlow® database a summary of the assessment is added which includes a literature search and a recommendation of provisional causality.
- These reports are then tabled before the Pharmacovigilance Advisory Committee for expert advice.
- This information is used by SAHPRA to help identify safety signals. A safety signal is a 'flag' for a possible safety concern. When SAHPRA identifies a signal, it undertakes a detailed evaluation to establish the possible role of the health product in causing the adverse event.

5.2 CAUSALITY ASSESSMENT OF SUSPECTED ADRs

There are several causality assessment tools used based on the Bradford-Hill criteria such as the WHO Aide-memoire, 2002, WHO Aide-memoire, 2013, the DAIDS causality assessment tool, the Bradford-Hill criteria etc.

5.2.1 The Bradford-Hill Criteria

These are summarized below, with comments relating to vigilance.

- **Strength:** A weak association does not mean that there is no causality but does weaken the case for common causality.
- **Consistency:** Consistent findings observed by different persons in different places, with different samples, strengthen the likelihood of causality.
- **Specificity:** Causality is more likely if the effect is observed in a very specific population at a specific geographic location and the disease has no other likely explanation.
- **Temporality:** The effect has to occur after the cause and, if there is an expected delay between the cause and the effect, the effect must occur after that delay.
- **Biological gradient:** A positive dose-response relationship strengthens the likelihood of a causal effect. With some interactions a negative dose response relationship may be suggestive.
- **Plausibility:** A plausible mechanism between cause and effect is an indicator of causality, but not all medicine-effect mechanisms are known.
- **Coherence:** Evidence from clinical laboratory or clinical pathology increases the likelihood of causality, but the same issue applies as in point 6: such evidence may be unavailable.
- **Experiment:** Other experimental evidence such as animal studies may be supportive.
- **Analogy:** The effect of similar factors may be important, such as class effects of medicines.
5.2.2 WHO Causality Assessment Tool

The WHO causality assessment criteria are used to evaluate the causal association of suspected products and adverse reactions. The categories of criteria are certain, probable/likely, possible, unlikely, inaccessible/unclassified and conditional/unclassified. The following table outlines the assessment criteria.

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment Criteria</th>
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| **Certain**             | • Event or laboratory test abnormality, with plausible time relationship to drug intake  
                         | • Cannot be explained by disease or other drugs  
                         | • Response to withdrawal plausible (pharmacologically, pathologically)  
                         | • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)  
                         | • Rechallenge satisfactory, if necessary                                                                                                           |
| **Probable / Likely**   | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
                         | • Unlikely to be attributed to disease or other drugs  
                         | • Response to withdrawal clinically reasonable  
                         | • Rechallenge not required                                                                                                                                 |
| **Possible**            | • Event or laboratory test abnormality with reasonable time relationship to drug intake  
                         | • Could also be explained by disease or other drugs  
                         | • Information on drug withdrawal may be lacking or unclear                                                                                       |
| **Unlikely**            | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  
                         | • Disease or other drugs provide plausible explanations                                                                                         |
| **Conditional / Unclassified** | • Event or laboratory test abnormality  
                          | • More data for proper assessment needed, or  
                          | • Additional data under examination                                                                                                              |
| **Unassessable / Unclassifiable** | • Report suggesting an adverse reaction  
                                | • Cannot be judged because information is insufficient or contradictory  
                                | • Data cannot be supplemented or verified                                                                                                       |
5.3 CATEGORISING OF EVENTS

5.3.1 Deaths
Relationships to death cannot be coded as probable or certain because there is no opportunity to see the effect of dechallenge or rechallenge. Death is however not considered as an ADR, but rather considered as an outcome. The events preceding death should be outlined in the ADR report. If there is a plausible time relationship and other causes can be excluded, a relationship to death should be coded as possible. If there is no plausible time to onset and other causes are evident, then the relationship should be coded as unlikely. If there is doubt, then they should be coded as unclassified and they can be reassessed as a group after an epidemiological analysis.

5.3.2 Developing a Case Series
SAHPRA recommends that sponsors initially evaluate a signal generated from post-marketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor’s global adverse event databases, the published literature, and other available databases. As part of the case-level review, the Authority recommends that applicants evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, the Authority recommends that applicants be vigilant for features that may suggest a causal relationship between the use of a product and the adverse event, including:

- Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
- Absence of symptoms related to the event prior to exposure;
- Evidence of positive dechallenge or positive rechallenge;
- Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
- Consistency of the event with the known effects of other products in the class;
- Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiological studies; and
- Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. SAHPRA recommends that applicants carefully evaluate these cases and not routinely exclude them. For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism).

Rigorous pharmacoepidemiological studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event. SAHPRA
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recommends that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification. If the safety signal relates to a medication error, SAHPRA recommends that applicants report all known contributing factors that led to the event.

5.3.3 Summary of Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, SAHPRA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

- The clinical and laboratory manifestations and course of the event;
- Demographic characteristics of patients with events (e.g., age, gender, race);
- Exposure duration;
- Time from initiation of product exposure to the adverse event;
- Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
- Use of concomitant medications;
- Recreational habits such as smoking, alcohol etc.
- The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
- The route of administration (e.g., oral vs. parenteral);
- Lot numbers, if available, for products used in patients with events; and
- Changes in event reporting rate over calendar time or product life cycle

5.4 Safety Signals that may warrant further investigation

It is not possible to characterize all events definitively because the actual risk to patients cannot be known and because there is invariably under-reporting to some extent and incomplete information about duration of therapy, number of patients exposed to the medicine, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

- New unlabeled adverse events, especially if serious;
- An apparent increase in the severity of a labeled event;
- Occurrence of serious events thought to be extremely rare in the general population;
- New product-product, product-device, product-food, or product-dietary supplement interactions;
- Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
- Confusion about a product's name, labeling, packaging, or use;
- Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment),
- Concerns arising from potential inadequacies of a currently implemented risk minimization action plan and
- Other concerns identified by the applicant or SAHPRA.
5.5 Signal Detection

5.5.1 Signal Identification - General Approach

A signal is defined as “Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously” (WHO definition). Usually more than a single report is required to generate a signal, depending on the seriousness and the quality of the information. The publication of a signal usually implies the need for some kind of review or action. Alternatively, several similar events have been identified with a strong relationship to a medicine (“certain” or “probable”) and there does not seem to be good evidence anywhere of these events being recognized as a signal.

Events coded as “possible” can be used as supporting evidence. A group of unexpected deaths coded as “possible” forms an exception to this general rule and will need to be taken seriously. Occasionally a single event (certain or probable), notable for its severity, seriousness or distinctiveness, can be regarded as a signal. There may be one or two case-reports in the literature, but this is insufficient as validation and the signal needs to be strengthened. Causality assessment varies over time as it is dependent not only on the information in a report but also on our knowledge of the medicine. As this knowledge increases over time, causality assessment of the same report might vary. Causality of previously assessed reports needs to be reviewed when signals are being investigated.

The identification of signals in the pharmacovigilance unit's database, or another database, of adverse events or suspected adverse reactions requires careful review of individual reports and events. Careful, informed, routine, systematic and standardized clinical review of the unit's reports with the recording and appropriate collation of good data provides the quickest and most satisfying way of identifying previously unsuspected adverse reactions. Following through the whole process from relationship assessment, to signal identification, to signal strengthening, to communicating the findings is essential.

It is important to stress that new pharmacovigilance systems may have very few reports and may not be able to detect signals. It is therefore important for them to follow closely what is going on in other centres and also to rely on the WHO Pharmaceuticals Newsletter and UMC’s Signal document to keep abreast of signals that may be of importance to them. International collaboration is always key to both signal identification and signal strengthening and should be encouraged including use of the WHO VigiBase® database.

The data in the report(s) need to be of good quality if a signal of a new ADR is to be considered. There should be sufficient data to fully assess the relationship of the medicine to the event. A well-documented report might lead to all degrees of causality: the good quality will simplify the process and ensure that the assessment is more reliable. The strongest signals will have several reports with a certain or probable relationship. According to the WHO, a signal may possibly be identified from one distinctive “certain” report. If there are no “certain” reports, at least three “probable” reports would be necessary for a signal.

Causality term "certain" is very rare. “Index cases” are fully documented cases with no confounders. Signal detection should follow a recognized methodology, which may vary depending on the type of health product it is intended to cover, and detailed guidance on methods of signal detection may be found in the Report of CIOMS Working group VIII Practical

The “unlikely” events should be scrutinized on a regular basis because they may contain hidden or unrecognized reactions. A cluster of similar events of significance may suggest an unexpected reaction that was not recognized at the time of clinical assessment. However, they should not be included in the assessment of a signal for which there are reports with certain, probable or possible relationships because differences could mask the characteristics of the signal being investigated.

5.5.2 Reviewing Other Experiences for Detection of Signals

- Are there other similar reports in the database? Look for related clinical events for the suspected medicine and not simply a single event term.
- Also, look at related medicines in the same Anatomical Therapeutic Chemical (ATC) classification grouping.
- Search the worldwide database of suspected adverse reactions of the WHO Collaborating Centre (UMC).
- The IC value for a medicine–event combination can be requested for by the National Centre from the UMC.
- Search the literature for similar reports, using search tools such as PubMed or Micromedex. Ask the applicants if they have received similar reports and ask for details.
- Were similar events identified in clinical trials? (Search the literature and/or ask the company for reports of clinical trials of the medicine)?
- Were similar events identified in preclinical studies? (Ask the pharmaceutical company.) Has event, or have any similar events, been identified in post marketing cohort event monitoring (i.e. prescription event monitoring) studies?

5.5.3 Selection Criteria for Events to Investigate for Signal Detection

- There is good data
- The event is clinically relevant
- There have been several reports of the event that show a credible and strong relationship with the medicine (certain/probable)
- What do we know about the medicine itself?
- What do we know about the way it is used?
- What do we know about similar medicines (class effect)?
- Is there a reasonable causal relationship between the medicine and reaction in the case reports?
- If validated, the event is of sufficient importance or interest to:
  - require regulatory action, e.g. labelling amendment;
  - require advice to prescribers;
  - be of scientific importance
5.5.4 Methods of Signal Detection
The main methods of identifying signals are:

- Clinical assessment of individual events
- Clinical review of collated events
- Record linkage
- Automated signal detection.

Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the identification of medicine-ADR pairs that might warrant further evaluation. Data mining simply identifies medicine-ADR combinations that have been reported more often than expected when compared to the whole database. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity).

Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate between different medicines and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.
PART 6

MEDICATION ERRORS AND THE ROLE OF THE PHARMACIST
6.1 MEDICATION ERRORS

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. To report any medication error to SAHPRA, an ADR reporting form is to be completed and submitted to the Authority.

Medication errors and medicines-related adverse events have important implications – from increased length of hospitalization 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.

6.1.1 Sources of Medication Errors
- Incomplete patient information
- Unavailable information on medicines (warnings)
- Miscommunication of medication order
- Confusion between medicines with similar names
- Lack of appropriate drug labeling
- Environmental conditions that distract healthcare providers
- Wrong diagnosis (inappropriate therapy)

6.1.2 Most Common Medication Errors
- Failure to adjust dosage in response to a change in hepatic/renal function
- History of allergy to the same or related medication
- Wrong medicine name, dosage form or abbreviation on order
- Incorrect dosage calculation
- Atypical or unusual critical dosage consideration

6.1.3 Medication Error Monitoring and Reporting Program Features
- Evaluate the medication use process in collaboration with other healthcare professionals.
- Establish a process for identifying and tracking medication errors.
- Define categories of medication errors, e.g., prescribing, dispensing, administration, monitoring, compliance errors.
- Simplify process for documenting errors by developing a medication error reporting and evaluation form.
- Increase awareness of medication errors through education and the importance of reporting ALL medication errors, regardless of their suspected significance.
• Establish systems for detecting medication errors in the facility and pharmacy, e.g. P method, random sampling, medication storage survey, etc.
• Involve healthcare professionals, patients, and care givers in the medication error detection and reporting process.
• Re-emphasize the focus on the punitive aspects to encourage medication error reporting and focus on the improvement of processes and systems.
• Respect the confidentiality of the patient, facility, and personnel involved with the medication error.

6.2 THE ROLE OF THE PHARMACIST

6.2.1 Assessment
• Examine and evaluate causes of medication errors.
• Analyze aggregate data to determine trends, significance, frequency, and outcomes of medication errors.

6.2.2 Prevention Strategies
• Examine processes and develop interventions for reducing medication errors. Some examples of interventions are production changes, instituting barcoding, using different distribution systems, training personnel, standard prescription format, developing protocols for recording and transmission of prescription orders, and developing policies and procedures for proper storage and administration of medication.
• Establish goals and measurable standards.
• Monitor interventions and make necessary changes.

6.2.3 Reporting
• Communicate the results of the medication error program to healthcare practitioners, patients, and care givers as appropriate and complete the ADR form.
• Promote reporting of medication errors to a national system for review and analysis, which will result in the development of recommendations to reduce and prevent medication errors and provide bench marking data.
PART 7

SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS (SF), AND PRODUCT DEFECTS
7.1 SUBSTANDARD and FALSIFIED MEDICAL PRODUCTS (SFs)

Counterfeiting can apply to both branded and generic products; SFs may include those with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging. Although the number of reported cases of SFs – with their serious health repercussions, especially for the poor – continues to rise, the exact magnitude of the problem is unknown. Counterfeiting relates to expensive hormones, steroids and anti-cancer medicines, and pharmaceuticals related to lifestyle; in others, it may relate to inexpensive generic medicines. In developing countries, the most disturbing trend is the common availability of SFs for the treatment of life-threatening conditions such as malaria, tuberculosis and HIV/AIDS.

Experience has shown that vulnerable patient groups who pay for medicines out of their own pocket are often the most affected. Counterfeiting is primarily motivated by its potentially huge profits. The success of counterfeiters is, at least in part, a function of their capacity both to adjust quickly to different contexts and products, and to change their focus of interest swiftly, according to where the most money can be made. Many factors facilitate the production or circulation of SFs, including lack of equitable access to essential medicines; the presence of outlets for unregulated medicines; a lack of appropriate legislation; and weak penal sanctions. The basic investigational elements of studies aimed at identifying the magnitude of the problem of counterfeiting in a national market are sound laboratory testing and verification of information available from national medicines regulatory authorities. Despite such measures, it is not always possible to trace the source of the problem. Close collaboration with the original manufacturers (which mostly use new technologies to identify their products unambiguously) and enforcement agencies (which use forensic means of analysis) has proved to be effective in tracing and fully identifying SFs in recent years.

7.1.1 Reporting of Suspected Cases of Substandard and Counterfeit Medicines and Other Related Products

The Licensing and Law Enforcement Division ensures good procurement practices and effective regulation of distribution chains, which closes opportunities for SFs to enter the regular supply system. SAHPRA initiates programmes for the prevention and detection of export, import and smuggling of falsely-labelled, counterfeit or substandard health products. Falsified medicines are more than simply substandard; combating falsified medicines is beyond the normal scope of regulatory control, as the manufacturer or distributor is usually difficult to trace. Combating falsified medicines is therefore a joint responsibility of the Authority, medical professional organizations, forensic investigation units, customs and other law enforcement agencies.

7.2 PRODUCT DEFECTS

7.2.1 Product Defect Reporting and Recall Procedures

The manufacturer must assume responsibility for the quality of the health products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization, including “Section 21” medicines, and do not place the patient at risk because of inadequate safety, quality or efficacy. When products are suspected of being potentially harmful to users due to their defective quality, safety or efficacy, they may be subjected to a recall and all related information must be reported to the Law Enforcement and Vigilance units of the Regulator.
Complaints must be handled positively and carefully reviewed, and corrective actions must be taken as necessary. This can mean amending a manufacturing process as well as implementing a recall of a defective product from all markets where it has been distributed. This is a very difficult area requiring professional judgement in coming to the correct decision. The applicant should have procedures to call into operation to decide whether a recall is required and how quickly it should be implemented. A recall situation may result from customer complaint, detection of GMP failure after release, result from the ongoing stability testing, request by the national authorities, result of an inspection, known counterfeiting or tampering, adverse reaction reporting, or the result of the quality control stability programme.

Please note that any person, MAH, healthcare professional, applicant who comes across a product defect is required to complete an ADR reporting form. The classification and level of recall will depend on the potential hazard of the defective product and the extent of product distribution. These are determined after consultation between the applicant and the Authority. For the approved recall procedure, please refer to the SAHPRA Guidelines for Recall or Withdrawal of Medicines found on the SAHPRA website.

PART 8

GUIDELINES FOR REPORTING OF ADRs BY MARKETING AUTHORISATION HOLDERS
8.1 GUIDELINES FOR REPORTING ADRs BY MARKETING AUTHORISATION HOLDERS (MAHs)

8.1.1 Scope
This guideline is intended to assist applicants/MAHs with the reporting of ICSRs associated with the use of registered medicines i.e. medicines that have attained marketing authorization in South Africa, and in the management of safety data which arise during post-marketing. For post-approval safety data, expedited reporting of serious and unexpected ADRs is required as soon as possible, no later than 15 calendar days of initial receipt of the information by the MAH. Cases of non-serious ADRs, whether expected or not, are also to be reported to the Authority.

8.1.2 Periodic Safety Update Report (PSUR)/ Periodic Benefit Risk Evaluation Reports (PBRERs)
This is a periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined times post marketing authorization. PSUR/PBRER is to be submitted to the Authority as part of the new chemical entity application for registration, and pharmacovigilance plan for the product in line with its risk management plan where applicable. Routine PSURs/PBRERs should not be submitted to the Authority unless the safety profile of the product has changed. The changes should be highlighted by the applicant/MAH to the Authority in writing including the appropriate regulatory action taken by other Regulatory Authority.

8.1.3 Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan
For most products, routine pharmacovigilance (i.e., compliance with applicable post market requirements) is sufficient for post-marketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the applicant/MAH of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by the applicant/MAH that is focused on detecting new safety risks and/or evaluating already identified safety risks.

Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post-marketing spontaneous reporting, and is designed to enhance and expedite the applicant's acquisition of safety information. The development of pharmacovigilance plan may be useful at the time of product launch or when a safety risk is identified during product marketing. It is recommended that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including but not limited to the following:

- The likelihood that the adverse event represents a potential safety risk;
- The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
- The severity of the event;
- The nature of the population(s) at risk;
The range of patients for which the product is indicated (broad range or selected populations only); and
The method by which the product is dispensed (through pharmacies or performance linked systems only).

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Plan (RMP). Pharmacovigilance plans may be appropriate for products for which:

- Serious safety risks have been identified pre- or post-approval, or
- At-risk populations have not been adequately studied. Applicants may discuss with the Authority the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

- Submission of specific serious adverse event reports in an expedited manner
- Routine required reporting (i.e., as 15-day reports);
- Submission of adverse event report summaries at more frequent, pre-specified intervals (e.g., quarterly rather than annually);
- Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be:
  - medicines based: identifying adverse events in patients taking certain products,
  - setting based: identifying adverse events in certain healthcare settings where they are likely to present for treatment (e.g., emergency departments, etc.), or
  - event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure).
- Additional pharmacoepidemiological studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs
- Creation of registries or implementation of patient or healthcare provider surveys and
- Additional controlled clinical trials.

8.1.4 Dear Healthcare Professional Letters and alert notices
Applicants/MAHs may be required to write dear healthcare professional letters (DHCP) and/or alert notices, including update of the professional information and patient information leaflet depending on the nature of the medicine safety issue or product defect and/or recall. MAH are required to submit the DHCP letter to the Authority for approval prior to distribution.

8.1.5 Risk Management Plans
A risk management plan (RMP) is a document that describes the current knowledge about the safety and efficacy of a medicinal product. The RMP provides key information on plans for activities to gain more knowledge about the safety and efficacy of a medicinal product. It also describes measures to be undertaken to prevent or minimize risks associated with the use of the product in patients.
An RMP may need to be submitted at any time in a product’s life cycle. In particular, an RMP should be submitted with the application for a new marketing authorization for:

- Any product containing a new, active substance
- A similar biological medicinal product
- A generic medicinal product with a safety concern, requiring additional risk minimization activities, that has been identified with the innovator medicinal product
- An application involving a significant change in a marketing authorization (e.g. new dosage form, new route of administration, new manufacturing process, significant change in indication) unless the Authority has agreed that submission is not required
- A request of the Authority
- A request by the MAH when a safety concern has been identified

In some circumstances, products not in the above categories that are seeking a new authorization may require an RMP, such as:

- Known active substances
- Generic medicinal products where the changes compared with the innovator medicinal product suggest different risks
- Fixed combination applications
PART 9

RISK MANAGEMENT AND COMMUNICATION STRATEGIES FOR SAFETY ISSUES
9.1 RISK MANAGEMENT STRATEGY

The regulatory authority has various options that can be considered when developing a risk management strategy for a particular safety issue. These include:

- Targeted safety studies or surveillance systems (e.g. patient registers for high risk products, targeted spontaneous reporting)
- Product labelling changes: including new warnings, changes in scheduling status, packaging and improved manufacturing
- Risk communications: such as dear healthcare professional letters, product alerts, media releases, targeted communication based on safety issues and affected groups
- Market withdrawal or product recall

9.2 COMMUNICATION STRATEGY

Safety communication aims at:

- providing timely, evidence-based information on the safe and effective use of medicines
- facilitating changes to healthcare practices (including self-medication practices) where necessary
- changing attitudes, decisions and behaviors in relation to the use of medicines
- supporting risk minimisation behavior
- facilitating informed decisions on the rational use of medicines
- supporting public confidence in the regulatory system

The following principles of safety communication should be applied:

- Safety communications should deliver relevant, clear, accurate and consistent messages and should reach the right audiences at the right time for them to take appropriate action.
- Safety communication should be tailored to the appropriate audiences (patients or healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.
- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and should be part of the risk assessment and risk minimisation measures.
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communication (e.g. marketing authorization holders)
- Safety communication should be subject to quality controls to ensure their accuracy and clarity.
9.2.1 Means of safety communication

Relevant communication tools and channels should be considered when issuing a safety communication in order to reach the target audiences and meet their growing expectations.

The different communication tools that could be used are as follows:

- dear healthcare professional letters
- media releases and briefings
- notification of the website of the regulatory authority
- social media and other online communications
- bulletins and newsletters
- responding to enquiries from the public
- publications in scientific journals and journals of professional bodies
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