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Health Products
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POST-MARKETING REPORTING OF ADVERSE DRUG REACTIONS TO HUMAN MEDICINES IN SOUTH AFRICA

This serves as a guideline to those reporting adverse drug reactions. It represents the South African Health Products Regulatory Authority's current thinking on the safety, quality and efficacy of medicines. The Authority reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments to the approved conditions of registration in keeping with the knowledge which is current at the time of consideration of safety data.

Guidelines and application forms are available from the office of the CEO and SAHPRA website.

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1 INTRODUCTION

This guidance document covers the collection of Adverse Drug Reactions (ADRs), Adverse Event Following Immunisation (AEFIs) and product quality issues by SAHPRA for the following registered and marketed health products:

- Medicines for use by humans, including biological medicines and vaccines (Category A)
- Complementary medicines for use by humans (Category D).
- Radiopharmaceuticals, including radionuclides.

This guideline does not apply to the reporting of ADRs/AEFIs and Serious Adverse Events (SAEs) related to unregistered medicines; obtained via section 21 of the Medicines and Related Substances Control Act; used in the context of pre-registration Phase 1, 2 or 3 clinical trials, active pharmaceutical ingredients used in compounded medicines (Category B) and registered and marketed veterinary medicines (Category C).

This guideline is intended to assist holders of a certificate of registration (holder)/ applicants in the reporting of ADRs/AEFIs associated with the use of registered medicines and "Old Medicines" and in the management of safety data which may arise during post-registration, including during Phase 4 post-marketing clinical trials.

For the purpose of this guideline, "SAHPRA" refers to the South African Health Products Regulatory Authority, hereafter referred to as the Authority, and "**NADEMC"** refers to the National Adverse Drug Event Monitoring Centre. The terms "holder of certificate of registration" (holder) and "applicant" are used interchangeably. The terms "medicine" and "drug" are also used interchangeably.

1.1 Legal Basis

The guideline pertains to Regulation 40 issued in terms of the Medicines and Related Substances Act 101, (Act 101 of 1965) as amended.

1.2 Purpose of the guideline

Every applicant is required to report ADRs/AEFIs known to them involving their marketed medicines in accordance with the requirements of *Regulation 40*. The success of the Authority's ADR/AEFI reporting system depends on the quality, completeness, and accuracy of the information submitted. Reporting of ADRs/AEFIs and monitoring thereof, remain a viable means of identifying previously unrecognised, rare or serious ADRs/AEFIs. This may result in changing product safety information, facilitating decisions on regulatory actions such as withdrawal of a product from the South African market, contributing to international data regarding risks and effectiveness of medicines, and imparting health product safety knowledge that benefits all South Africans.

2 DEFINITIONS

2.1 Adverse Event

"Adverse event/experience" is any untoward medical occurrence in a patient or clinical trial subject administered a medicine that may present during treatment with that medicine but which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicine, whether considered related to the medicine, or not.

2.2 Adverse Drug Reaction (ADR) or Adverse Reaction

"Adverse drug reaction" or "adverse reaction" means a response to a medicine in humans which is noxious and unintended, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse or abuse of a medicine

The definition of an adverse drug reaction or adverse reaction applies to registered medicines, medicines for which the applicant holds an application for registration (“Old Medicines").

Response in this context means that a causal relationship between a medicine and an adverse event is at least a reasonable possibility.

An adverse reaction includes adverse clinical consequences associated with the use of a medicine outside the terms of the approved professional information/ applicable product information or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

A reaction, contrary to an event (as in 2.1), is characterised by the occurrence of a suspected causal relationship between the drug and the reaction, as determined by the reporter or a reviewing healthcare professional / provider. The fact that the healthcare professional / provider is making a report to a holder of a certificate of registration, serves as an indication that the observed event may be caused by the medicine. All spontaneous reports are, therefore, suspected adverse drug reactions.

In the case of pre- and post-marketing studies, adverse “events” are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is better to treat the event as a reaction. For the purpose of post-marketing clinical trials, an adverse drug reaction includes any adverse event where the contribution of the study medication, concomitant medication or other medicinal intervention of the clinical trial, cannot be ruled out.

2.3 Adverse Events Following Immunisation (AEFIs)

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

2.4 Serious Adverse Drug Event or Adverse Drug Reaction or Adverse Events Following Immunisation

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

- results in death;
- is life-threatening;
- requires patient hospitalisation or prolongation of existing hospitalisation;
- results in a congenital anomaly/birth defect;
- results in persistent or significant disability/incapacity; or
- is a medically significant / important event or reaction.

The term “life-threatening” in the definition of “serious” refers to a reaction/event in which the patient was at risk of death at the time of the reaction/event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

Medical and scientific judgement should be exercised when deciding whether other situations are serious or not. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious’, which is based on patient/event outcome or action criteria.

2.5 Unexpected (unlisted) Adverse Drug Reaction/Adverse Events Following

Immunisation

For the purposes of this guideline, an "unexpected" adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the approved professional information for a registered medicine
An unexpected reaction includes class-related reactions which are mentioned in the applicable medicine information but which are not specifically described as occurring with a medicine. When the outcome of the adverse reaction is not consistent with the applicable medicine information the adverse reaction should be considered as unexpected.
An expected ADR/AEFI with a fatal outcome should be considered unexpected unless the South African labelling specifically states that the ADR/AEFI might be associated with a fatal outcome.

2.6 Significant safety issue

A significant safety issue is a new safety issue or validated signal considered by the applicant in relation to their medicines that requires urgent attention of the Authority. This may be because of the seriousness and potential major impact on the benefit-risk balance of the medicine and/or on patient or public health, which could warrant prompt regulatory action and / or communication to patients and healthcare professionals / providers. The applicant can identify significant safety issues as a result of ongoing review and analysis of all information that is pertinent to the safety and benefit-risk balance of the medicine. A safety issue leading to international regulatory action is considered to be significant at all times and hence reportable.

2.7 Individual Case Safety Report (Adverse Drug Reaction Report or Adverse Event Following Immunisation Report)

An individual case safety report (ICSR) is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

2.8 Spontaneous Report or Notification

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

2.9 Solicited Reports

Solicited reports are defined as those derived from organised data collection systems, which include clinical trials, registries, post-approval named patient programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, or information gathering on efficacy or patient adherence. For the purpose of safety reporting, solicited reports should be classified as an ICSR.

2.10 Reportable Adverse Reaction – Minimum Information

A reportable ADR/AEFI requires the following minimum information:

- an identifiable source (reporter) of the information. This should include the name or initials and address of the reporter and the reporter's qualification (e.g. doctor, dentist, pharmacist, nurse or lay person);
- an identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference number, or by age or gender;
- suspected medicine(s)/vaccine (s); and
- suspected reaction(s).

Information, additional to the minimum, should be actively sought and submitted as soon as it becomes available.

2.11 Periodic Safety Update Reports / Periodic Benefit-Risk Evaluation Reports

A periodic safety update report (PSUR) or a Periodic Benefit-Risk Evaluation Report (PBRER) is an update of the world-wide safety experience of a medicine at defined times post-registration, as determined from the international birth date.

Each safety update report should cover the period of time since the last update report. The PSUR or PBRER should be compiled in accordance with the requirements of the current ICH E2C Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

2.12 Line Listings

A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious-presenting sign or symptom according to Standard MedDRA Queries (SMQ). The headings usually included are:

- country of occurrence (if relevant);
- source (e.g. spontaneous, clinical trial, literature, regulatory authority);
- age;
- gender;
- dose(s) of suspected medicine(s)
- the diagnosis being treated by the suspect medicine;
- dosage form and/or route of administration, batch number when applicable;
- duration of treatment (prior to event) time to onset;
- description of reaction (as reported);
- patient outcome (e.g. fatal, resolved, etc.); and

In some instances, depending on the type or source, ADR/AEFI reports should be presented as line listings. A line listing serves to help the Authority to identify cases that it might wish to examine more completely by requesting full case reports.

2.13 Risk-Benefit Balance Evaluation

An evaluation of the positive therapeutic effects of the medicine in relation to the risks (any risk relating to the quality, safety or efficacy of the medicine as regards patients' health or public health).

2.14 Healthcare Professional / Provider

For the purposes of reporting suspected adverse reactions, "healthcare professionals / providers" are medical practitioners, pathologists, dentists, pharmacists, nurses, and other healthcare professionals including allied healthcare professionals and practitioners.

When reports originate from pharmacists or nurses, further information about the case should, where possible, be sought from a medical practitioner responsible for the patient. Furthermore, if there is more than one reporter, the healthcare professional / provider directly involved with the patient's care and who provides the most complete and clinically relevant information, will be considered the primary reporter.

2.15 Abuse of Medicine

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

2.16 Consumer

A consumer in relation to healthcare, means a person who uses or is a potential user of health services, as well as their family and caregiver; for example, a patient, lawyer, friend, relative or carer of a patient.

2.17 Medication error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to cause or lead to harm to the patient, regardless of whether the error is associated with adverse reaction(s) or not. This exclude intentional overdose, intentional prescribing error (that results in sub-therapeutic dose), off-label use, misuse and abuse. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures.

2.18 Lack of efficacy

"Lack of efficacy" is defined as failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines, including when used for an unapproved indication.

3 PHARMACOVIGILANCE OBLIGATIONS OF THE HOLDER OF A CERTIFICATE OF REGISTRATION/ APPLICANT

3.1 The Role and Responsibilities of the Holder of a Certificate of Registration/ Applicant

(i) The holder or applicant should ensure that it has in place an appropriate system for pharmacovigilance that will provide for the proper management of safety data for its medicines and to ensure that appropriate action can be taken when necessary. It is a requirement that the applicant has available, in South Africa, a full-time qualified person responsible for pharmacovigilance and post-marketing surveillance i.e. pharmacovigilance officer. This person should have experience and training in all aspects of pharmacovigilance and, if not a healthcare professional / provider, should have access to a medically qualified person.

(ii) The Responsible Pharmacist must nominate a specific individual, i.e. pharmacovigilance officer responsible for pharmacovigilance activities. The Authority must be informed in writing the name of the person who will assume responsibility for all matters pertaining to pharmacovigilance, including the person's contact details (postal and e-mail addresses and telephone and fax numbers).

(iii) The holder or applicant should ensure that there is full documentation covering all procedures and activities of the pharmacovigilance officer and that mechanisms are in place to ensure that the pharmacovigilance officer may receive or seek all relevant information.

(iv) It is the responsibility of the Responsible Pharmacist to ensure that all pharmacovigilance requirements enforced by the Authority are fulfilled at all times.

3.2 The Role and Responsibilities of the Holder of a Certificate Registration's/ Applicant's PV Officer

Responsibilities of the holder's or applicant's pharmacovigilance officer should include:

(i) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions/ adverse event following immunisation, which are reported to the holder or applicant, including to medical representatives and clinical research associates, is collected and collated so that it is accessible at a single point;

(ii) serving as a contact person for the Authority and NADEMC for all matters relating to pharmacovigilance;

(iii) the preparation of the following, either directly or by delegation/supervision, for submission to the Authority:
- ADR/AEFI reports;
- Periodic Safety Update Reports (PSURs) or Periodic Benefit-Risk Evaluation Reports (PBRER) (including a national appendix relevant to South Africa), when requested;
- company-sponsored post-registration study reports, when required; and
- ongoing pharmacovigilance evaluation during the post-registration period; and

(iv) ensuring that any request from the Authority for additional information deemed necessary for the evaluation of the risk-benefit ratio of a medicine, is provided to the Authority promptly and in accordance with all requirements,

(v) ensure that all the above responsibilities are met for all old and registered medicines on the Authority's Register that are marketed in South Africa. For products that are no longer marketed, post marketing surveillance and reporting of ADRs/AEFIs should continue until six months after the expiry date of the last marketed batch.

3.3 Contractual Arrangements

A holder or applicant may contract any or all of the pharmacovigilance tasks and functions, including the role of pharmacovigilance officer, to another person or organisation based anywhere in the world, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the holder or applicant.

4 REPORTING TIMEFRAMES FOR ALL ADVERSE DRUG REACTION / ADVERSE EVENT FOLLOWING IMMUNISATION

In order to report ADRs/AEFIs in accordance with the regulations, it is sufficient that each applicant report to the Authority the following domestic (South African) cases as stipulated below:

4.1 Time frames for ADRs/AEFIs occurring in South Africa

(i) All serious suspected ADRs/AEFIs, related or unrelated; and expected or unexpected, occurring in South Africa with any old or registered medicine, must be reported by the holder or applicant to the Authority within fifteen (15) calendar days of receipt of such information.

(ii) All non-serious, expected and unexpected, suspected adverse drug reactions / adverse event following immunisation, occurring in South Africa with any old or registered medicine, should not be routinely reported to the Authority. However, they must be presented as a line listing/summary tabulation (cumulative table) in a PSUR and submitted to the Authority when requested as stipulated under 4.3.

(iii) The reporting time clock (Day 0) for submission of serious ADRs/AEFIs starts on the day that the four minimum data elements (see 2.9) (Day 0) in relation to the ADR/AEFI report are received by any of the holder or applicant's personnel, including sales representatives and contractors. Where the applicant has entered into a relationship with another company for the marketing of, or research on the suspected medicines, Day 0 is as soon as any personnel of the holder or applicant receives the four minimum data elements. The timeframe for regulatory submission should be no longer than fifteen (15) days from the first receipt of the four minimum data elements by the holder or applicant.

(iv) The reporting time clock for follow-up information restarts when the holder or applicant receive additional clinical or medically relevant information for previously reported serious ADRs/AEFIs. This information must be reported as soon as possible and no later than fifteen (15) calendar days after the holder or applicant receive the additional information.

(v) Significant safety issues impacting on the risk-benefit profile of a product (including changes in nature, severity or frequency of risk factors), must be reported by the holder or applicant within five (5) calendar days of receipt or identification of such information. The holder must provide detailed information of the safety information and where possible provide sources of such information.

4.2 Time frames for reactions occurring outside South Africa

(i) Foreign individual case reports should not be forwarded to the Authority on a routine basis, but should be reported in the context of a significant safety issue or in response to a specific request by the Authority.

(ii) The holder or applicant should advise the Authority of any regulatory decision/action relating to safety that has been taken by any medicines regulatory agency/authority in another country, including the basis for such action, within five (5) calendar days of first knowledge of such action.

4.3 Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Reports

(i) PSURs or PBRERs should be compiled in accordance with the requirements of the current ICH E2C Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

A PSUR/PBRER must reflect new and cumulative information available to the holder / applicant.

(ii) The Authority may prescribe the frequency at which PSURs/PBRERs should be prepared and submitted as a condition of registration, or may prescribe the frequency in response to a safety signal.

(iii) In the absence of a specific frequency prescribed by the Authority, holders / applicants should refer to the European Union Reference Dates (EURD) list to determine the frequency of and target dates for the preparation of the PSUR/PBRER for each registered medicine. For medicines which do not appear in the EURD list, and for which the Authority has not prescribed otherwise, holders / applicants should prepare a PSUR/PBRER annually.

(iv) In addition to the PSUR/PBRER, the holder / applicant should prepare a national appendix relevant to South Africa on an annual basis. This national appendix should include the following:

- Patient exposure in SA
- ADRs/AEFIs reported in SA (in a line listing format as stipulated in 2.11)
- Approved local professional information

(v) The PSUR/PBRER and national appendix should be reviewed by the holder / applicant, and should be kept by the holder / applicant, to be ready for submission to the Authority upon request.

(vi) PSURs/PBRERs, together with the national appendix, should only be submitted to the Authority in the following situations:

- Whenever requested by the Authority.
- When the submission of PSURs/PBRERs is a condition of registration for a new medicine or range of medicines.
- As part of a submission to amend the conditions of registration when the PSUR/PBRER contains information supporting the amendment.

(vii) When requested by the Authority, PSURs/PBRERs must be submitted within 30 calendar days of the request. When submitted as a condition of registration, PSURs/PBRERs must be submitted within 30 calendar days of initial receipt from the parent company. The version of the PSUR/PBRER and national appendix submitted to the Authority should always be the most recent.

(viii) The holder or applicant should inform the Authority of any steps which are being taken, or to be taken, with regard to safety concerns raised in the PSUR/PBRER at the time of the submission.

4.4 South African Case Reports from Published Scientific Literature:

(i) Holders or applicants should, through screening of the worldwide literature (via search tools e.g. PubMed), report published accounts of serious suspected ADRs/AEFIs related to the active substance(s) of their medicines occurring in South Africa. A copy of the relevant scientific publication should always be provided.

(ii) An ADR/AEFI report should be completed for each identifiable patient (with an identifiable ADR/AEFI). For instance, if an article describes six identifiable patients with a given adverse experience, six ADR/AEFI reports should be submitted to the Authority.

(iii) If more than one medicine is mentioned in the literature report, only the holder or applicant whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s). All concomitant medicines reported in the article should be included in the report, whether belonging to the applicant of the suspect drug or not.

(iv) If the source of the medicine and/or the proprietary name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), dosage form or route of administration and marketing status of the product (refer to 3.2.v), the holder or applicant should assume that it is one of their medicines the publication refers to, although the report should indicate that the specific medicine source and/or the proprietary name was not identified.

(v) If the literature report is of a generalised nature with no identifiable patient, it should not be submitted as an individual case report. However, if the report identifies a safety concern this should be communicated to the Authority and include an opinion on the issue prepared on behalf of the holder or applicant.

4.5 Reports from Post-Registration Studies

(i) All suspected serious adverse drug reactions or adverse events following immunisation from Phase 4

post-registration studies taking place in South Africa must be reported according to 4.1 above. This applies to reports from any type of clinical or epidemiological investigation, regardless of design or purpose, involving a medicine.

(ii) Investigators involved in post-registration studies should be aware of the definition of what constitutes a serious adverse drug reaction, as well as the distinction between 'reactions' and 'events'.

(iii) In the case of post-registration studies, adverse "events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, the case should be reported as an adverse reaction. Events that are clearly unrelated to the medicine should not be reported.

(iv) If the manufacturer receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in section (v) below should be adhered to.

(v) **Managing blinded therapy cases:** When a serious, unexpected, suspected adverse reaction occurs which results in death or, which is life-threatening, and is, therefore, judged reportable on an expedited (rapid) basis, it is recommended that the blind be broken only for that specific patient by the sponsor, even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons responsible for analysis and interpretation of results at the study's conclusion. By retaining the blind, placebo and comparator (usually a marketed medicine) cases are filed in the database unnecessarily.

(vi) When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, agreement should be reached in advance with the Authority concerning serious events that would be treated as disease-related and not subject to expedited reporting. An independent data safety monitoring board should be established prior to commencement of the trial, and its composition and terms of reference, should be submitted with the clinical trial application documents to the Authority for evaluation.

4.6 On-Going Pharmacovigilance Evaluation

It should be noted that the requirements for on-going Pharmacovigilance Evaluation as described in this section takes precedence over other cumulative ADR/AEFI reporting requirements mentioned in this guideline.

(i) Holders or applicants must inform the Authority, whenever new evidence becomes available including any change in the nature, severity or frequency of expected ADRs/AEFIs or any new risk factors, (nationally and internationally) that could significantly impact on the benefit/risk assessment of a medicine or which would be sufficient to consider changes to the conditions of registration of the medicine. Holders or applicants must inform the Authority within five (5) calendar days of first knowledge of such information. The basis on which these assessments are made should be included.

(ii) Additional pharmacovigilance data, such as actual case reports, drug usage figures, the regulatory status of the medicine in other countries, independent pharmaco-epidemiology studies, pre-clinical studies or significant product quality data may be requested by the Authority as the situation warrants. This will be requested for submission within a time period specified by the Authority.

4.7 Consumer Reports

If a holder or applicant receives an adverse drug reaction/adverse event following immunisation report from a consumer, the holder or applicant should advise the consumer to report this reaction through his/her healthcare professional / provider.

If this approach fails, the holder or applicant should attempt to obtain as much information as possible from the consumer, including medical documentation. If the minimum four data elements for reporting (see 2.9) have been met, and the report is deemed to be relevant by a healthcare professional / provider within the company, the case is considered reportable, in line with 4.1 (i) and (ii).

4.8 Reports relating to pregnancy and breastfeeding

The holder or applicant must report suspected adverse drug reactions/adverse event following immunisation related to pregnancy or breastfeeding as specified in 4.1.and 4.2 above, regardless of whether the drug is contra-indicated in pregnancy and/or lactation. Reports on pregnancy should not be forwarded before the outcome is known, unless unintended pregnancy is suspected as an adverse drug reaction/adverse event following immunisation. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant. Reports of termination of pregnancy without information on congenital malformation should not routinely be reported.

4.9 Teratogenicity and Congenital Anomalies

For reports on congenital anomalies or teratogenicity, the following information should be provided:

- Age and sex of the infant
- the birth date or the date on which pregnancy was terminated
- date and/or duration of *in utero* exposure where possible
- any adverse reaction experienced by the mother must be considered a new initial case report on a separate report form.

4.10 Reports of lack of efficacy

Lack of efficacy with medicines (e.g. antimicrobial agents, vaccines or contraceptives or other classes of medicines) used for the treatment of life-threatening diseases/conditions, where lack of efficacy could result in serious consequences, should be reported according to 4.1(i). Lack of efficacy applies to registered medicines, including when used for an unapproved indication. Normal progression of disease does not imply lack of efficacy. The holder or applicant should use clinical judgement to consider whether a case qualifies as serious for reporting purposes. The lot number of the suspected medicine for a report of lack of efficacy must be included in the report.

4.11 Overdose

Suspected serious adverse reactions associated with an overdose should be reported according to 4.1(i) / (ii). This should include reports, which indicate that taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or of other medication(s).

4.12 Off-label use / misuse / abuse / occupational exposure

Reports of off-label use / misuse / abuse / occupational exposure should be submitted when the off-label use / misuse / abuse / occupational exposure was associated with an adverse reaction. An additional ADR/AEFI term that is reflective of the off-label use / misuse / abuse / occupational exposure should be included on the ICSR.

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4.13 Medication Errors

All medication errors should be reported to the Authority within 15 calendar days, whether serious or non-serious, expected or unexpected, suspected ADRs/AEFIs has occurred or not.

4.14 Medicine Defects

If an adverse event is suspected to be related to a medicine defect, it should be reported in the same manner as a suspected adverse reaction. The lot number of the suspected medicines must be included in the report. Holders or applicants should inform the Authority whether the implicated products have been tested for quality attributes and what, if any, corrective actions are being or have been taken.

4.15 Interactions

If an adverse event is suspected to be related to an interaction between two or more medicines, it should be reported as an adverse reaction in the prescribed manner.

4.16 Adverse Reaction Reports from the Internet

Holders or applicants should regularly screen websites and social media accounts under their management or responsibility for potential ADR/AEFI case reports. The frequency of the screening should allow for potential valid ADRs/AEFIs to be reported to the Authority within the appropriate timeframe, based on the date the information was posted. Unsolicited cases from the Internet should be handles as spontaneous reports. For determination of reportability, the same criteria should be applied as for cases provided via other means. In relation to such cases from the Internet, identifiability of the reporter refers to the existence of a natural person, i.e. it should be possible to verify that the patient and reporter exist (e.g. a valid e-mail address has been provided). Contact details should only be used for pharmacovigilance purposes.

4.17 Period after Suspension, Cancellation or Withdrawal of Holder of Certificate of Registration/ Applicant

The holder or applicant should continue to collect ADR/AEFI reports related to the concerned medicine and continue to report if information becomes available, even after suspension, cancellation or withdrawal of registration or “Old Medicine” status until six months after the last marketed batch expiry. After this date, the applicant should report any new follow-up information on the reported cases and continue to collect (but not report) safety information the applicant is made aware of for review of delayed onset adverse reactions or retrospectively notified cases.

5 PROCEDURES FOR REPORTING

5.1 To Whom to Report

All reports required by these guidelines should be sent to the Authority, through channels stipulated under 6.

5.2 Route of Notification

Reportable Safety Information as reflected in the Guidelines associated with **registered human medicines** must be sent to the Authority email through channels stipulated in 6.

5.3 Report Format and Details

(i) Reporting can be done using the adverse reaction report form available from the SAHPRA website and SAHPRA offices or the holders or applicants may use their in-house reporting forms (including the Council for International Organisations of Medical Sciences (CIOMS) I format) provided all the minimum data elements (see 2.9) are included on the form in a readable format, which include an identifiable reporter, an identifiable patient, a suspect product and an adverse reaction.

(ii) Reports can also be submitted to the Authority in the e2b format using an xml file.

(iii) Holders or applicants should submit **ALL** the **relevant** information available at the time of initial notification of an adverse drug reaction report, not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data, is encouraged.

(iv) The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The medicine name as reported by the initial reporter must be provided, preferably the proprietary name.

(v) Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

(vi) The holder or applicant is required to submit the name or initials, address and telephone number and qualification of the initial reporter on the adverse drug reaction report form. In order to ensure confidentiality, the initials of the reporter may be used. The full reporter information should be disclosed to the Authority upon request.

5.4 Follow-Up Reports

Any follow-up information from the holder or applicant relating to an initial ADR/AEFI report submitted to the Authority, must be cross-referenced to the unique number assigned by the holder or applicant. A CIOMS format "initial" report which follows a previous (first) communication from the applicant must be clearly marked that it is a follow up and linked through the applicant-assigned reference number. This is the only reliable way to minimise the duplication of reports, submitted by holders or applicants, in the Authority's database.

5.5 Another Holder of a Certificate of Registration / Applicant's Medicine

Spontaneous reports: If a holder or applicant receives a report of a suspected adverse reaction to a medicine marketed by another holder or applicant, the report should promptly be forwarded to the holder or applicant of that medicine. The holder or applicant to whom the event was originally reported should not forward such reports to the Authority to avoid duplication of reporting. A holder or applicant who receives such a report about its medicine from another holder or applicant is required to submit the report to the Authority within the same timeframe applicable to other reports. Details relating to the patient and the initial reporter are required as for any other report. In order to ensure confidentiality, initials of the patient and/or reporter may be used.

5.6 Confidentiality

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

6 VIGILANCE CONTACT DETAILS

The Authority should be contacted on the below contact details for vigilance related matters as required by these guidelines:

ADR/AEFI reports in an e2b in an xml format:	e2b@sahpra.org.za
All other Adverse Drug Reaction (ADR) or Adverse Event Following Immunisation (AEFI) reports:	adr@sahpra.org.za
Pharmacovigilance related queries:	pvqueries@sahpra.org.za
Documentation relating to identified safety concerns, responses to PV recommendations, PSURs/PBRER, Risk Management Plans (RMPs):	pvsubmissions@sahpra.org.za
Telephonic contact:	0125010311
Physical Address:	Loftus Park Building A (2rd FLOOR) 402 Kirkness Road, Arcadia

7 REFERENCES

1. European Agency for the Evaluation of Medicinal Products: Human Medicines Evaluation Unit. Notice to Marketing Authorisation Holders: Pharmacovigilance Guidelines: 29 January 1999: CPMP/PhVWP/108/99 corr.
2. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and recommended for adoption at Step 4 of the ICH process on 27 October 1994.
3. International Reporting of Periodic Drug-Safety Update Summaries. Final report of CIOMS Working Group II. Geneva 1992.
4. International reporting of Adverse Drug Reactions: Final report of the CIOMS working group. Geneva 1990.
5. Adverse Drug Reaction Reporting by Manufacturers for Marketed Drugs. Bureau of Drug Surveillance, Drugs Directorate, Health Canada.
6. U.S. Food and Drug Administration. Guideline for post-marketing reporting of adverse drug experiences. Docket No. 85D-0249, March 1992.
7. Guidelines on the reporting of Adverse Drug Reactions by Drug Sponsors. Therapeutic Goods Administration: Australia. July 1994.
8. ICH Topic E2D: Post-Approval Safety Data Management – Note for Guidance on Definitions and Standards for Expedited Reporting, May 2004.
9. The Rules Governing Medicinal Products in the EU, Vol. 9A – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. (Sept. 2008).
10. European Agency for the Evaluation of Medicinal Products: Good practice guide on risk minimisation and prevention of medication errors: 18 November 2015 EMA/606103/2014 Pharmacovigilance Risk Assessment Committee (PRAC)

8 APPENDICES

APPENDIX 1: TABULATED SUMMARY OF REPORTING REQUIREMENTS

Post-Registration ADR Reports (registered medicines)

Type of ADR report	Time frame for reporting	Format
South African Reports (spontaneous/published/study): 1. All serious (related or unrelated; and expected or unexpected)) 2. Non-serious (expected and unexpected)	1. ≤15 calendar days 2. Upon request within 30 calendar days	1. **ADR form/e2b 2. ADR Form 3. PSUR with National Appendix
Foreign Reports (spontaneous/published/ study): • Serious	On request or relating to a significant safety issue	As appropriate
Notification of Change in Nature, Severity or Frequency or Risk factors	5 calendar days	Detailed report(including
Significant safety issues - New safety information impacting on benefit-risk profile of a medicine including decisions by national medicines regulatory authorities other than the Authority	5 calendar days	Detailed report (including publications, other sources of information)

** The holder/applicant's in-house ADR report form or SAHPRA ADR reporting form.

9 GLOSSARY AND ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunisation
CIOMS	Council for International Organisations of Medical Science
HCR	Holder of Certificate of Registration
ICSR	Individual case safety report
NADEMC	National Adverse Drug Event Monitoring Centre
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
SAHPRA	South African Health Products Regulatory Authority

10 UPDATE HISTORY

Date	Reason for Update	Version & Publication
May 2003	Version for implementation	Version 1 May 2003
October 2010	Formatted, contact details updated	Version 1_1 Oct 2010
October 2010 June 2011	1 Inclusion of the section on Summary Report 2 Inclusion of additional information under the section on" Healthcare professional" 3 Dividing the guidelines into two: one for reporting pre-registration medicines adverse reactions/events (2.11) and the other for reporting post-registration medicines adverse reactions/events (2.33)	Version 2 July 2011
June 2011	Published for comment	
15 Oct 2011	Deadline for comment	
Oct 2012	New document number allocated (2.33) Published for implementation	Version 2 Dec 2012
Aug 2014	Amendment of 5.1 (ii) and inclusion of Appendix 3	Version 3 Aug 2014
April 2015	1 Replacement of "applicant" with "holder of certificate of registration 2 Replacement of "local", "regional" and "domestic" with "South Africa" 3 2.2 replacement of "any dosage" with "doses normally used in man" 4 2.4 addition of "unlisted" 5 3.5 addition of "Individual case safety reports" 6 Addition of definitions 2.7 and 2.14 7 2.11 addition of "evaluation" 8 2.13 replacement of "drug" with "medicinal product " 9 Amendments to 3.2, 3.3, 4.2 10 Addition of new 4.6 and related new Appendix 3 11 Amendment of 4.7 12 Amendment of 5, 5.1 (ii), 5.2 (ii), 5.3, 5.5 (v), 5.10, 5.13 13 Addition of 5.4 (v) 14 5.12 moved to 5.9 15 5.14 deletion of "drug" 16 Addition of new contact details in Appendix 1 17 Appendix 3 now Appendix 4	Version 4 Nov 2015
Nov 2015	Published for comment	
18 Dec 2015	Deadline for comment	
July 2016	Change in title Retention of "applicant"; Replacement of "medicinal product" with "medicine", and "authority" with "SAHPRA" Swop over of sections 4 and 5 Amendment of sections 1, 2.2-4, 2.6-7, 2.9, 2.12, 2.14 3.1-2, 4.1-4, 4.6-7, 4.9-10, 4.15-16 5.1, 5.3, 5.6, 5.6.1, 8; Appendix 2, 3, 4.	Version 4 Sept 2016
	Published for implementation	

Date	Reason for Update	Version & Publication
July 2016	Correction of sections 4.1, 5.6.1 and Appendix 3	Version 4.1 Nov 2016
	Published for implementation	
June 2017	1. Deletion of "as well as unregistered medicines being used under section 21 of Act 101 (1965)" in 2.2 2. Replacement of "formulation" with "dosage form" in 2.10 & 4.4 (iv) 3. Deletion of "holder or applicant" in 3.1 (ii) 4. Amendment of 4.1 (ii) 5. Replacement of "five (5)" days with "three (3)" in 4.2 (ii) 6. Deletion of "such as biometrics personnel" in 4.5 (v) 7. Replacement of "15 calendar days" with "3 Calendar days" in 4.6 (ii) 8. Addition of "via email" in 5.2 9. Amendment of 5.6 10. Deletion of "format of SR" in 5.6.1 11. Addition of email address in appendix 1 12. Amendment of appendixes 2, 3, & 4 13. Addition of AE in Glossary and Abbreviations	Version 5 June 2017
Dec 2019	1. Changed MCC to SAHPRA 2. Addition of products covered in this guideline 3. Purpose of the guideline 4. Change of Regulation number 5. Addition of definition of significant safety issue 6. Delete appendixes 1 and 3	Version 6 Jan 2020
August 2020	1. Remove Summary report requirement 2. Amend PSUR requirements 3. Change from 'working days' to 'calendar days' 4. Amendment of reporting time frames	Version 7 Sept 2020
April 2021	1. Amend PSUR requirements 2. Change from 'working days' to 'calendar days' 3. Amendment of reporting time frames 4. Amend medication errors,	Version 8 May 2021