South African Health Products
Regulatory Authority
Building A
Loftus Park
Arcadia
Pretoria

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GUIDELINE ON POST-MARKETING REPORTING OF ADVERSE DRUG REACTIONS (ADRs) TO HUMAN MEDICINES IN SOUTH AFRICA

This document serves as a guideline to Applicants/Holders of Certificates of Registration (HCRs) on the reporting of adverse drug reactions/events. It represents the South African Health Products Regulatory Authority's (SAHPRA'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.

Document History

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1	Document formatted and the contact details updated.	October 2010
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Final Version	Reason for Amendment	Effective Date
	– Amendment of report format and details in section 5.1 (ii) – Addition of 5.1 Note – General review of all sections with important amendments	

DR BOITUMELO SEMETE-MAKOKOTLELA
CHIEF EXECUTIVE OFFICER

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Glossary

Abbreviation/ Term	Meaning
Abuse of Medicine	"Abuse of Medicine" refers to the persistent or sporadic, intentional excessive use of medicines resulting in harmful physical or psychological effects.
Adverse Event	– "Adverse event/ experience" is any untoward medical occurrence in a patient or clinical trial subject to whom a medicine has been administered and 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.
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 the 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 HCR 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 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 described above), 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 HCR, 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.
Adverse Events Following Immunisation	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.
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.
European Union reference dates (EURD)	The EURD list is a comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different marketing authorisations, together with the corresponding EU reference dates, frequencies for submission of periodic safety update reports and related data lock points.
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.
Holder of a Certificate of Registration (HCR)	An entity or a person in whose name a registration certificate has been granted for manufacturing, distribution, exportation, and importation of medicines and who is responsible for all aspects of the medicine, including quality and safety and compliance with conditions of registration.

Individual Case Safety Report (ICSR)	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.
Line Listings	A line listing provides key information, but not necessarily all the details customarily collected on individual cases. Reactions are classified by a 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.
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 excludes 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.
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.

Patient Information Leaflet (PIL)	A document included in the package of a medicine that provides information for the patient and consumer about that particular medicine and its use. When a potential medicine safety concern arises, reviews are conducted within SAHPRA. Upon completion of reviews, SAHPRA makes regulatory decisions (such as an amendment of PI and PIL) which are communicated to the HCR for implementation.
Periodic Safety Update Reports (PSUR)/ Periodic Benefit-Risk Evaluation Reports (PBRER)	– A periodic safety update report (PSUR) or a Periodic Benefit-Risk Evaluation Report (PBRER) is an update of the worldwide 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.
Professional Information (PI)	A technical document (either printed or in a soft copy), prepared by the manufacturer and approved by SAHPRA, providing information for medical professionals about the use and dosing of a medicine, and includes pharmacokinetics, dosage forms, and other relevant information about a medicine.
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.
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 in regard to patients' health or public health).
Serious Adverse Drug Event/ Adverse Drug Reaction/ 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.
Significant safety issue	A significant safety issue is a new safety issue or validated signal considered by the Applicant/ HCR in relation to their medicines that require urgent attention from 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 prompt regulatory action and/ or communication to patients and healthcare professionals/ providers. The Applicant/ HCR 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 an international regulatory action is considered to be significant at all times and hence reportable.
Spontaneous Report/ 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.
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.
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.
SAHPRA	The South African Health Products Regulatory Authority, hereafter referred to as the Authority.

1. INTRODUCTION

Reporting of Adverse Drug Reactions (ADRs) and Adverse Events Following Immunisation (AEFIs) and the monitoring thereof, is a viable means of identifying previously unrecognised, rare, or serious ADRs/AEFIs. Every Applicant/ Holder of a Certificate of Registration (HCR) is required to report to the Authority, ADRs/AEFIs known to them involving their registered medicines in accordance with the requirements of Regulation 40 of the *Medicines and Related Substances Act, 101 of 1965,* as amended. The success of the Authority's ADR/AEFI reporting system depends on the quality, completeness, and accuracy of the information submitted. The Authority makes decisions and takes regulatory actions such as updating the Professional Information (PI) and Patient Information Leaflet (PIL), restricting the use of a product in certain populations and withdrawal of a product from the South African market, thereby contributing to international data regarding risks and effectiveness of medicines, and imparting health product safety knowledge that benefits all South Africans.

1.1 Purpose

This guideline is intended to assist Applicants/ HCRs in the reporting of ADRs/AEFIs associated with the use of health products, as provided for in the scope, and in the management of safety data which may arise during post-registration, including during Phase 4 post-marketing clinical trials.

1.2 Scope

This guidance document covers the collection of ADRs/AEFIs and product quality issues by SAHPRA for the following registered health products:

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

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).

2. LEGAL PROVISION

In accordance with Regulation 40 issued in terms 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. A holder of certificate of registration (HCR)/ Applicant and Licence Holder must inform 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 (1)

(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 sub regulation (1) above*.

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

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

In order to comply with the regulatory pharmacovigilance requirements, the Applicants/ HCRs shall:

(i) establish and operate a pharmacovigilance system to ensure monitoring and supervision of their medicines registered in South Africa, including the following critical pharmacovigilance processes:

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- continuous safety profile monitoring and benefit-risk evaluation of registered medicines;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation measures;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports/ Periodic Benefit Risk Evaluation Report;

- meeting commitments and responding to requests from the Authority timeously, including the provision of correct and complete information;

(ii) have an appropriately Qualified Person Responsible for Pharmacovigilance (QPPV) to be responsible for the establishment and maintenance of the pharmacovigilance system (refer to SAHPGL-CEM-PV-02 Pharmacovigilance systems guideline, for detailed requirements on the QPPV);

(iii) establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities;

(iv) ensure that there is full documentation covering all procedures and activities of the QPPV/ Local Pharmacovigilance Officer (LPVO) and that mechanisms are in place to ensure that the QPPV/ LPVO may receive or seek all relevant information.

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

Responsibilities of the Applicant/ HCR's QPPV/ LPVO include:

(i) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions or adverse events following immunisation, which are reported to the Applicant/ HCR, 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 in 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 applicable;
- company-sponsored post-registration study reports, when required; and
- ongoing pharmacovigilance evaluation outcomes 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 profile of a medicine is provided to the Authority promptly and in accordance with all requirements (in (i) – (iii) above).

(v) ensure that all the above responsibilities are met for all health products, as provided for in the scope 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 Back-up procedures

Back-up procedures in the case of absence of the QPPV/ local Pharmacovigilance Officer should be in place and should be accessible through the QPPV/ local Pharmacovigilance Officer's contact details. The QPPV/ local Pharmacovigilance Officer should ensure that the back-up person has all the necessary information to fulfil the role. The Back-up QPPV/ local Pharmacovigilance Officer shall meet all the requirements of a QPPV/ local Pharmacovigilance Officer. The Back-up QPPV/ local Pharmacovigilance Officer shall, however, receive training in pharmacovigilance appropriate for his/ her roles.

In addition to the above, the QPPV/ local Pharmacovigilance Officer and the Back-up QPPV/ local Pharmacovigilance Officer should reside in South Africa and have knowledge of applicable South African safety monitoring legislation and guidelines and international standards for Pharmacovigilance and also demonstrate (e.g., through qualifications and training) that he/ she has knowledge of the key pharmacovigilance activities performed as part of the Applicant/ HCR's pharmacovigilance system and how to implement them.

3.4 Contractual Arrangements

Applicants/ HCRs may subcontract certain activities of the pharmacovigilance system to third party organisations (where the same requirements apply). The Applicant/ HCR shall nevertheless retain full responsibility for:

- the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system.
- ensuring that an effective quality system is applied in relation to the subcontracted tasks.

4. REPORTING TIMEFRAME FOR ALL ADVERSE DRUG REACTIONS/ ADVERSE EVENTS FOLLOWING IMMUNISATION

In order to report ADRs/AEFIs in accordance with the regulations, it is sufficient that each Applicant/ HCR reports to the Authority 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 Applicant/ HCR to the Authority within fifteen (15) calendar days of receipt of such information as stipulated in Appendix 1 below.

(ii) All non-serious, expected, and unexpected, suspected adverse drug reactions/ adverse events 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 section 4.3 below.

(iii) The reporting time clock (Day 0) for submission of serious ADRs/ AEFIs starts on the day that the four minimum data elements (see glossary) in relation to the ADR/ AEFI report are received by any of the Applicant/ HCR's personnel, including sales representatives and contractors. Where the Applicant/ HCR 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 Applicant/ HCR 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 Applicant/ HCR.

(iv) The reporting time clock for follow-up information restarts when the Applicant/HCR receives 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 Applicant/ HCR receives 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), emerging from the following medicines regulatory authorities: European Medicine Agency (EMA), United State-Food & Drug Administration (U.S. FDA), Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, Health Canada, Therapeutic Goods Administration (TGA), Pharmaceutical & Medical Device Agency (PMDA), Health Sciences Authority (HSA) and Medsafe, must be reported by the Applicant/ HCR within five (5) calendar days of receipt or identification of such information. Significant safety issues previously submitted to the Authority, and those aligned with regulatory recommendations recently issued by the Authority may be excluded. The

Applicant/ HCR must provide detailed information as per the signal notification/ follow-up form (GLF-CEM-PV-04A, latest version is accessible on the SAHPRA website: https://www.sahpra.org.za/).

(vi) Significant safety issues impacting the risk-benefit profile of a product (including changes in nature, severity or frequency of risk factors), emerging from any regulatory authority, identified on a product not included in the EURD list, must be reported by the Applicant/HCR within five (5) calendar days of receipt or identification of such information. The Applicant/HCR must provide detailed information as per the signal notification/follow-up form (GLF-CEM-PV-04A, latest version is accessible on SAHPRA Website: https://www.sahpra.org.za/).

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 when specifically requested by the Authority.

(ii) The Applicant/ HCR should advise the Authority of regulatory action(s) on any "Significant Safety Issue" (as defined in the glossary) that has been taken by the following medicines regulatory authorities: EMA, U.S. FDA, Health Canada, MHRA, Swissmedic, TGA, PMDA, HSA and Medsafe including the basis for such action as required by the signal notification/ follow-up form (GLF-CEM-PV-04A), within five (5) calendar days of first local knowledge of such action.

(iii) The Applicant/ HCR should advise the Authority of regulatory action(s) on any "Significant Safety Issue" (as defined in glossary) that has been taken by any regulatory authority, identified on a product not included in the EURD-list, including the basis for such action as required by the signal notification/ follow-up form (GLF-CEM-PV-04A), within five (5) calendar days of first local 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 Applicant/ HCR.

(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 specified frequency prescribed by the Authority, Applicants/ HCRs 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, Applicants/ HCRs should prepare a PSUR/PBRER annually.

(iv) In addition to the PSUR/PBRER, the Applicant/ HCR 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 glossary);
- Approved local professional information;

(v) The PSUR/PBRER and national appendix should be reviewed by the Applicant/ HCR and should be kept by the Applicant/ HCR and 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 latest version of the PSUR/PBRER and national appendix should always be submitted to the Authority. If the PSUR/PBRER is for more than a year, the national appendix should also be for the cumulative years as per the PSUR/PBRER.

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

4.4 South African Case Reports from Published Scientific Literature

(i) Applicants/ HCRs should, through screening of the worldwide literature (via search tools, e.g. PubMed), report published accounts of serious suspected ADRs/AEFIs occurring in South Africa, related to the active substance(s) of their medicines. 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 (6) identifiable patients with a given adverse experience, six (6) ADR/AEFI reports should be submitted to the Authority.

(iii) If more than one medicine is mentioned in the literature report, only the Applicant/HCR 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 proprietary name is not specified and the 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 section 3.2.v), the Applicant/HCR 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 Applicant/ HCR.

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 section 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 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 that 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 the 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 Ongoing Pharmacovigilance Evaluation

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

(i) Applicants/ HCRs 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 balance of a medicine, or which would be sufficient to consider changes to the conditions of registration of the medicine. Applicants/ HCRs 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 period specified by the Authority.

4.7 Consumer Reports

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

If this approach fails, the Applicant/ HCR should attempt to obtain as much information as possible from the consumer, including medical documentation. If the minimum four data elements for reporting (see glossary) 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 section 4.1 (i) and (ii).

4.8 Reports relating to pregnancy and breastfeeding

The Applicant/ HCR must report suspected adverse drug reactions/ adverse events following immunisation related to pregnancy or breastfeeding as specified in section 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 on 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:

(i) Age and sex of the infant;

(ii) the birth date or the date on which pregnancy was terminated;

(iii) date and/ or duration of *in utero* exposure where possible;

(iv) 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 section 4.1 (i). Lack of efficacy applies to registered medicines, including when used for an unapproved indication. The normal progression of disease does not imply a lack of efficacy. The Applicant/ HCR 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 of a medicine should be reported according to section 4.1 (i) or (ii). This should include a report which indicates 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.

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 have 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.

An Applicant/ HCRs 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 via online submissions

Applicants/ HCRs should regularly screen online applications such as 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 via online submissions should be handled 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 via online submissions, the 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

The Applicant/ HCR 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/ HCR should report any new follow-up information on the reported cases and continue to collect (but not report) any new safety information for the purpose of reviewing delayed onset adverse reactions or retrospectively notified cases.

5. PROCEDURES FOR REPORTING

5.1 Report Format and Details

(i) Reporting can be done using the Council for International Organisations of Medical Sciences I (CIOMS I) format or Applicants/ HCRs may use their in-house reporting forms provided all the minimum data elements (identifiable reporter (including the primary/ initial reporter as well as the sender), identifiable patient, a suspect product and an adverse reaction - see glossary) are included on the form in a readable format.

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

Note: Only one of the above methods is allowed for submission of individual case safety report/s.

(iii) Applicants/ HCRs should submit **ALL relevant** information available at the time of the 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 as a follow-up report.

(vi) The Applicant/ HCR 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. The initials of the reporter may be used to ensure confidentiality. The detailed reporter's information should be disclosed to the Authority upon request.

5.2 Follow-Up Reports

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

5.3 Another Holder of a Certificate of Registration's Medicine

Spontaneous reports: If an Applicant/ HCR receives a report of a suspected adverse reaction to a medicine marketed by another Applicant/ HCR, the report should promptly be forwarded to the Applicant/ HCR of that medicine. The Applicant/ HCR to whom the event was originally reported should not forward such reports to the Authority to avoid duplication of reporting. An Applicant/ HCR who receives such a report about its medicine from another Applicant/ HCR 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. The initials of the patient and/ or reporter may be used to ensure confidentiality.

5.4 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 using the following contact details for vigilance-related matters as required by these guidelines:

Issues	Contact Details
Pharmacovigilance related queries	pvqueries@sahpra.org.za
All **paper-based** adverse events reports	adr@sahpra.org.za
Documentation relating to safety concerns, responses to PV recommendations, submissions of PSURs/ PBRERs and Risk Management Plans (RMPs)	pvsubmissions@sahpraorg.za
All E2B XML Files	E2b@sahpra.org.za
Telephonic contact	012 501 0311
Physical Address	Loftus Park Building A (2nd Floor) 402 Kirkness Road Arcadia Pretoria

7. REFERENCES

7.1 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.

7.2 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.

7.3 International Reporting of Periodic Drug-Safety Update Summaries. Final report of CIOMS Working Group II. Geneva 1992.

7.4 International Reporting of Adverse Drug Reactions: Final report of the CIOMS working group. Geneva 1990.

7.5 Adverse Drug Reaction Reporting by Manufacturers for Marketed Drugs. Bureau of Drug Surveillance, Drugs Directorate, Health Canada.

7.6 U.S. Food and Drug Administration. Guideline for post-marketing reporting of adverse drug experiences. Docket No. 85D-0249, March 1992.

7.7 Guidelines on the reporting of Adverse Drug Reactions by Drug Sponsors. Therapeutic Goods Administration: Australia. July 1994.

7.8 ICH Topic E2D: Post-Approval Safety Data Management – Note for Guidance on Definitions and Standards for Expedited Reporting, May 2004.

7.9 The Rules Governing Medicinal Products in the EU, Vol. 9A – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. (Sept. 2008).

7.10 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. VALIDITY

This guideline is valid for a period of five (5) years from the effective date of this revision and replaces the old guideline for Post-Marketing Reporting of ADRs to Human Medicines in SA, revision 9. It will be reviewed on this timeframe or as and when required.

9. APPENDICES

9.1 APPENDIX 1: Tabulated Summary of Reporting Requirements

Type of ADR report	Time frame	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 publications)
Significant safety issues - new safety information impacting on the benefit-risk profile of a medicine including decisions by the following medicines regulatory authorities EMA, U.S. FDA, Canada, MHRA, Swissmedic, TGA, PMDA, Medsafe and HSA.	5 calendar days	Signal notification/ follow-up form information (GLF-CEM-PV-04A).
Significant safety issues - new safety information impacting on the benefit-risk profile of a medicine identified by any regulatory authority on a product not included in the EURD-List.	5 calendar days	Signal notification/ follow-up form information (GLF-CEM-PV-04A).

** The HCR's in-house ADR report form or SAHPRA ADR reporting form