MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

REPORTING OF POST-MARKETING ADVERSE DRUG REACTIONS TO HUMAN MEDICINAL PRODUCTS IN SOUTH AFRICA

Important Note:

Guideline 2.11 "Reporting ADRs in South Africa" should be referred to for reporting of Pre-registration and Section 21 ADRs and SAEs

This document has been prepared to serve as a guideline to those reporting adverse drug reactions. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments 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 Registrar of Medicines and the website

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TABLE OF CONTENTS

Page

TABLE OF CONTENTS

Page

1 INTRODUCTION

This guideline is intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with the use of registered medicines and in the management of safety data which arise during post-registration and post-marketing clinical trials.

For the purposes of this guideline, "**Authority**" refers to the Medicines Control Council and the **NADEMC** refers to the National Adverse Drug Event Monitoring Centre of the Medicines Control Council. The terms medicine and drug are used interchangeably. "Applicant" and "Holder of Certificate of Registration" may be used interchangeably.

1.1 Legal Basis

The guideline pertains to Regulations 34 and 37 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended.

2 DEFINITIONS and Terminology

2.1 Adverse Event

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

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product, 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 or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and 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", as well as unregistered medicines being used under Section 21 of Act 101 (1965). This definition includes any significant hazards to patients.

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

An adverse reaction includes adverse clinical consequences associated with use of a medicine outside the terms of the approved package insert/ 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).

2.2 Adverse Drug Reaction (ADR) or Adverse Reaction - continued

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. The fact that the healthcare professional is making a report to an applicant, 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 Serious Adverse Drug Event or Adverse Drug Reaction

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,**
- **is a congenital anomaly/birth defect,**
- **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.

2.4 Unexpected Adverse Drug Reaction

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 applicable product information (i.e. with the approved package inserts for registered medicines, or the investigator's brochure or other product information for unregistered medicines being used under section 21 of Act 101, 1965).

2.4 Unexpected Adverse Drug Reaction - continued

An unexpected reaction includes class-related reactions which are mentioned in the applicable product information but which are not specifically described as occurring with a product. When the outcome of the adverse reaction is not consistent with the applicable product information the adverse reaction should be considered as unexpected.

2.5 Adverse Drug Reaction Report

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

2.6 Spontaneous Report or Spontaneous Notification

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

2.7 Reportable Adverse Reaction – Minimum Information

A reportable ADR 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 layperson)**
- **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 product(s)**
- **Suspected reaction(s)**

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

2.8 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.

2.9 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. The headings usually included are:

- **Country of occurrence**
- **Source (e.g. spontaneous, clinical trial, literature, regulatory authority)**
- **Age**
- **Gender**
- **Dose(s) of suspected medicine(s)**
- **Formulation 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.)**
- **Comment (if relevant)**

In some instances, depending on the type or source, ADR 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.

2.10 Risk-Benefit Balance

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

2.11 Healthcare Professional

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

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 directly involved with the patient's care and who provides the most complete and clinically relevant information, will be considered the primary reporter.

2.12 Drug Abuse

Refers to the persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

3 PHARMACOVIGILANCE OBLIGATIONS OF THE APPLICANT

3.1 The Role and Responsibilities of the Applicant

(i) The 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 strongly recommended that the applicant has available, in South Africa, a full-time qualified person(s) responsible for pharmacovigilance, both for pre- and post-marketing surveillance. This person(s) should have experience and training in all aspects of pharmacovigilance and, if not a healthcare professional, should have access to a medically qualified person.

(ii) The Responsible Pharmacist of a pharmaceutical company must nominate a specific individual(s) responsible for pharmacovigilance activities. The Medicines Regulatory Authority (MRA) and NADEMC must be informed in writing who the person(s) is that 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 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.

3.2 The Role and Responsibilities of the Applicant's Pharmacovigilance Officer

Responsibilities of the applicant's pharmacovigilance officer should include:

(i) The establishment and maintenance of a system which ensures that information about all suspected adverse reactions, which are reported to the company or organisation, 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 MCC and, in particular, the NADEMC for all matters relating to pharmacovigilance.

(iii) The preparation of the following, either directly or by delegation/supervision, for submission to the Authority
- adverse drug reaction reports
- summary report of ADRs
- Periodic Safety Update Reports (PSURs), when necessary
- company-sponsored post-registration study reports, when required
- ongoing pharmacovigilance evaluation during the post-registration period.

(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 fully.

3.3 Contractual Arrangements

An applicant may transfer any or all of the pharmacovigilance tasks and functions, including the role of pharmacovigilance, to another person(s) or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the applicant.

4 PROCEDURES FOR REPORTING

4.1 Who to Report To

All reports required by these guidelines should be sent to the Authority at the addresses reflected in Appendix 1.

4.2 Route of Notification

Reports may be sent by post, or by facsimile.

4.3 Report Format and Details

(i) Reporting can be done using the adverse reaction report form available from the NADEMC, or applicants may use their in-house report forms, provided all the necessary data elements are included on the form in a readable format.

(ii) Applicants should submit **ALL** the **relevant** information available at the time of initial notification of an adverse drug reaction report, i.e. 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.

(iii) 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 trade (proprietary) name.

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

(v) The 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 initials of the reporter may be used.

4.4 Follow-Up Reports

Any follow-up information from the applicant, relating to an initial ADR report submitted to the NADEMC, must be cross-referenced to the unique number assigned by the applicant. A CIOMS (Council for International Organisations of Medical Science) 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 applicants, in the NADEMC’s ADRI database**.

4.5 Another Applicant’s Product

Spontaneous reports: If a pharmaceutical company receives a report of a suspected adverse reaction to a medicine marketed by another applicant, the report should promptly be forwarded to the applicant of that medicine. The applicant to whom the event was originally reported should not forward such reports to the Authority to avoid duplication of reporting. An applicant who receives such a report about its medicine from another applicant, is required to submit the report to the Authority within the same time constraints 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.

4.6 Summary Report

Every applicant shall submit to the NADEMC all ADR reports which occurred in South Africa received during the specified reporting period on an annual basis as a summary report (SR). The Authority may also request a SR for any other time period if deemed necessary.

Format of the SR: Each applicant should submit a single report which covers all medicines for which it received ADR reports. The format used should include for each medicine (Appendix 3):

(i) the local usage of each formulation for the review period (e.g. sales data or patient exposure).

(ii) a concise critical analysis of the reported ADRs for each medicine.

The critical analysis should

- identify any new ADRs and risk factors associated with the medicine
- indicate any changes in the reporting rates of ADRs in a comparable period using estimated exposure (local) of the medicine, and with reference to international and cumulative data
- address any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment

(iii) any actions taken or to be taken, including actions taken by any other regulatory authority or marketing authorisation holder

(iv) in a conclusion a simple risk-benefit statement for ongoing use and monitoring of the medicine.

(v) a line listing which includes the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified. (See also 2.9)

Depending on the medicine or circumstances, it may be useful or practical to have more than one line-listing, such as dosage forms or indications, if such differentiation facilitates presentation and interpretation of data. It may also be useful to have separate tabulations for serious reactions and for non-serious reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

Time frame for submission of SR: Each applicant will specify the 12-month period which it will use for the SR. The 12-month period and the data lock-point selected by an applicant should be communicated to the NADEMC.

ADR reports to be included: All domestic (South African) spontaneous reports (serious and non-serious) received by the applicant during the specified 12-month period, all published reports of suspected ADRs, all domestic lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).

If an applicant has received no reports during the time period, it must communicate this to the NADEMC.

4.7 Confidentiality

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

5 POST-REGISTRATION Adverse Drug Reaction REPORTS

5.1 Time frames for reactions occurring in South Africa

(i) All serious, suspected adverse drug reactions, whether expected or unexpected occurring in South Africa with any medicine, must be reported by the applicant within 15 calendar days of receipt of such information. The date of receipt of information is day 0.

(ii) All non-serious, expected or unexpected, suspected adverse drug reactions, occurring in South Africa with any medicine, should not be reported immediately, but should be reported as a summary report as specified in 4.6, or as individual reports on request. The summary report must be submitted within 90 days of the last day of the previous 12-month period.

5.2 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 specific safety issue or on specific request by the Authority.

(ii) The applicant should advise the Authority of any action relating to safety that has been taken by a foreign agency, including the basis for such action, within five (5) days of first knowledge.

(iii) These guidelines [i.e. 5.2(i) and (ii)] apply to medicines for which the applicant holds an application for registration.

5.3 Periodic Safety Update Reports

(i) PSURs should **only** be submitted in the following situations:

- Whenever requested by the Authority.
- When the submission of PSURs is a **condition of registration** for a new medicinal product or range of medicinal products. The applicant must submit these PSURs within **30 calendar days** of initial receipt from the parent company.
- As part of a submission to amend the conditions of registration when the PSUR contains information supporting the amendment.
- When a new medicinal product is **submitted to Council for registration** and where the product has already been marketed elsewhere, PSURs should be sent to the Authority during the evaluation period prior to registration. The applicant must submit these PSURs within **30 calendar days** of initial receipt from the parent company.
- When a clinical trial under section 21 of Act 101 (1965) is being carried out with a product which is already registered in other countries.

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

(iii) PSURs for unregistered medicines, or medicines for which no submission for registration has been made, must not be submitted routinely.

5.4 Local Case Reports from Published Scientific Literature:

(i) Applicants should report published suspected adverse drug reactions related to the active substance(s) of their medicinal products, as relevant to the categories identified in 4.1 and 4.2 above. A copy of the relevant published article should be provided.

5.4 Local Case Reports from Published Scientific Literature - continued

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

(iii) If more than one medicine is mentioned in the literature report, only the 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).

(iv) If the medicinal product source and/or the proprietary name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration, the applicant should assume that it is one of their products the publication refers to, although the report should indicate that the specific product source and/or the proprietary name was not identified.

5.5 Reports from Post-Registration Studies

(i) All suspected adverse drug reactions from post-registration studies taking place in South Africa must be reported according to 5.1 above. This applies to reports from any type of clinical or epidemiological investigation, regardless of design or purpose, involving a medicinal product.

(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) 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, such as biometrics personnel, 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 routine expedited (rapid) 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.

5.6 On-Going Pharmacovigilance Evaluation

(i) Applicants must inform the Authority, within three calendar days of first knowledge, whenever new evidence becomes available (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.

(ii) Applicants must report any change in the nature, severity or frequency of expected adverse drug reactions or any new risk factors identified within 15 calendar days. The basis on which these assessments are made should be included.

(iii) Additional pharmacovigilance data, such as actual case reports, drug usage figures, the regulatory status of the product 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.

5.7 Consumer Reports

If an applicant receives an adverse drug reaction report from a consumer, the applicant should advise the consumer to report this reaction through his/her medical practitioner, pharmacist, nurse, dentist or veterinarian. If this approach fails, the applicant should attempt to obtain as much information as possible from the consumer, including medical documentation. If the minimum information for reporting has been met, and the report is deemed to be relevant by a healthcare professional within the company, the case is considered reportable, in line with 5.1 (i) and (ii).

5.8 Reports relating to pregnancy and breastfeeding

The applicant must report suspected adverse drug reactions related to pregnancy or breastfeeding as specified in 5.1.and 5.2 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. 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 normally be reported.

5.9 Reports of lack of efficacy

“Lack of efficacy” is defined as failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines only, including when used for an unapproved indication. Reports of lack of efficacy should not be routinely reported as serious reports.

However, in certain circumstances reports of lack of efficacy should be treated as serious cases for reporting purposes. Medicinal products used for the treatment of life-threatening diseases (e.g. antimicrobial agents), vaccines and contraceptives are classes of medicines where lack of efficacy should be considered as serious, requiring reporting. Normal progression of disease does not imply lack of efficacy. Clinical judgement should be used in considering whether a case qualifies as serious for reporting purposes.

All reports for lack of efficacy not considered serious for reporting purposes, must be included in the summary report (see attached template).

The lot number of the suspected medicine for a report of lack of efficacy should be included in the report.

5.10 Overdose

Reports of overdose should be submitted only when the overdose was associated with an adverse reaction. Suspected adverse reactions, associated with an overdose, should be reported, as well as other reactions. 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). Reports of overdose that are associated with serious adverse reactions must be reported according to 5.1(i).

5.11 Medication Errors

Medication errors that are associated with serious adverse reactions must be reported according to 5.1(i). Information on medication errors, whether resulting in an adverse reaction or not, should be included in the Summary Report.

5.12 Teratogenicity and Congenital Anomalies

For reports on congenital anomalies or teratogenicity:

- Give age and sex of the infant.
- Follow-up reports for the infant should be considered as follow-up to the initial report.
- The birth date or the date on which pregnancy was terminated should be the event onset date.
- Include 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.

5.13 Product Defects

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

5.14 Drug 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.

5.15 Adverse Reaction Reports from the Internet

Applicants should regularly screen websites under their management or responsibility for potential ADR case reports. The frequency of the screening should allow for potential valid ADRs to be reported to the MRA within the appropriate expedited 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 ways. In relation to such cases from the Internet, e.g. e-mail, identifiability of the reporter refers to the existence of a real person, i.e. it should be possible to verify that the patient and the reporter exist (e.g. a valid e-mail address has been provided). Contact details should only be use for Pharmacovigilance purposes.

5.16 Period after Suspension, Cancellation or Withdrawal of Holder of certificate of registration

The holder of certificate of registration should continue to collect adverse reaction reports related to the concerned medicine and continue to report if information becomes available.

6 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)

7 APPENDICES

7.1 APPENDIX 1: ADDRESSES

Reportable Safety Information as reflected in the Guidelines associated with **registered human medicines** must be sent to:

National Adverse Drug Event Monitoring Centre
Medicines Control Council
C/o Division of Pharmacology
University of Cape Town
Observatory
7925

Tel: 021 4471 618
Fax: 021 448 6181

Registrar of Medicines
Pharmacovigilance Unit
Private Bag X828
Pretoria
0001

Tel: 012 395 8176
Fax: 012 395 8775

7.2 APPENDIX 2: TABULATED SUMMARY OF REPORTING REQUIREMENTS

Post-Registration ADR Reports (registered medicinal products)

Type of ADR report	Time frame for reporting	Format
Local Reports (spontaneous/published/study): • Serious (expected and unexpected) • Non-serious (expected and unexpected)	15 days Annually	ADR form # Summary report
Foreign Reports (spontaneous/published/ study): • Serious	On request or relating to specific safety issue	As appropriate
Notification of Change in Nature, Severity or Frequency or Risk factors	15 days	Detailed report (including publications)
New information impacting on benefit-risk profile of product including international regulatory decisions	3 days	Detailed report (including publications)

Applicant's in-house ADR report form or NADEMC ADR report form.

7.3 APPENDIX 3: TEMPLATE FOR SUMMARY REPORT

Each applicant should submit a single summary report (SR) which covers all medicines for which it received ADR reports. If an applicant has received no reports during the time period, it must communicate this to the NADEMC.

The format of the SR used should include for each medicine:

1. Review period

Specify the dates for the 12-month period applicable to the data presented. If periods differ for different medicines, this needs to be specified. It should be kept in mind that the data must be presented annually.

2. Local usage of each formulation for the review period

This may be sales data or patient exposure.

3. Critical (concise) analysis of the reported ADRs for each medicine

3.1 New ADRs identified

Indicate whether any new ADRs have been identified and whether such are serious or non-serious

3.2 New risk factors identified

3.3 Changes in reporting rate

Any changes in reporting rate(s) of ADRs reported in a comparable period, using estimated exposure (local) of the medicine, and with reference to international and cumulative data

3.4 Other new safety issues

This includes any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment, if not included in any of the above points

3.5 Actions taken or to be taken

This includes actions taken or to be taken by any other regulatory authority or marketing authorisation holder (includes the local applicant)

4. Conclusion

A simple risk-benefit statement for ongoing use and monitoring of the medicine is required.

5. Line-listing

The line listing should include the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified.

5 Line-listing – continued

Depending on the medicine or circumstances, it may be useful or practical to have more than one line-listing, such as dosage forms or indications, if such differentiation facilitates presentation and interpretation of data. It may also be useful to have separate tabulations for serious reactions and for non-serious reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

The line-listing should include all domestic (South African) spontaneous reports (serious and non-serious) received by the applicant during the specified 12-month period, all published reports of suspected ADRs, all domestic lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).

8 GLOSSARY AND ABBREVIATIONS

ADRI	Adverse Drug Reaction Information
Authority	Refers to MCC
Domestic	Refers to local or South African
MCC	Medicines Control Council
MRA	Medicines Regulatory Authority
NADEMC	National Adverse Drug Event Monitoring Centre
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
SR	Summary Report

9 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