MEDICINES CONTROL COUNCIL

REPORTING ADVERSE DRUG REACTIONS IN SOUTH AFRICA

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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REGISTRAR OF MEDICINES
MS M HELA

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1 INTRODUCTION

The following guidelines pertain to Regulations 34 and 37 of Act 90 of 1997 [the Medicines and Related Substances Act, 1965 (Act 101 of 1965).]. These guidelines are intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with medicines and in the management of safety data, which arise during clinical trials.

For the purposes of these guidelines, "**Authority**" refers to the Medicines Control Council and the **NADEMC** refers to the National Adverse Drug Event Monitoring Centre of the Medicines Control Council.

2 DEFINITIONS AND TERMINOLOGY

2.1 ADVERSE EVENT

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

An adverse event can be any unfavourable and unintended sign, symptom or disease 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, as well as unregistered medicines being used under Section 21 of Act 101 (1965). This definition includes any significant hazards to patients.

A reaction, contrary to an event, is characterised by the occurrence of a suspected causal relationship between the drug and the reaction, as determined by the reporter or a reviewing health care professional. The fact that the health care 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 clinical trials conducted under Regulation 34, 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,**
- **results in persistent or significant disability/incapacity, or**
- **is a congenital anomaly/birth defect**

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the 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 if other situations are serious. 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.

In the case of medicines used in animals, a serious adverse event/reaction includes any such event, which may occur, even in a single animal, within a herd or flock of animals.

2.4 UNEXPECTED ADVERSE REACTION

For the purposes of this regulation, 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

2.5 HEALTH CARE PROFESSIONAL

For the purposes of reporting suspected adverse reactions, "health care professionals" are medical practitioners, pathologists, dentists, pharmacists, nurses, veterinarians and paraveterinary professionals including veterinary nurses and animal health technicians.

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

2.6 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

2.7 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.

2.8 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 (for e.g., doctor, dentist, pharmacist, nurse or veterinarian)**
- **An identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference number. For Veterinary Medicines an identifiable patient requires a description of the animal (particularly species).**
- **Suspected product(s).**
- **Suspected reaction(s)**

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

2.9 PERIODIC SAFETY UPDATE REPORTS

A periodic safety update report (PSUR) 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 should be compiled in accordance with the requirements of the ICH E2C (CPMP/ICH/288/95) Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

2.10 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**
- **Source (physician, literature, etc)**
- **Age**
- **Sex**
- **Dose of drug**
- **Duration of treatment (prior to event); time to onset**
- **Description of reaction (as reported)**
- **Patient outcome (for e.g., fatal, resolved, etc)**
- **Comment**
- **Company Reference Number**

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.

3 PROCEDURES FOR REPORTING

3.1 GENERAL PRINCIPLES

3.1.1 Who to report to

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

3.1.2 Route of Notification

Reports may be sent by post, facsimile or electronically.

3.1.3 Follow-up reports

After initial receipt of an adverse reaction report, a notice of acknowledgement will be sent to the applicant quoting the number assigned to the case report. Any follow-up correspondence from the applicant, relating to the same case report, should be cross-referenced to the assigned database number or to an appropriate unique number assigned by the applicant (relating specifically to the initial notification). **This is the only reliable way to minimise the duplication of reports submitted by applicants**.

3.1.4 Internal pharmacovigilance system

(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 health care professional, should have access to a medically qualified person.

(ii) The managing director of a pharmaceutical company must nominate a specific individual(s) responsible for pharmacovigilance activities. The NADEMC must be informed in writing who the person(s) will 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) Responsibilities of the applicant's pharmacovigilance officer should include:

- 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.
- Serving as a contact person for Council and, in particular, the NADEMC for all matters relating to pharmacovigilance.
- The preparation of the following for submission to the Authority
  - adverse drug reaction reports

3.1.4 Internal pharmacovigilance system - continued

- Periodic Safety Update Reports (PSURs), when necessary
- company-sponsored pre- and post-registration study reports
- ongoing pharmacovigilance evaluation during the post-registration period.

• 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.

3.1.5 Report Format and Details

(i) **Post-registration:** Reporting can be done using the adverse reaction report form available from the NADEMC (appendix 3), 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) **Pre-registration:** A Serious Adverse Event/Reaction (SAE) reporting form (appendix 4) should be used for reporting of pre-registration clinical trial adverse event/reaction reports. Applicants may use their in-house Adverse Event report forms to submit such reports, provided all the data elements are included on the form in a clearly readable format.

(iii) 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.

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

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

(vi) 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 case report form. In the case of a report from a clinical trial, the trial site at which the reaction occurred, needs to be submitted in addition to other information requested.

3.1.6 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 other medication.

3.1.7 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.

3.1.8 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.

3.1.9 Drug Interactions

Any drug interaction, which results in an adverse reaction, should be reported as an adverse reaction in the prescribed manner.

3.1.10 Another Applicant's Product

(i) **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. An applicant, who receives such a report about its medicine from another applicant, is required to submit the report to the Authority with the same time constraints applicable to other reports.

(ii) **Clinical trials:** When serious, unexpected reactions are found for another applicant's medicine that is being used concomitantly with that of the applicant conducting the clinical trial, a report about the event should be submitted directly to the Authority by the applicant responsible for the study.

3.1.11 Confidentiality

Strict confidentiality will be maintained by the NADEMC regarding the identities of the patient and the reporter. Other details relating to the adverse drug reactions, however, are in the public domain.

3.1.12 Lack of Efficacy reports

"Lack of efficacy" is defined as failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines only. The lot number of the suspected medicine should be included in the report. If the report of "lack of efficacy" is for an unapproved indication, the event is still reportable.

4 POST-REGISTRATION ADVERSE DRUG REACTION REPORTS

4.1 Reactions occurring in South Africa

(i) All serious, suspected adverse drug reactions, occurring in South Africa with any medicine, must be reported by the applicant within 15 calendar days after first notification.

(ii) All non-serious, unexpected, suspected adverse drug reactions, occurring in South Africa with any medicine, must be reported by the applicant within 15 calendar days after first notification. Do not report non-serious, expected adverse reactions.

4.2 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 three days of first knowledge.

(iii) These guidelines [i.e. 2.2(i) and (ii)] also apply to medicines for which the applicant holds an application for registration.

4.3 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 periodic safety update report 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.

4.4 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.

(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).

4.5 Reports from post-registration studies

(i) All suspected adverse reactions from 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 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 5.3 below should be adhered to.

4.6 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 pharmacoepidemiology 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 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. If the minimum information for reporting has been met, and the report is deemed to be relevant by a health care professional within the company, the case is considered reportable.

4.8 Reports Relating to Pregnancy and Breast-Feeding

The applicant must report suspected adverse drug reactions related to pregnancy or breast-feeding 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. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant.

5 PRE-REGISTRATION ADVERSE DRUG REACTION/EVENT REPORTS

This applies to reports from any type of clinical or epidemiological trial, regardless of design or purpose, conducted under Section 21 of Act 101 (1965).

5.1 Adverse Drug Reaction reporting for Clinical Trials

(i) **All fatal and life-threatening, unexpected** adverse drug reactions occurring in clinical trials in South Africa conducted under Section 21 of Act 101 (1965), should be reported within 7 calendar days after first knowledge by the applicant. The initial notification must be followed by as complete a report as possible, within an additional 8 calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicines.

(ii) **Serious, unexpected adverse drug reactions that are not fatal or life-threatening**, which occur in clinical trials in South Africa registered under section 21 of Act 101 (1965), must be reported as soon as possible, and not later than 15 calendar days after first knowledge by the applicant.

(iii) All suspected **serious, unexpected** adverse drug reaction reports originating from world-wide clinical sites **outside South Africa** for clinical trials conducted with the same medicine under section 21 of Act 101 (1965), should be reported as part of the 6-monthly progress reports in a line listing format.

(iv) The Authority must be notified, within 15 calendar days after first knowledge by the applicant, when there is a suggestion of a change in the nature, severity or frequency of **expected** adverse drug reactions or when new risk factors are identified. The basis on which these assessments are made should be included.

(v) Any information, which may in any way influence the benefit-risk assessment of a medicine or which would be sufficient to consider changes in the administration of the medicine or in the overall **conduct of a clinical trial,** must be reported to the Authority. The applicant must submit this information to the Authority within three calendar days of first knowledge thereof. This could include individual case reports or a major safety finding from other sources.

(vi) All serious adverse **events** must be included as part of the 6-monthly progress reports in a line listing format only.

(vii) All non-serious unexpected suspected adverse drug reactions must be included as part of the 6-monthly progress reports in a line listing format only.

(viii) A clinical investigator, who has been approved by the Authority, must sign all reports originating from South Africa. A single copy of the original report should be submitted to the Authority.

(ix) If the sponsor of a clinical trial or the applicant for the trial does not agree with the causal association assigned by the initial reporter or the investigator, the reaction should still be reported.

(x) Expedited (rapid) reporting will be inappropriate for serious events from clinical trials that are considered not related to the study product. All cases judged by the clinical investigator or the sponsor, as having a reasonable suspected causal relationship to the medicine, qualify as adverse drug reactions. (Refer point 2.2.)

5.2 Managing Blinded Therapy Cases

(i) When a serious, unexpected, suspected adverse drug 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.

(ii) 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.

5.3 Post-study events

Serious adverse events that occur after the patient has completed a clinical trial (including any post-treatment follow-up required according to the protocol) should be considered for expedited (rapid) reporting purposes as though they were study reports. A causality assessment and determination of expectedness are needed for a decision on whether or not expedited (rapid) reporting is required.

5.4 Medicines used under Section 21 of Act 101 (1965), not within a clinical trial

The prescriber of a medicine approved for use under Section 21of Act 101 (1965) for patients not enrolled in a clinical trial (for e.g., compassionate use, named-patient use, etc.), must report any serious suspected adverse drug reaction that occurred with the use of the medicine in the specified patient(s) within 15 calendar days of first knowledge by the prescriber.

5.5 Protocol design details

(i) Each clinical trial protocol submitted to Council, should include a risk management procedure, including unblinding procedures, for dealing with serious, unexpected events or reactions which may arise during the conduct of the trial and which could significantly impact on the safety of the study subjects.

(ii) There may be differences in the clinical safety profile for different presentations, for e.g., dosage form, formulation or delivery system of the pharmacologically active compound(s) or different indications/uses of a given product. All adverse reactions which qualify for reporting should be cross-referenced with all other dosage forms and uses for that product. The Investigator's Brochure must, therefore, cover adverse drug reaction information that applies to all product presentations and uses.

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.

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 Department of Pharmacology

University of Cape Town

Observatory

7925

Tel.: 021 4471 618

Fax: 021 448 6181

Office of the Registrar of Medicines

Pharmacovigilance Unit

Private Bag X828

Pretoria

0001

Tel: 012 395 8176/7/8

Fax: 012 395 8775

Reportable Safety Information as reflected in the Guidelines associated with **medicines** used under section 21 of Act 101 (1965) and in clinical trials involving **unregistered medicines** must be sent to:

Office of the Registrar of Medicines

Clinical Trials Business Unit

Private Bag X828

Pretoria

0001

Tel: 012 395 8176/7/8

Fax: 012 395 8775

All Adverse Drug Reactions associated with **registered and unregistered veterinary medicines** must be sent to:

Veterinary Pharmacovigilance Centre
C/o Department of Paraclinical Sciences
Section of Pharmacology
Faculty of Veterinary Science
University of Pretoria
Private Bag x 04
Onderstepoort
0110

Tel.: (012) 529-8353
Fax: (012) 529-8304

All safety information associated with medicines (**human and veterinary**) for which an application for registration has been submitted must be sent to:

Office of the Registrar of Medicines
The Clinical Business Unit
Private Bag X828
Pretoria
0001

Tel: (012) 395 8765
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)	15 days	ADR form #
• Non serious (unexpected)	15 days	ADR form #
• Non serious (expected)	No report	Not required
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.

Pre-Registration ADR/ADE reports (i.e. unregistered medicines being used under section 21 of Act 101, 1965 or Regulation 34 of Act 90, 1997)

TYPE OF ADR REPORT	TIME FRAME FOR REPORTING	FORMAT
Local Reports:		
• Fatal or life-threatening (unexpected)	7+8**	SAE form
• Other serious (unexpected)	15 days	SAE form
All (local & foreign) reports:		
• Serious (unexpected and expected) events	6-monthly##	Line listing
• Non-serious unexpected reactions	6-monthly	Line listing
Notification of Change in Nature, Severity or Frequency of Risk factors	15days and in 6 monthly report##	Detailed report
New information impacting on risk-benefit profile of product or conduct of trial	3 days and in 6-monthly report##	Detailed report

6-monthly progress report which should be submitted to Council during the entire duration of the clinical investigation.

** 7+8 - initial notification to Council as soon as possible but within 7 calendar days followed by a complete report within 8 calendar days of the initial notification.