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PART 1 OF 2



AIDS HELPLINE: 0800-0123-22 Prevention is the cure

GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. R. 609

2 May 2003

MEDICINES CONTROL COUNCIL

MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965)

**GUIDELINES WITH RESPECT TO THE MEDICINES AND RELATED SUBSTANCES ACT
(ACT 101 OF 1965), AS AMENDED**

Guidelines for medicines regulation in South Africa as determined by the Medicines Control Council with reference to regulation as published in regulation gazette number 7470 (1230).

Ms M. P. MATSOSO

Registrar of Medicines

Reporting of Adverse Drug Reactions

MEDICINES CONTROL COUNCIL



DEPARTMENT OF HEALTH
Republic of South Africa



MEDICINES CONTROL COUNCIL

ADVERSE DRUG REACTIONS REPORTING FORM

Version: MCC2003/1

ADVERSE DRUG REACTION

SPONTANEOUS REPORTING of ADVERSE DRUG REACTIONS

The Medicines Control Council has a system for spontaneous reporting of suspected adverse drug reactions (ADRs) mainly through the National Adverse Drug Event Monitoring Centre (NADEMC). When an ADR report form is received by the NADEMC, the data is entered into the Centre's Adverse Drug Reaction Information (ADRI) database and given a unique identification number. The reporter will receive an acknowledgement letter, which will quote the unique identification number of the report. ADR reports are evaluated by the NADEMC to assess the causal relationship between the medicine and the reported reaction. The data, together with data from other sources, are used to assist in the evaluation and monitoring of the post-marketing safety of medicines.

HOW TO REPORT

The **Adverse Drug Reaction and Product Quality Problem Report Form** is available on this website and can be downloaded for printing. The form is also available from the Medicines Control Council pharmacovigilance units listed below.

The offices of the MCC for the monitoring of suspected adverse drug reactions are:

- The Medicines Regulatory Affairs in Pretoria for all products

Registrar of Medicines
Medicines Control Council
Private Bag X828
PRETORIA
0001

- The NADEMC in Cape Town for all products

Tel. #: 021 447 1618
Fax #: 021 448 6181

- The Pharmacovigilance Unit (PVU) for Focused Monitoring of Anti-retroviral medicines, unregistered medicines, and complementary and alternative medicines

Fax #: 012 521 4335

NOTE:

Any of the units may be contacted for information on any area of safety of medicines.

The completed forms can be returned by fax to the relevant fax number, or by post to the following address.

BUSINESS REPLY SERVICE
Free Mail Number: BNT 178

BESIGHEIDSANTWOORDDIENS
Vryposnommer: BNT 178

Department of Health
Registrar of Medicines
Private Bag X828
PRETORIA
0001

Departement van Gesondheid
Registrateur van Medisyne
Privaatsak X828
PRETORIA
0001

WHO SHOULD REPORT?

The MCC invites all health care professionals (e.g. medical practitioners, dentists, pharmacists, nurses) to report all suspected ADRs.

Reports are not usually accepted directly from patients as a medical opinion on any adverse reaction is important. Patients who experience a suspected adverse reaction are advised to report this to a medical practitioner, dentist, pharmacist, nurse or other health professional who should then report to the MCC, NADEMC, or PVU.

WHAT TO REPORT?

Report suspected adverse experiences

- with all medicines, including vaccines
- with medical devices
- with complementary medicines
- with traditional and herbal medicines
- with homeopathic medicines

Report suspected product quality problems such as

- possible contamination
- questionable stability
- defective components
- poor packaging or labelling

Report especially

- adverse reactions to recently marketed products
- serious reactions with all products
- adverse reactions which are not clearly reflected in the product package insert
- therapeutic failure

REPORT EVEN IF YOU ARE NOT CERTAIN THE PRODUCT CAUSED THE EVENT

PATIENT CONFIDENTIALITY

Patient confidentiality is strictly maintained. It is, however, important to provide some patient identification for ongoing communication between the reporter and the MCC, NADEMC, and PVU. Patient initials and age are sufficient as an identifier. A practice or hospital number may also be provided.

REPORTER CONFIDENTIALITY

Reporter confidentiality is strictly maintained. It is, however, important to provide the name, address and qualification of the reporter to allow for further communication, and to identify the source of the report.

Department of Health
Logo Here

AND PRODUCT QUALITY PROBLEM REPORT FORM
(Identities of reporter and patient will remain strictly confidential)
NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

Medicines Control Council,
The Registrar of Medicines,
Department of Health

Tel : (021) 447-1618
Fax : (021) 448-6181

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials): Age: Weight (kg) :
Sex: M F DOB : Height (cm) :

ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse reaction¹ and/or Product Quality problem² Date of onset of reaction:
Time of onset of reaction:h.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES/VACCINES/DEVICES (include all concomitant medicines)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/> death	<input type="checkbox"/> life-threatening	Event reappeared on rechallenge: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> Rechallenge not done	Recovered: <input type="checkbox"/> Y <input type="checkbox"/> N
<input type="checkbox"/> disability	<input type="checkbox"/> hospitalisation		Sequelae: <input type="checkbox"/> Y <input type="checkbox"/> N
<input type="checkbox"/> congenital anomaly	<input type="checkbox"/> Other	Treatment (of reaction).....	Describe Sequelae.....
<input type="checkbox"/> required intervention to prevent permanent impairment damage

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results lab data)

2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation?: Y N

REPORTING DOCTOR/PHARMACIST Etc:
NAME: QUALIFICATIONS:.....
ADDRESS: Signature Date
TEL: (.....).....

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- traditional and herbal remedies
- **For Adverse Events Following Immunisation (AEFI), please follow the reporting procedure recommended by the Expanded Programme in Immunisation (EPI)**

Please report:

- adverse drug reactions to recently marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report Product Quality Problems such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Important numbers:
Investigational Products and Product Quality Problems:

- (012) 326-4344 to fax a report
- (012) 312-0000 to report by phone

Registered Medicines and Traditional and Herbal remedies:

- (021) 448-6181 to fax a report
- (021) 447-1618 to report by phone

Adverse Events Following Immunisation:

- (012) 312 0110 to phone for information
- (012) 321 9882 to fax a report

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of drug safety and therapy in South Africa.

PLEASE USE ADDRESS PROVIDED BELOW- JUST FOLD IN THIRDS, TAPE and MAIL

Postage will be
paid by Addressee
*Posgeld sal deur
die geadreseerde
betaal word*

No postage stamp
necessary if posted
in the Republic of
South Africa
*Geen posseel nodig nie
indien in die Republiek
van Suid-Afrika gepos*

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Vryposnommer: BNT 178

DEPARTMENT OF HEALTH
DEPARTEMENT VAN GESONDHEID
REGISTRAR OF MEDICINES
REGISTRATEUR VAN MEDISYNE
PRIVATE BAG/ PRIVAATSAK X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL



DEPARTMENT OF HEALTH
Republic of South Africa



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 for 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.

REGISTRAR OF MEDICINES

MS. M.P. MATSOSO

DATE: 29/4/2003

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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 Control Act (Act 101, 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 be 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
 - 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.
- (i) **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.
- (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 (or trade) name must be provided as reported by the initial reporter.

- (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 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.
- (iii) **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.
- (iv) 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.
- (v) 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.
- (vi) 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.

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