AUSTRALIAN GUIDELINE FOR PHARMACOVIGILANCE RESPONSIBILITIES OF SPONSORS OF REGISTERED MEDICINES REGULATED BY DRUG SAFETY AND EVALUATION BRANCH

July 2003
Amended 31 May 2005
ABOUT THIS GUIDELINE
This guideline is specifically for the reporting of adverse reactions to registered medicines regulated by the Drug Safety and Evaluation Branch (DSEB) of the TGA. It replaces the advice contained within Appendix 20 of the Australian Guidelines for the Registration of Drugs on reporting requirements for DSEB-registered medicines. Throughout the document the terms ‘product’ and ‘registered medicinal product’ are used to mean registered medicines regulated by DSEB.

All sponsors are expected to comply with the requirements set out in this document from 1 January 2003.
# Table of contents

1. **LEGAL BASIS AND PURPOSE** ................................................................................................. 5  
   1.1 Roles and Responsibilities of Sponsors and the TGA ................................................................. 5  
   1.1.1 Sponsors ............................................................................................................................ 5  
   1.1.2 The Role of the TGA .......................................................................................................... 6  
   1.2 Pharmacovigilance Guideline .................................................................................................. 6  

2. **ADVERSE REACTION REPORTING** .......................................................................................... 7  
   2.1 Scope ..................................................................................................................................... 7  
   2.2 Expedited Reporting Requirements .......................................................................................... 7  
   2.2.1 Spontaneous ADR case reports .......................................................................................... 8  
   2.2.2 Case reports from the worldwide literature ......................................................................... 9  
   2.2.3 Reports from post-registration studies ............................................................................... 9  
   2.3 Content of Suspected Serious ADR Reports ............................................................................ 10  
   2.4 Reporting Forms ..................................................................................................................... 10  
   2.5 Impact of Reported ADRs on the Overall Safety Profile of a Product and the Approved Product Information ................................................................................................................. 11  
   2.6 Consumer Reports ................................................................................................................. 11  

3. **REPORTING REQUIREMENTS IN SPECIAL SITUATIONS** ..................................................... 13  
   3.1 Reporting in the Period between the Submission of the Registration Application and the Granting of the Registration ......................................................................................................................... 13  
   3.2 Reporting of Outcomes of Use during Pregnancy ..................................................................... 13  
   3.3 Reporting from Other Post-marketing Initiatives: Surveys, Registries ........................................ 14  
   3.4 SAS (Compassionate Use/Named Patient) Supplies .................................................................. 14  
   3.5 Lack of Efficacy ....................................................................................................................... 14  
   3.6 Reporting of Overdoses ........................................................................................................... 15  

**ANNEX 1 DEFINITIONS AND STANDARDS FOR REPORTING** .................................................... 16  
1. **DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH POST-APPROVAL DRUG SAFETY EXPERIENCE** .......................................................................................................................... 16  
   1.1. Adverse Event (AE) ................................................................................................................... 16  
   1.2. Adverse Drug Reaction (ADR) ............................................................................................... 16  
   1.3. Serious AE/ADR ..................................................................................................................... 16  
   1.4. Unexpected ADR .................................................................................................................... 17  
   1.5. Healthcare Professional ........................................................................................................ 17  
   1.6. Consumer ............................................................................................................................. 17  
   1.7. Post-registration Safety Study (PRSS) .................................................................................... 18  
   1.8 Post-registration study ............................................................................................................. 18  

2. **STANDARDS FOR EXPEDITED REPORTING** .......................................................................... 18  
   2.1. What Should Be Reported? ..................................................................................................... 18  
   2.1.1. Serious ADRs .................................................................................................................... 18  
   2.2. Reporting Time Frames .......................................................................................................... 18  
   2.3. Non-serious ADRs .................................................................................................................. 19  

3. **GOOD CASE MANAGEMENT PRACTISES** ............................................................................ 19  
   3.1. Assessing Patient and Reporter Identifiability ....................................................................... 19  

**ANNEX 2** ..................................................................................................................................... 20  
**RECOMMENDED KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS** .............................................................................................................. 20  
1. Patient Details ............................................................................................................................. 20  
2. Suspected Medicinal Product(s) ................................................................................................... 20  
3. Other Treatment(s) ....................................................................................................................... 20  

*Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch (July 2003 – Amended 31 May 2005)*

Page 3 of 22
4. Details (all available) of Adverse Drug Reaction(s) ................................................................. 20
5. Details on Reporter of an ADR .................................................................................................... 21
6. Administrative and Sponsor Details ........................................................................................ 21
ANNEX 3 ADDRESSES FOR REPORTING ....................................................................................... 22
1. LEGAL BASIS AND PURPOSE

1.1 Roles and Responsibilities of Sponsors and the TGA.

1.1.1 Sponsors
Each sponsor of registered medicines must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.

The sponsor should have permanently and continuously at its disposal, in Australia, a qualified person responsible for pharmacovigilance. This person should have experience in all aspects of pharmacovigilance and if not medically qualified should report to or have access to a medically qualified person. Although the medically qualified person does not necessarily have to be resident in Australia, he/she is expected to be able to address adverse drug reactions (ADRs), significant safety issues and the balance of the benefits and risks of a registered medicinal product in an Australian context. It is preferable that the medically qualified person be registered and resident in Australia. The name of the qualified person responsible for pharmacovigilance should be provided to TGA.

- The responsibilities of the qualified person for pharmacovigilance are as follows:
  - The establishment and management of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the sponsor, including to medical and sales representatives, is collected and collated so that it may be accessed at a single point within Australia.
  - The coordination of the preparation and submission to TGA of ADR reports, including reports arising from company-sponsored Australian post-marketing studies.
  - Ensuring that any request from the TGA for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a registered medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the product concerned.

Sponsors should ensure that all information relevant to the balance of benefits and risks of a registered medicinal product is reported to the TGA fully and promptly. Some circumstances in which a sponsor must give information are specified in section 29A, Therapeutic Goods Act, 1989. Note that these circumstances apply more broadly than just to adverse reactions to the product. They are where the sponsor becomes aware of information:

- that contradicts information already furnished by the sponsor under the Therapeutic Goods Act;
- that indicates that the use of the registered medicinal product in accordance with the recommendations for its use may have an unintended harmful effect;
- that the registered medicinal product, when used in accordance with the recommendations for its use, may not be as effective as information submitted previously suggests.
• When sponsors are involved in relationships including those that are contractual, arrangements for meeting pharmacovigilance obligations should be clearly specified in writing to the TGA at the time the medicine is registered, and subsequently when any changes to the arrangements are proposed.

When two or more separately registered medicinal products, which are identical in all respects apart from their trade name, are marketed in Australia by separate sponsors, each sponsor is obliged to meet the pharmacovigilance obligations described below. Where co-marketing arrangements exist, the sponsors may enter into practical arrangements, in order to meet their obligations. Such arrangements must be notified in writing to the TGA when the medicine is registered and subsequently when any changes to the arrangements are proposed. Such arrangements for joint pharmacovigilance data collection and analyses are acceptable to the TGA, provided each sponsor confirms in writing to the TGA that it understands that legal responsibility in respect of pharmacovigilance rests with it.

Separate sponsors may consider it appropriate to appoint the same person as the qualified person responsible for pharmacovigilance for products where the above arrangements apply.

1.1.2 The Role of the TGA

Consistent with the legislation, the TGA has established a pharmacovigilance system for the collection and evaluation of information relevant to the benefit to risk balance of registered medicinal products. The TGA continually monitors the safety profile of the products available in Australia and takes appropriate action where necessary.

1.2 Pharmacovigilance Guideline

The following guidance for sponsors covers:
• Adverse reaction reporting
• Reporting requirements in special situations

The definitions of relevant terms used in this Guideline are provided in Annex 1. This Guideline draws heavily on sections 1.1 to 1.3 of Volume 9 – Pharmacovigilance Rules Governing Medicinal Products in the European Union, published by the European Commission, Directorate Enterprise, Regulatory Framework and Market Authorisations (Version December 2001). The definitions and standards for expedited reporting in Annex 1 and the recommended key data elements for inclusion in expedited reports listed in Annex 2 are based on CPMP/ICH/3945/03 Note for Guidance on definitions and standards for expedited reporting.
2. ADVERSE REACTION REPORTING

The sponsor is responsible for reporting suspected adverse reactions to the TGA as described in section 2.2.

2.1 Scope

For registered medicinal products, reports of suspected adverse reactions received from all sources including health-care professionals and consumers (see section 2.6) should be reported. Spontaneously reported suspected adverse reactions, suspected adverse reactions from post registration studies and those reported in the world-wide literature are included. A reaction is suspected if either the reporting person or the sponsor believes there is a possible causal relationship between it and the medicine in question. Spontaneous reports of suspected adverse medicine reactions should be reported even if the sponsor does not agree with the reporter’s assessment of a possible causal association, or if the reporter has not provided a causal assessment. Adverse events that are not suspected of being product-related by the health-care professional attending the patient should not be reported unless the sponsor has reason to believe that a causal relationship is possible.

If the sponsor is aware that a person has reported a reaction to one of its products directly to the TGA, the sponsor should still report the reaction, informing the TGA that the report is likely to be a duplicate of a previous report. In this situation it is essential for the sponsor to provide all the available details including any record number provided to the initial reporter by the TGA, in order to aid identification of the duplicate.

Sponsors are expected to validate and follow-up all serious reactions reported by them to the TGA. In order to meet the expedited reporting timeframes, sponsors may submit an initial report containing at least the minimum data required (see section 2.3 and Annex 1) and submit a follow-up report containing more detailed information. All clinical information that becomes available to the sponsor as a result of follow-up activities should be provided.

Adverse reactions should be considered reportable according to the requirements outlined in these guidelines regardless of whether or not the registered medicinal product was used in accordance with the approved Product Information (including, for example, prescribed doses higher than those recommended); however, with regard to reporting of overdoses see section 3.6.

The addresses for reporting are provided in Annex 3.

2.2 Expedited Reporting Requirements

All expedited reports should be reported immediately and in no case later than 15 calendar days from receipt. The clock for expedited reporting starts as soon as one or more of the following has received the minimum information (see section 2.3 and Annex 1) required for the submission of an adverse reaction report:

- any personnel of the sponsor – including sales representatives,
- the qualified person responsible for pharmacovigilance or persons working for or with this person,
• where the sponsor has entered into relationships with a second company for the marketing of, or research on, the suspected product, the clock starts as soon as any personnel of the sponsor receives the minimum information; however, wherever possible, the time frame for regulatory submission should be no longer than 15 days from first receipt by the second company and explicit procedures and detailed agreements should exist between the sponsor and the second company to facilitate achievement of this objective,

• In the case of relevant world-wide scientific literature (see section 2.2.2), the clock starts with awareness of the publication by any personnel of the sponsor; the sponsor is expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database, such as Medline, Excerpta Medica or Embase, no less frequently than once a week, or by making formal contractual arrangements with a second party to perform this task; sponsors are also expected to ensure that relevant publications in Australia are appropriately reviewed.

2.2.1 Spontaneous ADR case reports

The sponsor should report suspected adverse reactions to the TGA in an expedited manner in accordance with the following:

i. Serious unexpected and serious expected reactions occurring in Australia must be reported on an expedited basis.

ii. Sponsors are not required to submit on an expedited basis reports of foreign (i.e. not occurring in Australia) serious unexpected or serious expected adverse medicine reaction reports. Sponsors are required instead to advise the TGA within 72 hours of any:

• significant safety issue identified by the sponsor as a result of its ongoing review and analysis of all information (including foreign reports of ADRs) that is pertinent to the safety or benefit-risk assessment of the product; or

• action which has been taken by a foreign regulatory agency, including the basis for such action.

The 72-hour clock starts from the time of awareness of any personnel of the sponsor. This is considered to have occurred where the sponsor’s review and analysis have been completed and a conclusion is drawn that a significant safety issue exists, or when the sponsor becomes aware of the actions of an overseas regulatory agency.

What constitutes a significant safety issue may require judgement on the part of the sponsor but would generally include but not be limited to any matter about the safety of the product which results, in a country other than Australia, in the:

• withdrawal or suspension of availability of the product;

• the addition of a contraindication, warning or precaution statement to the approved product information; or

• the modification for safety reasons of an existing contraindication, warning or precaution statement in the approved Product Information.

A sponsor is expected to be able to provide promptly on request to the TGA copies of those foreign adverse reaction reports in its possession which formed the basis for such actions.
These situations are quite different from the reporting of individual spontaneous ADRs, where the sponsor is allowed up to 15 days to confirm and follow up details before submitting an individual serious ADR report to the TGA.

iii. Any suspected increase in the frequency of serious reactions should also be reported on an expedited basis. The basis on which the frequency assessment has been made should be provided.

iv. All other reports of ADRs occurring in Australia do not need to be reported on an expedited basis, but should be reported on request or as line listings in a Periodic Safety Update Report (if one is required).

Individual adverse reaction reports initially becoming known to the sponsor from the TGA should be included in the next Periodic Safety Update Report, if one is required, and not reported in an expedited manner. However, if these TGA reports could lead to a change in the benefit/risk evaluation for the product, this possibility should be communicated to the TGA without delay.

2.2.2 Case reports from the worldwide literature

The sponsor is expected to screen the worldwide scientific literature (see paragraph 2.2) and report within 15 calendar days case reports of suspected serious adverse reactions occurring in Australia associated with the use of the active substance(s) of its products.

A copy of the relevant published article should be provided in English or, if not published in English, accompanied by a summary or translation in English. Where difficulty is experienced in meeting the 15-calendar day requirement, the TGA should be notified in writing.

2.2.3 Reports from post-registration studies

The definition of a post-registration study is provided in Annex 1. Serious suspected adverse reactions occurring in all post-registration studies in Australia of which the sponsor is aware should be reported on an expedited basis to the TGA. This includes studies conducted under the joint ADRAC-APMA Guidelines for the Design and Conduct of Company-Sponsored Post-Marketing Surveillance (PMS) Studies (May 1993).

In instances where the post-registration study is conducted by an investigator independent of the sponsor of the registered medicine (eg, “investigator-initiated post-registration study”), the responsibility for reporting adverse reactions to the TGA will rest with the investigator and not the sponsor. Where the sponsor is aware of the study, the sponsor should ensure that this responsibility for reporting is understood by and documented with the investigator.

Blinded cases and adverse events not suspected of being due to the study product(s) should not be reported as individual cases. For the management of blinded cases the ICH guideline E2A (CPMP/ICH/377/95) should be referred to. Thus, cases of serious unexpected reactions should be unblinded by the sponsor prior to reporting. Cases of serious expected reactions should only be reported in an expedited manner if the blind has already been broken for some reason. Otherwise, cases of serious expected reactions in blinded studies should be submitted immediately on...
unblinding at study end. Non-serious adverse events should be included in tabulations in end-of-study reports and do not need to be submitted separately.

For reports from ongoing clinical trials conducted outside the terms of the approved Product Information, the TGA’s Clinical Trial Guidelines should be followed.

2.3 Content of Suspected Serious ADR Reports

The data elements for individual adverse medicine reaction reports are defined in the ICH guideline E2B(M) (CPMP/ICH/287/95 modification corr.). It is essential for the sponsor to provide as many data elements as possible for cases of serious suspected ADRs to facilitate assessment. The information should be as complete as possible.

The minimum information required for the submission of an initial report is an identifiable patient, an identifiable reporter, a suspected reaction, and a suspect medicine. Annex 1 sets out the minimum criteria to allow identification of a reporter. In the interests of both good case management and detection of duplicate reports, sponsors should aim to have the name, professional or other group and address including postcode of the person making the report to the sponsor on each and every report (see sections 2.4 and 2.6 for possible exceptions). If this information is not available at the time of the initial report, it should be sought and subsequently provided to the ADRU. In every individual ADR case report, the medicinal substance/product name shall be provided as reported by the primary reporter.

The original words used by the reporter to describe the adverse reaction should be provided as well as the appropriate Lowest Level Terms from MedDRA (Medical Dictionary for Regulatory Activities).

The sponsor is expected to follow-up all reports of serious suspected adverse reactions to its products to obtain comprehensive information where available. Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

Sponsors may comment on whether they consider there is a causal association between the suspect product(s) and reaction(s) and should provide the criteria on which they have made the assessment.

2.4 Reporting Forms

Reporting forms acceptable to the TGA should be used. Each and every report should include the name, professional or other group and address including postcode of the person making the report to the sponsor. In any instance where the person making the report explicitly requests that their identity not be disclosed to the TGA, the sponsor should provide as much information about the person’s professional or other group and location in Australia such as postcode as is consistent with the person’s request for anonymity (see also Consumer Reports, section 2.6). Each and every report should clearly indicate the name of the person taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in that report and should be signed by that person, who need not necessarily be the qualified person responsible for pharmacovigilance.
Reports submitted to the TGA should be legible, and should not be photoreduced before submission. Ten point font or larger should be used; if it is necessary to submit a report with a font size less than 10 point, the report should be posted, rather than faxed, to the TGA. The font used should be easy to read (e.g., Times, Arial) and not condensed, because the submitted report may be photocopied.

Computer-generated forms are acceptable provided they are legible and follow a generally accepted content and layout, but must individually include the name of the person in Australia taking responsibility of behalf of the sponsor and be signed by that person. The TGA will advise a sponsor if it regards a report form format to be unacceptable.

2.5 Impact of Reported ADRs on the Overall Safety Profile of a Product and the Approved Product Information

In exceptional cases, when a reported ADR impacts significantly on the established safety profile of the product, the sponsor should indicate this in the report. Examples might be where the report is one of a series of similar or linked cases which are being simultaneously reported, or where there is prima facie evidence in favour of a causal relationship for a serious and unexpected reaction. Other situations include a suggestion of a change in the nature, severity or frequency of expected ADRs or when new risk factors are identifiable. Information on the frequency of ADRs should also provide the basic data on which the estimate of the frequency has been made, including data on the total number of ADR reports and number of patients exposed.

In situations where reported ADRs impact on the established safety profile, the sponsor should indicate what action it proposes in relation to the conditions of registration including the approved Product Information.

2.6 Consumer Reports

Reports from consumers are a potentially valuable source of information and should receive appropriate attention. As a general guiding principle, emphasis should be placed on the quality and completeness of the report and not its source. However, in recognition of the difficulties posed by the lack of medical detail and clinical confirmation of consumer reports, it is important that sponsors exercise judgement in relation to how such reports are recorded, followed-up, clarified and analysed for possible ADRs. The following is intended to guide sponsors on a general approach to consumer reports:

- Consumers should be encouraged to report adverse events and seek medical attention through their healthcare provider;
- During all contacts, attempts should be made to obtain information sufficient to ascertain the nature and seriousness of the event;
- Permission should be sought and documented, allowing contact with the consumer’s primary healthcare provider to obtain confirmation by a healthcare professional and additional relevant medical information. If permission is not forthcoming, information obtained from the consumer may permit judgement (by the pharmacovigilance officer and/or medically qualified person, see section 1.1.1) as to whether the case is apparently serious or non-serious and may guide subsequent handling of the report on a case by case basis. Additional follow-up or medical
confirmation may not be necessary for an apparently non-serious ADR. On the other hand, if the event is apparently serious and/or unexpected, reasonable additional efforts should be made to either obtain voluntary informed consent to contact the treating doctor or have the consumer provide the relevant medical documentation to allow a reasonable assessment of causality;

- All consumer reports should be documented as for any other types of cases and should be taken into account when overall safety assessments are made.

Sponsors should be familiar with and discharge obligations in relation to the collection, use and disclosure of personal information in accordance with the National Privacy Principles based on the Privacy Act 1988. These obligations are set out in the *Guidelines on Privacy in the Private Health Sector*, Office of the Federal Privacy Commissioner, November 2001. This is particularly important in those circumstances where the consumer is the reporter. In these cases TGA’s requirement for sponsors to provide information on an identifiable reporter does not override these privacy principles and explicit consent to the disclosure of the consumer’s identity to TGA should be sought. In situations where a consumer explicitly withholds consent to his/her identification as a reporter, the sponsor should indicate on the reporting form that it is a consumer report and that the name and contact details have been withheld at the request of the reporter.
3. REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

There are some situations, which are not covered directly by the reporting requirements detailed in section 2. The recommendations below refer to worldwide experience with the registered medicinal product.

3.1 Reporting in the Period between the Submission of the Registration Application and the Granting of the Registration

In the period between the submission of a registration application, but prior to registration, routine single case expedited reporting is not required except according to the separate guidelines where the product is being used in Australia in a clinical trial. However, in the pre-registration period, information that impacts on the benefit/risk evaluation may become available from the applicant, or countries where the medicine is already in use on a compassionate basis, or from countries where the medicine is marketed. This information should be submitted immediately by the applicant to the DSEB.

What constitutes a change to the benefit to risk balance is a matter of judgement for the applicant but an applicant may be required to justify a decision not to report. For example, normally another report of a well-known adverse reaction would not be considered significant, but a report of an unexpected or new serious suspected reaction with good evidence of a causal relationship, or where there is suspicion of a change in the frequency of severity of a known effect, would be considered relevant to the evaluation. Similarly results from studies which impact on the assessment of efficacy would be significant. When an application for registration is about to be considered by the Australian Drug Evaluation Committee (ADEC), sponsors are required to submit with their pre-ADEC response a tabulation of any serious unexpected adverse drug reactions that are not mentioned in the proposed Australian Product Information and have not been submitted previously. Parallel submission to meet the requirements of this section (3.1) at the time of the submission of the Pre-ADEC response is not required. Information as required by this section that becomes known after submission of the Pre-ADEC response must be provided to the TGA.

In instances where an application for registration of a registered medicinal product is withdrawn or lapses, section 29B, Therapeutic Goods Act 1989 provides that the Secretary of the Department of Health and Ageing may require a sponsor to disclose whether certain sorts of information about the product are known to the sponsor and, if that is the case, to provide that information to the Secretary.

3.2 Reporting of Outcomes of Use during Pregnancy

Sponsors are expected to follow up all individual reports to the sponsor of pregnancies where the fetus could have been exposed to one of its products. Where reports originate from consumers, reasonable attempts should be made at follow-up via the patient’s health-care professional. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a fetus could have been exposed (i.e., products taken before the gestational period need to be considered).
If a pregnancy results in an abnormal outcome which the reporting health-care professional considers might be due to the medicine, this should be treated as an expedited report and should follow the reporting requirements outlined in sections 2.2.1(i) and (ii). This includes cases where termination of pregnancy has occurred due to exposure to the drug. These cases together with other reports of abnormalities in pregnancy should also be available on request and be included in the next Periodic Safety Update Report (PSUR) together with aggregated data of overall exposure and details of normal/abnormal outcomes. Reports from prospective registries should also be available on request and be included and evaluated in the PSUR.

If, in the period between PSURs, a sponsor becomes aware of a signal of a possible teratogenic effect (e.g., a cluster of similar abnormal outcomes) the TGA should be informed immediately.

3.3 Reporting from Other Post-marketing Initiatives: Surveys, Registries

A sponsor may be involved in post-marketing initiatives, which result in the collection of information related to its products. In these situations, there is a distinction to be made between where there is a systematic process for reporting of adverse events to the sponsor and where no such process exists. Only those events that are specifically reported as suspected serious adverse reactions to a particular medicine are subject to expedited reporting. Reporting and subsequent reports should be dealt with in the same way as for post-registration studies (section 2.2.3).

3.4 SAS (Compassionate Use/Named Patient) Supplies

Sponsors should follow the requirements set out as a condition of authorisation of the use of the particular unregistered product.

3.5 Lack of Efficacy

A single case report of lack of efficacy will not generally constitute information requiring a notification to the TGA under Section 29A of the Therapeutic Goods Act. Individual case reports of lack of efficacy should not normally be expedited, but should be available on request and be discussed in the next Periodic Safety Update Report. However in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. Medicines used for the treatment of life-threatening diseases, vaccines and contraceptives are examples of classes of products where lack of efficacy should be considered as requiring expedited reports. Judgement should be used in reporting. For example, antibiotics used in life-threatening situations where the medicine was not in fact appropriate for the infective agent should not be reported. However, life-threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible should be reported on an expedited basis.

Lack of efficacy for anti-neoplastic agents should not be routinely reported as an expedited report unless the lack of efficacy indicates a change in the benefit to risk balance – for example a lower than expected efficacy or a higher than expected number, or rate, of deaths due to progressive disease.
3.6 Reporting of Overdoses

Reports of overdose with no associated adverse reactions should not be reported as adverse reactions. They should be routinely followed up by the sponsor to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome of an overdose. The sponsor should report cases of overdose (accidental or intentional) that lead to suspected serious adverse reactions in Australia on an expedited basis to the TGA. This should include reports that indicate that the taking of the suspect medicine led to suicidal intention and a subsequent overdose of the suspect medicine or other medication.
ANNEX 1 DEFINITIONS AND STANDARDS FOR REPORTING

1. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH POST-APPROVAL DRUG SAFETY EXPERIENCE

1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to this medicinal product.

1.2. Adverse Drug Reaction (ADR)

Adverse drug reactions concern noxious and unintended responses to a medicinal product.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

1.3. Serious AE/ADR

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

- results in death
- is life-threatening
  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is a medically important event or reaction.
Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

1.4. Unexpected ADR

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the Product Information should be considered unexpected. When a sponsor is uncertain whether an ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the Product Information specifically states that the ADR might be associated with a fatal outcome.

"Class ADRs" should not automatically be considered to be expected for the subject drug. "Class ADRs" should be considered expected only if described as specifically occurring with the product in the Product Information. This is illustrated in the following examples:

"As with other drugs of this class, the following undesirable effect occurs with Drug X."
"Drugs of this class, including Drug X, can cause..."

If the ADR has not been documented with Drug X, statements such as the following are likely to appear in the Product Information:

"Other drugs of this class are reported to cause..."
"Drugs of this class are reported to cause..., but no reports have been received to date with Drug X."

In these situations, the ADR should not be considered as expected for Drug X.

NOTE: The term "listedness" is not applicable to expedited reporting but should be used to characterise the ADR according to the Company Core Safety Information.

1.5. Healthcare Professional

Healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, or coroner.

1.6. Consumer

Consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, or relative of a patient.
1.7 Post-registration Safety Study (PRSS)

A post-registration safety study is a pharmacoepidemiological study, or a clinical trial carried out in accordance with the approved Product Information, conducted with the aim of identifying or quantifying a safety hazard related to a registered medicinal product. For the purpose of this guideline, any study where the number of patients to be included will add significantly to the existing safety data for the product will also be considered a PRSS.

1.8 Post-registration study

A post-registration study is any study conducted within the conditions of registration or under normal conditions of use. A post-registration study may sometimes also fall within the definition of a post-registration safety study (PRSS). In relation to ADR reporting and PSUR requirements, reference to a post-registration study means any post-registration study of which the sponsor is aware.

2. STANDARDS FOR EXPEDITED REPORTING

2.1. What Should Be Reported?

2.1.1. Serious ADRs

All serious adverse drug reactions are subject to expedited reporting. All other reports of ADRs occurring in Australia do not need to be reported on an expedited basis, but should be reported on request or as line listings in a periodic safety update report (if one is required).

For reports from studies and other solicited sources, all cases judged by either the reporting healthcare professional or the sponsor as having a possible causal relationship to the medicinal product would qualify as ADRs. For purposes of reporting, spontaneous reports associated with approved drugs imply a suspected causal relationship.

2.2. Reporting Time Frames

In general, expedited reporting of serious ADRs is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the sponsor.

The regulatory reporting time clock is considered to start on the date when any personnel of the sponsor first receive a case report that fulfils minimum criteria as well as the criteria for expedited reporting. In general, this date should be considered day 0.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be reclassified (e.g., from non-serious to serious).
2.3. Non-serious ADRs

Cases of non-serious ADRs, whether expected or not, would not normally be considered reportable on an expedited basis. Non-serious ADRs should be reported on request from the TGA and included in the periodic safety update report (if one is required).

3. GOOD CASE MANAGEMENT PRACTICES

3.1. Assessing Patient and Reporter Identifiability

Patient and reporter identifiability is important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases. The term identifiable in this context refers to the verification of the existence of a patient and a reporter.

Sponsors should be familiar with and discharge obligations in relation to the collection, use and disclosure of personal information in accordance with the National Privacy Principles based on the Privacy Act 1988. These obligations are set out in the Guidelines on Privacy in the Private Health Sector, Office of the Federal Privacy Commissioner, November 2001. This is particularly important in those circumstances where the consumer is the reporter. In these cases TGA’s requirement for sponsors to provide information on an identifiable reporter does not override these privacy principles and explicit consent to the disclosure of the consumer’s identity to TGA should be sought. In situations where a consumer explicitly withholds consent to his/her identification as a reporter, the sponsor should indicate on the reporting form that it is a consumer report and that the name and contact details have been withheld at the request of the reporter.

One or more of the following should automatically qualify a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number. In addition, in the event of second-hand reports, every reasonable effort should be made to verify the existence of an identifiable patient and reporter.

All parties supplying case information or approached for case information should be identifiable: not only the initial reporter (the initial contact for the case), but also others supplying information.

In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, "Two patients experienced..." or "a few patients experienced" should be followed up for patient-identifiable information before regulatory reporting.
ANNEX 2

RECOMMENDED KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

Some data elements might not be relevant, depending on the circumstances. Attempts should be made to obtain follow-up information on as many other listed items as are pertinent to the case.

1. Patient Details
   Initials
   Other relevant identifier (patient number, for example)
   Gender
   Age, age category (e.g., adolescent, adult, elderly), or date of birth
   Concomitant conditions
   Medical history
   Relevant family history

2. Suspected Medicinal Product(s)
   Brand name as reported
   International Non-Proprietary Name (INN)
   Batch/lot number
   Indication(s) for which suspect medicinal product was prescribed or tested
   Dosage form and strength
   Daily dose (specify units e.g., mg, ml, mg/kg) and regimen
   Route of administration
   Starting date and time
   Stopping date and time, or duration of treatment

3. Other Treatment(s)
   The same information as in item 2 should be provided for the following:
   Concomitant medicinal products
     (including non-prescription, over-the-counter medicinal products, herbal remedies, dietary supplements, complementary and alternative therapies, etc.).

   Relevant medical devices

4. Details (all available) of Adverse Drug Reaction(s)
   Full description of reaction(s), including body site and severity
   The criterion (or criteria) for regarding the report as serious
   Description of the reported signs and symptoms
   Specific diagnosis for the reaction
   Onset date (and time) of reaction
   Stop date (and time) or duration of reaction
   Dechallenge and rechallenge information
   Relevant diagnostic test results and laboratory data
Setting (e.g., hospital, out-patient clinic, home, nursing home)
Outcome (recovery and any sequelae) For a fatal outcome, stated cause of death
Relevant autopsy or post-mortem findings
Relatedness of product to reactions/event(s)

5. Details on Reporter of an ADR
Name
Mailing address
Electronic mail address
Telephone and/or facsimile number
Reporter type (consumer, healthcare professional, etc.)
Profession (specialty)

6. Administrative and Sponsor Details
Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
Date the event report was first received by manufacturer/company
Country in which the event occurred
Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to authorities
Name and address of sponsor
Name, address, electronic mail address, telephone number, and facsimile number of contact person at the sponsor’s Australian address.
Identifying regulatory code or AUST R number.
Company/manufacturer’s identification number for the case (the same number should be used for the initial and follow-up reports on the same case).
ANNEX 3 ADDRESSES FOR REPORTING

Address for submitting individual case reports of suspected adverse drug reactions occurring in Australia, and for notification of sponsors’ qualified person responsible for pharmacovigilance:

Mail:
The Secretary, ADRAC
Reply Paid 100
Woden ACT 2606

Fax:
The Secretary, ADRAC
(02) 6232 8392

Address for submitting all other information described in Section 29A, Therapeutic Goods Act:

Mail:
The Director
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Fax:
The Director, DSEB
(02) 6232 8140