Australian Government
Department of Health
Therapeutic Goods Administration

Consultation paper: Biovigilance responsibilities of sponsors of biologicals

Australian requirements and recommendations

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TGA Health Safety Regulation

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Summary

All sponsors of human tissue and cell-derived products regulated as biologicals under the biologicals framework are required to:

- report adverse events and serious threats to public health related to the biological within the specified time frames
- ensure that any request from the TGA for the provision of additional information related to the biological is answered fully and within the specified time frame.

In order to achieve this, it is recommended that sponsors have a biovigilance system in place and nominate a biovigilance contact person. A summary of reporting requirements is in the table below.

Reporting requirements for biological adverse events

Adverse event	Method of reporting	Reporting time frame
Serious threat to public health	In writing to: The Signal Investigation Coordinator, Pharmacovigilance and Special Access Branch, TGA, by Email: si.coordinator@tga.gov.au	48 hours
Recalls, quality defects and contaminated or counterfeit biologicals	Human blood & tissues recall report form or Phone: 1800 020 653	with the least possible delay
An event or occurrence that led to a death or serious deterioration in the state of health of an individual, i.e. a serious adverse event	A number of forms are available - electronic structured data preferred	10 calendar days
An occurrence that, if it occurred again, might lead to a death or serious deterioration in the state of health of an individual, i.e. a near serious adverse event	A number of forms are available - electronic structured data preferred	30 calendar days

Time frames are in relation to when the sponsor becomes aware that there is an issue for which there is a reasonable possibility of causal relationship.

1. Introduction

This guidance is for sponsors of human tissue and cell-derived products regulated as biologicals and does not apply to sponsors of biological medicines or other therapeutic goods that are not regulated as biologicals.

Biovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other problem related to biologicals. Biovigilance for biologicals is analogous to pharmacovigilance for medicines and devices vigilance for medical devices. Biovigilance is part of Australia's therapeutic product vigilance system.

Relevant legislation

Biologicals are defined in Part 3-2A of the *Therapeutic Goods Act 1989* (the Act) as a thing made from, or that contains, human cells or human tissues and that is used to:

- treat or prevent disease, ailment, defect or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to a disease
- replace or modify a person's body parts.

A sponsor must notify the TGA of certain matters in relation to biologicals that are included in the Australian Register of Therapeutic Goods (ARTG) and it is a criminal offence, or a civil penalty, to fail to make such notifications, according to section 32DQ of the Act. The specified periods within which sponsors must comply for the purposes of section 32DQ of the Act are prescribed in Regulation 16AB of the *Therapeutic Goods Regulations 1990* (the Regulations).

The imposition of conditions at the time of inclusion of a biological in the ARTG is provided for in sections 32EC and 32ED of the Act. New conditions may be imposed and existing conditions removed or varied at any time while the biological remains included in the ARTG under section 32EE of the Act. Requirements imposed as conditions of inclusion under sections 32EC and 32ED continue to apply for biologicals where the application has been withdrawn or lapses, where the Secretary gives notice in accordance with section 32DR of the Act.

Refusal or failure to comply with conditions of inclusion in the ARTG, according to sections 32EF, 32EG and 32GC of the Act, is grounds for cancellation or suspension of a biological from the ARTG, and is also grounds for prosecution for an offence in accordance with section 21A of the Act.

Under section 32DQ(3) of the Act, the sponsor must report the following information:

a. information that contradicts information already given by the sponsor under the Act in relation to the biological (including information given about the quality, safety or efficacy of the biological)

b. information that indicates that the use of the biological in accordance with the recommendations for its use may have an unintended harmful effect

c. information that indicates that the biological, when used in accordance with the recommendations for its use, may not be as effective as the application for inclusion of the biological in the ARTG or information already given by the sponsor under this Act suggests.

The information must be reported in accordance with the time frame specified in paragraph 16AB of the Regulations.

In this document we describe legislated reporting requirements for sponsors of biologicals. Where the word 'must' or 'required' is used, a legal requirement is being described.

We also provide guidance on what, when and how to report and make recommendations about best practice biovigilance systems.

TGA requirements do not override applicable privacy laws. Sponsors should be familiar with and discharge their obligations in relation to the collection, use and disclosure of personal information in accordance with the Australian Privacy Principles as set out in the *Privacy Act 1988* and any applicable state and territory privacy legislation.

Role of the TGA

The TGA has established vigilance systems for collecting and evaluating information relevant to the benefit-risk balance of all therapeutic goods, including biologicals. The TGA continually monitors the safety profile of therapeutic goods available in Australia and takes appropriate action where necessary.

2. Biovigilance contact person

Every sponsor is legally responsible for meeting biovigilance requirements for their products, even if their products are the same as products belonging to other sponsors.

We recommend that sponsors have a person who takes responsibility for biovigilance of the sponsor's products. We recommend that this person:

- lives in Australia
- is permanently and continuously available
- is trained or experienced in biovigilance
- is a medically qualified person, or has ready access to a medically qualified person. It is preferred that the medically qualified person is registered as a medical practitioner with the Medical Board of Australia, so that adverse events, serious threats to public health and benefit-risk balance of the sponsor's biological products are considered in the Australian context.

Ideally the person responsible for biovigilance is also the nominated contact person responsible for all biovigilance reporting and record-keeping requirements. The name and contact details of the biovigilance contact person need to be provided to the TGA in every biovigilance report.

We recommend that the sponsor nominates the same biovigilance contact person for all of the biologicals they sponsor. The TGA will direct requests for biovigilance information to the nominated contact person, who is responsible for coordinating biovigilance communication between the sponsor and the TGA.

Sponsors can nominate the biovigilance contact person via the TGA Business Services site, or by contacting the TGA by email ebs@tga.gov.au.

We ask that sponsors notify biovigilance contacts to the TGA:

- within 15 calendar days of a product being entered in the ARTG
- within 15 calendar days of any change in details of the nominated contact person.

More contact information for TGA Business Services is available on the TGA website at https://www.tga.gov.au/tga-business-services

3. Adverse events related to biological products

An adverse event is any undesirable medical event that occurs in a temporal relationship with (i.e. during or after) the administration or use of a biological product. It is a harmful and unintended response and can be any unfavourable and unintended symptom, sign (for example, an abnormal laboratory finding), disease or injury that occurs related to the use of a biological.

For **biovigilance**, the TGA uses the term *adverse event* to mean an undesirable medical event for which there is at least a reasonable possibility of a causal relationship between the use of the biological and the event. Such adverse events are considered to be related events and are reportable in accordance with the timeframes and guidance in this document.

How to determine when an adverse event may be related to a biological

All spontaneous reports of biologicals adverse events notified to the sponsor by healthcare professionals, patients or consumers are considered to be related adverse events as they convey the suspicions of the person reporting the information (the 'primary source') that there is a causal relationship. They are reportable in accordance with the guidance in this document, unless:

- the person reporting to the sponsor specifically states that they believe the events to be unrelated or that a causal relationship can be excluded and
- the sponsor agrees with this assessment.

If the sponsor disagrees with the primary source about the reasonable possibility of a causal relationship, then both opinions should be recorded in the adverse event report given to the TGA. The sponsor should include the criteria on which the assessment was made.

For non-spontaneous reports, that is those from post-ARTG inclusion studies and other post-marketing initiatives, all events judged by the reporting healthcare professional, the investigator or the sponsor as having at least a possible causal relationship with the biological should be considered related adverse events and reported.

Non-spontaneous reports of adverse events do not need to be reported if they are not suspected to be causally related to the biological.

There are different methods for determining causality. One system is the World Health Organization Uppsala Monitoring centre system (WHO-UMC) for standardised case causality assessment <http://who-umc.org/Graphics/24734.pdf>.

Adverse events may be associated with any aspect of the biological

Adverse events may be associated with the biological itself or any aspect of the biological, such as:

- solutions
- excipients
- other substances or materials
- packaging
- delivery systems.

Potential for adverse events

The potential for adverse events related to a biological depends on several factors including the:

- origin of the biological (autologous or allogeneic)
- ability of cells constituting a biological to proliferate or differentiate
- ability of the biological to initiate an immune response
- life span of the biological in vivo
- site and mode of administration
- type and level of cell manipulation during production
- storage time and conditions
- out-of-specification findings identified during in-process testing of the biological.

These factors may be taken into consideration when assessing causality.

Spontaneous reports

A spontaneous report is an unsolicited communication by a health professional or consumer to a sponsor, manufacturer, regulatory authority or other organisation (e.g. WHO) that describes one or more suspected adverse events in a patient who was given a biological.

For a report to be spontaneous it should not be derived from a study or any organised data collection system where adverse event reporting is actively sought (solicited). Stimulated reports are considered to be spontaneous. Stimulated reporting can occur as a result of:

- notification by a 'Dear Health Professional' letter
- publication in the press or on social media
- questioning of health professionals by company representatives
- communication from patients' organisations to their members
- class action lawsuits.

Types of adverse events

Adverse events include:

- serious adverse events
- near serious adverse events
- non-serious adverse events.

Serious adverse events and near serious adverse events

In accordance with the legislative requirements for biologicals, the TGA distinguishes between ***serious adverse events*** and ***near serious adverse events.***

- The term ***serious adverse event*** for a biological means 'an event or occurrence that led to a death or serious deterioration in the state of health of a patient, a user of the biological or another person'.
  - Such events occurring in Australia must be reported to the TGA within ten days of the sponsor becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(b)).
- The term ***near serious adverse event*** for a biological means 'an event or occurrence that, if it occurred again, might lead to the death, or serious deterioration in the state of health, of a patient, a user of the biological or another person'.
  - Such events occurring in Australia must be reported to the TGA within thirty days of the sponsor becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(c))

A ***serious adverse event*** for a biological is an adverse event for which one or more of the following is true:

- results in death
- is life-threatening
- requires inpatient hospitalisation
- prolongs existing hospitalisation
- results in persistent or significant disability or incapacity, including permanent impairment of a body function or permanent damage to a body structure
- necessitates medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
- is a congenital anomaly or birth defect or
- is a medically important event (see below).

Any transmission of an infectious agent via a biological is a ***serious threat to public health*** and must be reported as described in accordance with the time frame and procedure described in Section 4.

An unexpected lack of efficacy may be a serious adverse event or *a* ***serious threat to public health***. See Section 4 for information on assessing cases of unexpected lack of efficacy.

A ***near serious adverse event*** for a biological is an adverse event which, if it occurs again, might result in one or more of the above outcomes. Timely intervention by a healthcare practitioner may have prevented such an outcome from occurring. This category also includes the situation where testing or examination of the biological, or information supplied with the biological or scientific literature has indicated some factor that could lead to one or more of the above outcomes.

Medically important events

Medical and scientific judgement should be used to determine whether an event is medically important. Events that make one of the outcomes above more likely, or that require intervention to prevent one of these outcomes, should be considered as serious. For example, events that require intensive treatment in an emergency department or at home but do not result in hospitalisation, such as:

- allergic bronchospasm
- a blood disorder
- convulsions

are considered serious adverse events.

Non-serious adverse events

All adverse events that do not meet the definition of serious or near serious adverse events are considered to be non-serious adverse events. Reporting requirements for non-serious events are described in Section 6.

4. Serious threat to public health

The TGA considers a ***serious threat to public health*** in relation to a biological exists when any safety issue is identified which may change the benefit-risk assessment of the product and require action to eliminate or reduce the risk.

Sponsors must report serious threats to public health to the TGA within 48 hours of becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(a)) in accordance with the procedures below: see Time frame for reporting a serious threat to public health and How to report a serious threat to public health.

Safety issues which may change the benefit-risk assessment of a biological

Safety issues which may change the benefit-risk assessment of a biological include:

- a report of an unexpected or previously unknown serious or near serious adverse event
- a change in the nature, severity or frequency of expected (known) adverse events
- the identification of previously unknown risk factors
- the transmission of an infectious agent, including reactivation of any viral vector
- a signal of a possible teratogenic effect

- a signal of possible tumorigenicity
- unexpected lack of efficacy
- issues related to the raw materials used in the biological
- issues related to the delivery system used for the biological
- issues due to misinformation in the product documentation
- issues related to use outside the approved indication or intended use.

Transmission of an infectious agent

Any suspected transmission of an infectious agent is considered a serious threat to public health.

Infectious agents include:

- bacteria
- viruses
- infectious particles such as prions.

Transmission of an infectious agent may be suspected from clinical signs or symptoms or laboratory findings. In ascertaining the type of infection, the sponsor should focus on the agents known to be potentially transmitted by a biological, but should also consider unknown agents and reactivation of any viral vector.

When considering contributors to the transmission, care should be taken to distinguish (if possible):

- the cause, for example, injection or administration
- the source, for example, the tissue donor or contamination
- the clinical condition of the patient, for example, immunosuppressed.

Confirmation of contamination of the biological increases the evidence for transmission and may suggest a quality defect for which action should be taken. In this context, 'contamination' includes inadequate inactivation or attenuation of infectious agents known to be present.

Possible teratogenic effect

A signal indicating a possible teratogenic effect may come from a cluster of cases of similar abnormal outcomes in clinical situations or from nonclinical data.

Unexpected lack of efficacy

Clinical judgement should be used when considering if cases of lack of therapeutic efficacy qualify for reporting as serious adverse events or as serious threats to public health.

- Lack of efficacy of a biological used to treat a critical condition or a life-threatening disease is considered to be a serious adverse event, unless the person reporting to the sponsor has specifically stated that the outcome was due to disease progression and was not related to the biological.

- If a lack of therapeutic efficacy is thought to have contributed to a change in or modification (for example, aggravation, progression or recurrence) of the condition for which the biological was administered, this should be submitted as a serious adverse event report. The report should include the nature of the effect on the medical condition.

In all cases, lack of therapeutic efficacy of a biological should be recorded by the sponsor and followed-up if the report is incomplete. Sponsors are expected to retain all reports of cases not considered to qualify as serious adverse events and to provide them if requested and consider them in the next Periodic Safety Update Report (PSUR), if PSURs are required.

Where lack of efficacy is an unexpected serious adverse event, it should be reported as a serious threat to public health.

Lack of efficacy may flag a change in:

- the quality of manufacturing
- a property of the biological
- responsiveness to the biological.

We expect the sponsor to take all reasonable steps to investigate these possibilities. If the investigation concludes that such a change has occurred, the sponsor should report the issue as a serious threat to public health. If a quality defect is identified, the sponsor should report this as soon as possible as detailed in Section 5.

Products to be considered

Clinical or scientific judgement needs to be used in discerning which products available in Australia and worldwide are likely to provide relevant safety information for an Australian sponsor's biological product. It is anticipated that this may be more difficult for biologicals than for medicines or medical devices.

Information sources

Serious threats to public health related to a biological are identified by the sponsor as a result of its ongoing review and analysis of all information pertinent to the benefit-risk assessment of the product.

Serious threats to public health may be identified from:

- signal detection activities
- review and analysis of adverse event reports
  - including adverse events which have occurred in a country other than Australia
- reports about unexpected lack of efficacy
- studies that impact on the evidence for efficacy
- major safety findings from newly completed
  - nonclinical studies
  - post-ARTG inclusion studies
  - clinical trials

- other post-market activities
- the scientific or medical literature
- action taken by an overseas regulatory agency, such as:
  - withdrawal or suspension of the availability of the product
  - addition of a contraindication, warning or precaution statement to the product documentation or label
  - modification of an existing contraindication, warning or precaution for safety reasons
  - modification or removal of an indication or intended use for safety reasons.

Time frame for reporting a serious threat to public health

The sponsor must report serious threats to public health to the TGA within 48 hours of identification [*Therapeutic Goods Regulations 1990*, Regulation 16AB(a)].

The 48 hour clock starts from the time any personnel of the sponsor becomes aware of the issue. This is considered to be when

- the sponsor's review and analysis has resulted in the conclusion that a serious threat to public health exists or
- the sponsor becomes aware of actions taken by an overseas regulator.

If the sponsor is unsure as to whether the incident should be classified as a serious threat to public health, we recommend that the TGA be contacted within 48 hours.

How to report a serious threat to public health

Reports of serious threats to public health need to be in writing and preferably sent by email to the Signal Investigation Coordinator si.coordinator@tga.gov.au. We ask that such reports:

- format the subject line as 'Urgent – serious threat to public health – [descriptor: name or number of biological, name of sponsor, or some other descriptor]'
- describe the evidence for the threat
- indicate the action that the sponsor is proposing to take to eliminate or reduce the risk
  - the action may relate to conditions of inclusion in the ARTG including amendments to the label or the product information or any other change
- clearly identify the person in Australia who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report
- include contact details of the person reporting on behalf of the sponsor, who is preferably the nominated biovigilance contact person.

Where the serious threat to public health is identified from an increase in the frequency of serious adverse events, provide in the report the data used to derive the frequency estimate, including the total number of adverse event reports and the total number of individuals exposed.

If requested by the TGA, a sponsor must be able to provide within the specified time frame any additional information to assist with the evaluation of benefits and risks of the biological, including information about the extent of use of the product concerned.

If requested by the TGA, the sponsor is to provide to the TGA copies of overseas adverse event reports in its possession that formed the basis for actions undertaken by an overseas regulator.

5. Recalls, quality defects and contaminated or counterfeit biologicals

Suspected or confirmed quality defects and contaminated or counterfeit biological products are to be notified to the TGA with the least possible delay in accordance with the Uniform Recall Procedure for Therapeutic Goods (URPTG). This procedure is a result of consultation between the therapeutic goods industry and Commonwealth, state and territory health authorities.

Notification needs to be prompt because it may be necessary to implement urgent measures, such as the recall of one or more defective batch(es) of a biological from the market, to protect public health.

To notify the TGA of any recalls, quality defects and contaminated or counterfeit biological products sponsors may use the Human blood and tissues recall report form. For problems requiring urgent attention, you may also telephone TGA Recalls on 1800 020 653 (see *Contact details for enquiries about product recalls* on the TGA website at <https://www.tga.gov.au/product-recalls#contacts>

Sponsors are expected to have a system in place to ensure that reports of adverse events suspected of being related to quality defects of a biological or an adulterated or counterfeit biological are investigated in a timely manner.

In addition to reporting a suspected or confirmed quality defect or an adulterated or counterfeit biological, all serious adverse events or serious threats to public health associated with the quality defect need to be reported within the required time frames.

6. What adverse events to report

Sources of information

Information on adverse events comes to sponsors from a variety of sources including:

- reports made directly to the sponsor by health professionals or consumers
- reports in the world-wide scientific and medical literature
- reports in internet and digital media
- reports in the lay press or other media
- post-ARTG inclusion studies
- other post-market initiatives
- reports in world-wide literature of adverse reactions that occurred in Australia.

Post-ARTG inclusion trial data

Sponsors must report all serious adverse reactions occurring in post-ARTG inclusion studies undertaken in Australia that are assessed by the reporting healthcare professional, the investigator or the sponsor as having at least a possible causal relationship with the biological.

A post-ARTG inclusion study is any study carried out in accordance with the conditions of inclusion of a biological in the ARTG, label indications or product document indications. This includes studies that may have commenced prior to approval and are ongoing after the product has been included in the ARTG. A post ARTG-inclusion study may sometimes also fall within the definition of a safety study.

Such a study may be:

- carried out as a condition of ARTG inclusion of that biological
- carried out by the sponsor or by a researcher other than the sponsor.

Sponsors are **not** required to report as individual cases:

- adverse events not suspected of being due to the biological
- blinded cases
  - report serious adverse events only if the blind has been broken or when un-blinding occurs at the end of the study

  For guidance on the management of blinded cases sponsors should refer to Section D of the *Note for guidance on clinical safety data management: Definitions and standards for expedited reporting* (CPMP/ICH/377/95).

For post-ARTG inclusion studies conducted or initiated by an investigator independent of the sponsor, the investigator is responsible for reporting adverse events to the TGA. However, if the sponsor is aware of the study, then we recommend that the sponsor requests the investigator to notify them of adverse events that occur in the study.

Other post-market initiatives

Sponsors may be involved in other post-market initiatives that collect information related to their products. These include, but are not limited to:

- patient support and disease management programs
- surveys of patients, health professionals or health providers
- information gathering on efficacy or patient compliance
- market research programs
- compassionate use or named patient use programs
- registries.

These activities may involve the receipt of information about adverse events. Sponsors are expected to have a system in place to collect full and comprehensive case information and to evaluate that information to determine whether these adverse events are possibly related to the biological.

All serious and near serious adverse events in Australia must be reported

The sponsor must notify the TGA of all serious and near serious adverse events in Australia, whether expected or unexpected:

- even when the sponsor does not agree with the reporter's assessment of a possible causal association
- regardless of whether the biological was used in accordance with the approved indications or intended use; all serious and near serious adverse events in Australia from overdose, off-label use, misuse, administration error or occupational exposure are to be reported (but if used under the Special Access Scheme, there are separate reporting requirements)
- in addition to another person reporting the serious or near serious adverse event; in this case the sponsor should inform the TGA that it is likely to be a duplicate of a previously submitted report, and provide the TGA with as many details as possible to aid in identifying the duplicate, including the record number allocated to the initial report by the TGA, if this is known.

Minimum information for a valid report

Adverse event reports are valid if the following information exists:

1. an identifiable patient (see Section 8 for the definition of identifiable patient
2. one or more suspected biological, delivery system or other aspect of a biological
3. one or more suspected adverse events (events with a reasonable possibility of causal relationship)
4. one or more identifiable reporters (see Section 8 for the definition of an identifiable reporter)

Sponsor reports to the TGA should not include the full names of the patient. The name and contact details of the reporter should only be provided to the TGA with the reporter's agreement.

The reporting time frame does not begin until the report is valid, that is, it contains the minimum four data elements (patient, substance, event and reporter).

If you choose to report an adverse event without the minimum information required for validity, your report must include the biological substance or product name provided by the primary reporter.

Adverse event reports are valid only if they contain the minimum four data elements:

1. patient
2. biological
3. event: reasonable possibility of causal relationship
4. reporter

Reporting non-serious adverse events

Sponsors are not routinely expected to report non-serious adverse events to the TGA. If these occur in Australia, sponsors should keep records of such events and:

- report them, if specifically requested by the TGA, in the requested format and timeframe
- include them in ongoing monitoring activities including in signal investigation processes
- consider them in future Periodic Safety Update Reports (PSURs), if PSURs are required.

If a case does not initially qualify as being serious, but later information results in a reclassification to a serious or near serious adverse event, then the reporting time frame starts from the date of reclassification.

Reporting adverse events that occur in other countries

Sponsors are not required to submit individual reports of serious, near serious or non-serious adverse events that occur in countries other than Australia, but sponsors are expected to:

- keep records of such adverse events
- provide the report to the TGA if requested
- consider the report in future Periodic Safety Update Reports (PSURs), if PSURs are required
- include the report in any analysis of global adverse events undertaken by the sponsor.

Where such adverse events impact on the benefit-risk balance or overall safety profile of the biological, sponsors need to report the information as a serious threat to public health.

Reporting exposure during pregnancy and breastfeeding

Sponsors should follow up on all individual reports of pregnancies where the fetus could have been exposed to a biological so that information on the outcome of the pregnancy and development of the child after birth can be collected. Possible exposure through the mother or father should be considered.

The likelihood of a biological administered to a parent contributing to a short-term or long-term adverse effect on a fetus or newborn should be considered on a case-by-case basis.

Reports of adverse events related to exposure to a biological product during pregnancy should contain as much detail as possible to help with assessing the causal relationship between a reported adverse event and the exposure.

Teratogenicity is a serious threat to public health

A signal of a possible teratogenic effect is considered to be a serious threat to public health and needs to be reported within 48 hours. Such a signal might come from a cluster of similar abnormal outcomes in clinical situations.

Serious adverse events occurring during pregnancy or breastfeeding

If the sponsor becomes aware of cases where a pregnancy results in an abnormal outcome that the reporting health professional considers might be due to a biological then this is a reportable serious adverse event. This includes:

- congenital anomalies or developmental delay in the fetus or child
- fetal death and spontaneous abortion
- suspected adverse events in the neonate that are classified as serious.

Suspected serious adverse events that occur in infants following exposure to a biological product via breast milk are also reportable.

Other events during pregnancy

Cases that are not to be reported routinely to the TGA because there is no suspected adverse event include:

- induced termination of pregnancy without information on congenital malformation
- pregnancy exposure without outcome data
- pregnancies that have a normal outcome.

However, the sponsor is expected to collect these reports and provide them to the TGA if requested. If a Periodic Safety Update Report (PSUR) is required, these reports should be included together with aggregated data of overall exposure and details of normal, abnormal and unknown outcomes. The TGA may also request reports from prospective pregnancy registries to be included and evaluated in the PSUR.

Overdose, abuse, off-label use, misuse, administration error or occupational exposure

Sponsors are expected to follow up on all individual reports of serious or near serious adverse events in Australia associated with overdose, abuse, off-label use, misuse, administration error or occupational exposure. Information in these cases needs to be as complete as possible with regards to early symptoms, treatments, outcomes and context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population etc.).

Sponsors are required to report to the TGA all such cases associated with serious adverse events or near serious adverse events in Australia in accordance with the time frames in Section 3.

When such reports constitute serious threats to public health impacting on the benefit risk balance of the biological product, they must be reported as described in Section 4.

When there is no associated adverse event, or the associated adverse event is non-serious, these cases are not to be reported routinely to the TGA. Reports of such incidents should be collected and included in ongoing review and analysis of the biological, and be provided on request to the TGA.

7. When and how to report

Time frames

The time frames for reporting serious threats to public health and adverse events related to biologicals are specified in section 16AB of the Regulations and can be summarised as:

- within 48 hours of becoming aware of an event or occurrence that represents a serious threat to public health
- within 10 days of becoming aware of an event or occurrence that led to the death or serious deterioration in the state of health of a patient, a user of the biological or another person (serious adverse event)
- within 30 days of becoming aware of an event or occurrence that, if it occurred again, may lead to the death or serious deterioration in the state of health of a patient, a user of the biological or another person (near serious adverse event).

Issues related to quality defects are to be reported as soon as possible.

Timeframes will be provided for Periodic Safety Update Reports (PSURs) and when the TGA requests specific information.

Information on how to report a serious threat to public health is provided in Section 4.

The remainder of this Section provides information on how to report serious and near serious adverse events.

When is Day 0 for serious and near serious adverse events?

The reporting time frame begins on the day that the minimum four data elements (patient, substance, event and reporter) that constitute a valid adverse event report are received by one or more of the following:

- any personnel of the sponsor, including sales representatives
- any personnel of partners, vendors, contractors and contract manufacturers
- the person responsible for biovigilance or persons working for or with this person.

The reporting time clock begins each time any of the personnel mentioned above receives additional clinical or medically-relevant information for a previously reported serious or near serious adverse event.

If a case does not initially qualify as being serious, but later information results in a re-classification to a serious or near serious adverse event, then the reporting time frame starts from the date of re-classification.

Explicit procedures and detailed agreements should exist between the sponsor and any contracted company to enable reporting to occur in accordance with the required time frames.

Day 0 for literature reports

Where the adverse event is identified through screening the worldwide literature, the clock starts when the sponsor becomes aware of a publication of reports of cases which occurred in Australia and contain at least the minimum four data elements.

Reporting requirements for serious and near serious adverse events

All reports need to be in writing and in English. Text should be legible and preferably in Times or Arial font, with a font size no less than 10 point. If text is in a font size less than 10, then the report should be posted or emailed, not faxed. Reports should not be photo-reduced or condensed, because the TGA needs to be able to produce legible copies of reports.

All reports need to identify the name and contact details of the person in Australia who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report. It is preferable for the nominated contact person for biovigilance to submit all reports.

The TGA will advise the sponsor if a report format is considered to be unacceptable.

A detailed description of what needs to be included in reports of serious and near serious adverse events is in the *What to include in adverse event reports* section.

We prefer that adverse event reports are submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable. This enables information to be entered into our database more easily, and enables international cooperation over safety issues.

Reports of adverse events may be in free text, or you may use one of a number of different forms that are available:

- online through the TGA Australian Adverse Drug Reaction Reporting System
- E2B formatted reports can be submitted to e2b.reports@tga.gov.au
- blue card adverse reaction reporting form
- form provided by CIOMS (Council for International Organizations of Medical Sciences)

The following CIOMS publication is useful: *Reporting adverse drug reactions: definitions of terms and criteria for their use* <http://www.cioms.ch/publications/reporting_adverse_drug.pdf>.

Providing publications

When a publication is the source of information about a serious or near serious adverse event or other safety information, then this publication needs to be provided to the TGA, preferably at the same time as the initial report. If the publication is not in English, then a summary or translation in English should be provided.

If the article is not available at the time of the initial report, then it must be provided to the TGA within the following time frames:

- within 10 days of submission of a serious adverse event report to the TGA
- within 30 days of submission of a near serious adverse event report to the TGA

If it will be difficult to meet the specified timeframe, notify the TGA in writing prior to the end of the specified period.

Contact details

Once a biological is included in the ARTG, report adverse events to the Pharmacovigilance and Special Access Branch at the TGA by:

- using forms provided by the TGA
- email: adr.reports@tga.gov.au
- mail:

  Pharmacovigilance and Special Access Branch
  Therapeutic Goods Administration
  PO Box 100
  WODEN ACT 2606

- Phone: 1800 044 114

8. What to include in adverse event reports

Privacy

The TGA does not wish to have the names of patients on record; we only require information that is necessary for us to perform our functions. General privacy information is available on our website.

TGA requirements do not override applicable privacy laws. Sponsors should be familiar with and discharge their obligations in relation to the collection, use and disclosure of personal information in accordance with the Australian Privacy Principles as set out in the *Privacy Act 1988* and any applicable state and territory privacy legislation.

Personal information is often collected to assist in the post-market monitoring of the safety of therapeutic goods under the *Therapeutic Goods Act 1989* (the Act). The TGA collects personal information in reports of adverse events and safety issues related to biologicals to:

- assess the safety of biologicals under the Act
- contact the reporter of the adverse event if further information is required
- contact representatives of entities that supply therapeutic goods, to discuss reported adverse events
- check that the same information has not been received multiple times for the same adverse event.

At times, this information is collected from someone other than the individual to whom the personal information relates. This can occur when an adverse event is reported to a person or an entity other than the TGA (such as a health professional or a hospital) and that person or entity passes the information on to the TGA.

Personal information collected may be disclosed by consent or where the disclosure is required by, or authorised under, a law (for example, under section 61 of the Act). Where a report relates to vaccine events, personal information about the reporter or the patient may be disclosed by the TGA to state and territory health agencies under subsection 61(3) of the Act.

Data elements to include

Below is a full list of key data elements recommended for inclusion in an individual adverse event report. It is recommended that sponsors make attempts to obtain information on as many of these items as are pertinent to the case (some data elements might not be relevant).

The TGA would like to have as many data elements as possible to facilitate assessment of the adverse event, however, initial reports should contain at least the minimum four data elements.

Sponsors should follow-up cases to obtain the minimum four data elements and detailed supplementary information relevant to the scientific evaluation of the adverse event(s). Once a case has been reported, additional information should be provided as a *follow-up report*. Follow-up reports should include the TGA adverse event (ADRS) number allocated to the initial report and the additional information should be clearly identified.

Patient details

A patient needs to be ***identifiable***, by which we mean that the existence of the patient needs to be verifiable. The TGA does not wish to be given the full name of a patient; initials or a patient identification number are sufficient. Identification of the patient is important to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases.

With second-hand reports, the sponsor should make every reasonable effort to verify the existence of an identifiable patient located in Australia or treated in Australia.

Provide all relevant information pertaining to the case in the report, such as:

- initials, but not the full name of the patient
- other relevant identifiers (patient number, for example)
- gender
- age, date of birth or age category (e.g. adolescent, adult, elderly) - see importance of age
- concomitant conditions, including pregnancy
- medical history including relevant smoking, alcohol and illegal drug history
- relevant family history
- ethnicity
- weight and height of patient

For a parent-child or parent-fetus report:

- the gestation period at time of exposure
- information concerning the parent, such as:
  - parent identification
  - parent age or date of birth
  - last menstrual period date for mother
  - weight
  - height
  - gender
  - relevant medical history and concurrent conditions
  - relevant smoking, alcohol and illegal drug history.

Importance of age

The collection of safety information in paediatric and elderly populations is important to assist in identifying potential safety signals specific to particular age groups.

Reasonable attempts should be made to obtain and submit the date of birth or the age of the patient when a serious or near serious adverse event is reported. If the reporter does not wish to specify the exact age, try to obtain an age group.

Details of biological

Provide as much information as possible about the biologicals involved:

- brand name
- International Non-Proprietary Name (INN) or Australian Cell and Tissue Name (ACN)
- active ingredients:
  - for combination biologicals that include a delivery system and more than one ingredient, each active ingredient should be listed
  - if the primary source suspects a possible causal role of one of the ingredients, this information should be provided in the report
- batch number
- lot number
- ARTG number
- indication(s) for which the biological was used
- dosage form
- dose (specify units if available) and regimen if relevant
- route of administration (or parent route of administration in cases of a parent-child or parent-fetus report)
- starting date and time
- if relevant, duration of treatment and stopping date and time
- actions taken with the biological, such as:
  - implant withdrawn
  - antidote administered
  - other treatment given
  - no action
  - unknown
  - not applicable
- any additional information about the biological

Other treatment(s)

The same information as for the biological described above should be provided for the following:

- concomitant medicines including dosage form and strength, daily dose and regimen:
  - prescription medicines
  - over-the-counter medicines

  - complementary medicines
  - herbal remedies
  - dietary supplements
  - alternative therapies
- relevant medical devices.

If the adverse event is suspected to be the result of an interaction between a biological and another substance or product, this is to be clearly stated in the report and the names of the suspected interacting products or substances provided. Interactions could be with:

- another biological
- a medicine
- food
- alcohol
- illegal drugs
- a medical device.

Details of adverse event(s)

Provide details of the adverse event(s):

- a full description of the event(s), including body site and severity
  - preferably, use the appropriate Lowest Level Terms from the Medical Dictionary for Regulatory Activities (MedDRA)
- the event as reported by the primary source
  - provide the original words that were used by the reporter to describe the adverse event(s)
- the criteria for regarding the report as serious
- description of the reported signs and symptoms
- specific diagnosis for the event(s)
- onset date (and time) of event(s)
- stop date (and time) or duration of event(s)
- time interval between administration of the suspect biological and start of event(s)
- relevant diagnostic test results and laboratory data
- setting e.g. hospital, out-patient clinic, home, nursing home
- outcome of event(s) at the time of last observation e.g. recovered or resolved, recovering or resolving, not recovered or not resolved, recovered or resolved with sequelae—describe sequelae

- if death occurred:
  - date of death
  - whether autopsy was performed
  - relevant autopsy or post-mortem findings, including coroner's report
  - stated cause of death
- assessment of the relatedness of the product to the event(s):
  - source of assessment e.g. initial reporter, investigator, regulatory agency, sponsor
  - method of assessment: global introspection, algorithm, Bayesian calculation
  - result of assessment
  - whether you consider there to be a causal association between the suspect product(s) and event(s) and provide the criteria on which you have made your assessment
- where possible, provide a case narrative for the adverse event(s)—present this in a logical time sequence of the patient's experience including:
  - clinical course
  - therapeutic measures
  - outcome
  - other relevant information

The information provided in the narrative should be consistent with the data in other parts of the report.

- sponsor's comments e.g. diagnosis, syndrome, reclassification of event(s)
- whether the case was medically confirmed. Where the report was made by a consumer, the following is sufficient to consider the report as medically confirmed:
  - provision by the consumer of medical documentation, such as laboratory or other test data, that supports the occurrence of the suspected adverse event(s) or that indicates that an identifiable health professional suspects a reasonable possibility of causal relationship between the biological and the reported adverse event(s)
  - if the consumer initially reports more than one event and at least one receives medical confirmation, then the whole report should be documented as a spontaneous report that has been medically confirmed
  - if the report is submitted by a medically qualified patient, friend, relative or carer, the case should be considered as medically confirmed.

Details about reporter

Identification of the reporter is important for good case management, detection of duplicate reports or fraud and the facilitation of follow-up. The term ***identifiable reporter*** refers to the verification of the existence of the reporter. With second-hand reports, the sponsor should make every reasonable effort to verify the existence of an identifiable reporter.

Sponsors should record contact details for the reporter to enable follow-up. However, if the reporter does not wish to provide contact details, the adverse event is still valid providing the sponsor is able confirm the case directly with the reporter.

Ideally, sponsors will collect the following information about the person making the report to the sponsor:

- the name of the reporter
- email address
- postal address, including postcode
- telephone number
- fax number
- reporter type (consumer, health professional etc.)
- for health professionals, the profession (specialty) or the name of the professional association or other group of which he or she is a member
- for non-health professionals, any professional qualification e.g. lawyer.

The TGA does not ask sponsors to provide identifying information about the reporter, unless the person has given permission for these details to be provided.

The TGA requests that information about the person such as the reporter type, profession (for health care professionals) and location in Australia, for example the postcode, be provided.

All who provide information

All parties who provide case information or are approached for case information should be identifiable, not just the primary source; identification refers to the verification of the existence of the parties and their knowledge of the case.

A primary source is a person who reports the facts to the sponsor or other agency. Sometimes there are several primary sources, such as several health professionals or several consumers who provide information on the same case. In this situation, the sponsor should provide details of all primary sources, including their qualifications, in the case report. Reports provided directly to the TGA from more than one primary source will be regarded as duplicates.

Administrative details

Provide the following details:

- source of report (spontaneous, epidemiological study, patient survey, literature etc.)
- date the event report was first received by the sponsor
- country in which the event occurred
- type of report: initial or follow-up (if follow-up, provide the TGA adverse event [ADRS] number allocated to the initial report)
- name and address of sponsor

- name and contact details of the person who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report
- sponsor's identification number for the case (the same number should be used for the initial and follow-up reports on the same case)
- the adverse event identification number(s) (if known) of possible duplicate reports initially submitted by a consumer or health professional.

Validation

Sponsors are expected to validate all serious and near serious adverse event reports and, once validated, to report them to the TGA within the specified time frames. A validated report contains the minimum four data elements (patient, substance, event and reporter).

Information that does not need to be reported individually to the TGA includes:

- reports for which the minimum information is incomplete
- adverse events for which there is not a reasonable possibility of causal relationship, such as if the primary source has made an explicit statement that a causal relationship between the biological product and the adverse event has been excluded and the sponsor agrees
- when a patient experienced an unspecified adverse event but no information was provided on the type of adverse event
- when only an outcome (or consequence) is notified and
  - no further information about the clinical circumstances supporting the suspicion of an adverse event is provided
  - the primary source has not indicated a possible causal relationship between the outcome and the suspected biological

A report of sudden unexplained death in a patient who had been treated with a biological would usually be considered as a case of suspected adverse event and reported.

All of the above information should be recorded within the sponsor's biovigilance system for use in on-going safety evaluation activities.

Follow-up

Sponsors are expected to exercise diligence in following up cases to collect missing data elements. All attempts to obtain follow-up information should be documented.

All serious and near serious adverse event reports are to be validated by the sponsor and all clinical and medically-relevant information that becomes available is to be given to the TGA.

Follow-up is required:

- to validate an initial report
- to obtain detailed supplementary information significant to the scientific evaluation of the cases.

Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern.

Particular effort should be taken to obtain as many details as possible for:

- monitored events of special interest
- prospective reports of pregnancy, where reports of pregnancy following the use of the biological are monitored until the outcome of the pregnancy is known
- reports of adverse events during pregnancy
- cases notifying the death of a patient
- cases reporting new risks or changes in known risks
- reports associated with overdose, abuse, off-label use, misuse, administration error or occupational exposure—information in these cases needs to be as complete as possible with regards to early symptoms, treatments, outcomes and context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population etc.).

Following up consumer reports

Reports from consumers are a valuable source of information. Sponsors should document all adverse event reports from consumers in the same way as they would document adverse event reports from any other source and should take consumer reports into account when overall safety assessments are made.

The TGA encourages consumers to report adverse events through their health professional; one of the reasons for this is that it is important for the consumer to be provided with any necessary medical attention. Please encourage consumers to talk to their health professional about any adverse events they are experiencing.

If a consumer reports an adverse event, sponsors are asked to seek and document permission from the consumer to allow contact with the treating doctor to obtain confirmation and additional relevant medical information, which will then be included in the report to the TGA. It is easier for the sponsor to obtain clinical information from a health professional, both when the report is followed up initially and when there is follow-up related to possible long-term events, such as when a biological has been used during pregnancy.

The report to the TGA should state that the reporter is a consumer, however, the TGA does not require the reporter's name or contact details as long as the sponsor is able to contact the reporter if the TGA wishes to obtain further information.

It is important to ascertain the seriousness of the event. For a non-serious adverse event, additional follow-up or medical confirmation may not be necessary. For serious events, the sponsor is expected to make every attempt to obtain voluntary informed consent to contact the treating doctor, or to obtain the relevant medical documentation directly from the consumer so that causality can be assessed.

9. Biovigilance system

A biovigilance system is used to fulfil the tasks and responsibilities associated with the detection, assessment, understanding and prevention of adverse effects of biologicals. It needs to be designed to monitor the safety of authorised biologicals and detect any change to their benefit-risk balance.

A biovigilance system is not in itself required by Australian legislation, but such a system is required for a sponsor to be able to meet legislated requirements for reporting adverse events and serious threats to public health.

A biovigilance system will:

- allow sponsors to take responsibility and liability for their products
- ensure appropriate action is taken when necessary.

Where a risk management plan (RMP) is required, the biovigilance system must support the ability of the sponsor to undertake the biovigilance activities described in the plan. An RMP is usually a requirement for new applications for class 3 and 4 biologicals and selected class 2 biologicals (see *Risk management plans for medicines and biologicals*).

Objectives

The sponsor's biovigilance system needs to enable the sponsor to undertake:

- all routine biovigilance requirements described in these guidelines
- any additional biovigilance activities required through the RMP (if an RMP is required)
- all traceability and other biovigilance requirements placed on the sponsor through Therapeutic Goods Orders, an RMP or as conditions of registration
- the investigation and reporting of product quality issues
- the critical analysis of adverse events and other safety and quality information
- any activities needed to mitigate an identified safety issue.

Adverse event recording and reporting

For recording and reporting adverse events, the system should:

- ensure that collected reports are authentic (verifiable), legible, accurate, consistent and as complete as possible for clinical assessment
- be structured to enable serious adverse event reports to be validated in a timely manner and submitted to the TGA within the legal reporting time frames
- enable the sponsor to provide within a specified time frame any additional information requested by the TGA to assist with evaluation of the benefits and risks of a biological, including information about the volume of sales or prescriptions of the product concerned.

Traceability of biologicals

Under Therapeutic Goods Order (TGO) No. 87, subsection 6(1) sponsors are required to be able to trace a biological product from donor to product release. For higher risk biological products where a RMP is required, a product specific condition of registration is included that requires product traceability from the donor to the recipient.

Procedures are to be documented for tracing products from donor to recipient and from recipient to donor, so that disease transmission between donor and recipient can be investigated.

It is important that the sponsor can locate and identify a biological during any step:

- donor
- procurement
- processing
- testing
- storage
- distribution to the recipient
- disposal.

The donor, tissue establishments, manufacturing facilities, medical facilities and recipients must all be identifiable.

Traceability also covers the ability to locate and identify all relevant data relating to products, materials and people that have come into contact with the biological.

Analysis

Biovigilance does not just consist of collection, but also of scientific evaluation and critical analysis of adverse event reports and any other safety issues associated with the biological.

Safety issues

Safety issues arise from adverse event reports, but also arise from more general situations and may occur at any stage in the development, manufacturing, administration or follow-up of a product.

There needs to be a system in place for detecting and investigating such issues (see Signal detection and investigation).

Signal detection and investigation

The sponsor needs to have systems in place to detect safety signals. Such signals arise from one or multiple sources (including observation and experiments) and suggest a new potentially causal association or a new aspect of a known association, between the biological and an event or set of related events.

Signals which are judged to be of sufficient likelihood of being true associations require active investigation to determine whether they can be verified or refuted. If a verified signal may

change the benefit-risk profile of a biological product, it must be reported to the TGA as a serious threat to public health.

A useful resource is *Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII*.

Periodic safety update reports (PSURs)

A Periodic Safety Update Report (PSUR) is a systematic review of the global safety data that becomes available to the sponsor of a marketed product during a specific time period. PSURs are produced in an internationally agreed format.

The objective of a PSUR is to present a comprehensive and critical analysis of the benefit-risk balance of a therapeutic good taking into account new and emerging information in the context of cumulative information on benefits and risks.

PSURs are required to be submitted at defined time-points for:

- all Class 4 biologicals
- all Class 3 biologicals
- some Class 2 biologicals (when imposed under section 32ED of the Act).

The frequency of PSURs is specified in the non-standard conditions of approval for Class 3 and Class 4 biologicals and in the conditions of inclusion in the ARTG for Class 2 biologicals. The report is to be submitted to the TGA within 90 days of the data lock point, which is the date after which no further data is included in the PSUR.

For more information about PSURs, refer to the EMA guideline EMA/816292/2011 Rev 1* (9 December 2013) *Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report* .The format of a PSUR is described on pages 11 and 12 of this guideline.

Sources

A biovigilance system should encompass the collection and analysis of information from as many sources as possible.

Reports made to sponsor

Information on all suspected adverse events reported to the sponsor or people who work for or have a contractual relationship with the sponsor (such as medical and sales representatives, vendors, partners and contract manufacturers) is to be collected, collated, analysed, followed up and held so that it may be accessed at a single point within Australia.

Australian products marketed overseas

For a biological manufactured in Australia and marketed overseas, the Australian sponsor is expected to request that any information on suspected adverse events in other countries is brought to the attention of the Australian sponsor by the overseas sponsors in a timely manner. The sponsor is not required to report individual adverse events that have occurred overseas to the TGA but they must include overseas events in their ongoing monitoring of the product and report to the TGA if analysis of the events indicates a change in the benefit-risk of the product.

Australian products from overseas

Some biologicals included in the ARTG and marketed in Australia may be manufactured overseas and marketed by different sponsors overseas. In these cases, the Australian sponsor is to have a commercial agreement with the overseas sponsors so that the Australian sponsor is provided with details in a timely manner of any adverse events that have occurred overseas. The sponsor is not required to report individual adverse events that have occurred overseas to the TGA but they must include overseas events in their ongoing monitoring of the product and report to the TGA if analysis of the events indicates a change in the benefit-risk of the product.

Post ARTG-inclusion studies

Sponsors should have mechanisms in place to collect full and comprehensive case information from post-ARTG inclusion studies and to evaluate that information in a timely manner.

Literature reviews

The medical and scientific literature is a significant source of information for the monitoring of the safety profile and risk-benefit balance of biologicals and for the detection of new safety signals and emerging safety issues.

Sponsors are requested to

- undertake regular (weekly) systematic review of the literature in widely used reference databases that contain the largest reference of scientific and medical publications in relation to the biological and its properties
- review and assess reports of adverse events from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, to identify and record adverse events and serious threats to public health
- ensure that, where contractual arrangements are made with a person or organisation to perform literature searches, detailed agreements exist that enable the sponsor to comply with all reporting obligations.

Adverse events in worldwide literature

For adverse events reported in the worldwide literature, the sponsor should endeavour to identify the cases that occurred in Australia and report these to the TGA if they are serious or near serious. When the sponsor cannot determine whether the event occurred in Australia, the sponsor is to:

- keep records of the adverse events
- produce a report if requested by the TGA
- consider the report for discussion in any future Periodic Safety Update Reports (PSURs), if a PSUR is required
- consider the report in any global analysis of adverse events.

Internet and social media

Sponsors should regularly screen the internet, social media and digital media under the sponsor's management or responsibility for reports of suspected adverse events. For such

reports, it is important that the reporter is identifiable, that is, a real person with verifiable contact details (such as an email address).

For digital media that is owned, paid for or controlled by the sponsor the reporting timeframes are considered to start on the date that the information was posted. This means that screening needs to be sufficiently frequent to report:

- serious threats to public health within 48 hours
- serious adverse event reports within ten calendar days.

If a sponsor becomes aware of a report of a suspected adverse event described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting, and if so, it should be reported within the time frames stated above.

Non-medical sources

A report of a suspected adverse event from a non-medical source, for example the lay press or other media should be handled as a spontaneous report. Every attempt should be made to follow up the case to obtain the minimum information that constitutes a valid adverse event report and to determine the seriousness of the adverse event.

Processes

It is important to have an appropriate quality management system in place and to document all of the processes in place for the biovigilance system.

Training

Personnel undertaking biovigilance should be trained at a minimum in:

- applicable biovigilance legislation and guidelines
- privacy legislation
- report processing and evaluation.

Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, marketing, legal, quality control) should be trained in adverse event collection and reporting.

Written procedures

The roles, responsibilities and required tasks of biovigilance need to be understood by and available in writing to all relevant parties.

Clear written standard operating procedures should provide for:

- quality control of the biovigilance system
- change to the biovigilance system.

This is also applicable to activities that are contracted out to third parties, whose procedures the sponsor should review to verify that they are adequate and compliant with applicable requirements.

Collecting data using the sponsor's website

We encourage sponsors to use their websites to facilitate the collection of adverse event reports. This can be done by providing reporting forms or contact details for direct communication. Reports from all sources, including health professionals and consumers, are to be encouraged.

Retention of records

It is recommended that sponsors retain all biovigilance documents, including records of all reports of adverse events associated with the use or administration of their biological product, for as long as the product is approved for inclusion in the ARTG and for at least 10 years after it ceases to be included in the ARTG.

Data quality control

Data security

Sponsors must be familiar with and discharge obligations in relation to the collection, use and disclosure of personal information in accordance with the Australian Privacy Principles under the *Privacy Act 1988,* and any relevant state or territory privacy legislation.

Electronic data and paper reports of suspected adverse events should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with data privacy laws.

Strict controls should be applied to documents and to databases to assure security and confidentiality of biovigilance data with access to authorised personnel only. This security extends to the complete data path.

Procedures should be implemented to ensure security and non-corruption of data during data transfer.

Data accessibility

Data needs to be collected, collated and held so that it may be accessed at a single point within Australia.

Data entry

It is preferable for data entry to use the appropriate Lowest Level Terms from the Medical Dictionary for Regulatory Activities (MedDRA).

Data entry staff should be instructed in the use of the terminologies, and their proficiency should be confirmed.

Quality assurance auditing, either systematically or by regular random evaluation, should verify that data is being entered correctly with the appropriate use of terminologies.

Data storage

There should to be an audit trail for electronic data. It needs to be possible to trace:

- data entry
- data modification
- dates and sources of received data
- dates and destinations of transmitted data.

Handling duplicate cases

There should be a procedure to identify and manage duplicate cases at data entry and during the generation of aggregated reports.

Source data (e.g. letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible. This enables initial and follow-up reports to be verified against the original data. Quality control procedures need to include this verification procedure.

Data transfer

When biovigilance data is transferred within an organisation, or between organisations with contractual agreements, there should be mechanisms to establish that all notifications are received. This includes, but is not limited to, undertaking a confirmation or reconciliation process.

10. Reporting in special situations

Use of a biological through an exemption scheme

There are different reporting requirements when a biological is not being used through its inclusion in the ARTG but is being used because access has been granted through an exemption scheme, such as the Special Access Scheme, Authorised Prescriber Scheme and Clinical Trials Scheme.

Special Access Scheme

The procedures for reporting of adverse events for biologicals accessed under the Special Access Scheme is outlined on pages 22 to 26 of Access to unapproved therapeutic goods - Special Access Scheme.

Authorised prescriber

The procedures for reporting of adverse events for biologicals accessed under the Authorised Scheme are outlined on pages 25 to 30 of Access to unapproved therapeutic goods - Authorised Prescribers.

Clinical trials for unapproved indications

For reports from clinical trials in Australia where the biological is being used outside the approved indications or intended use, sponsors should refer to pages 76-80 of Access to unapproved therapeutic goods – Clinical trials in Australia as well as the Note for guidance on clinical safety data management: Definitions and standards for expedited reporting (CPMP/ICH/377/95).

Reporting in the period between submission of a biological registration application and granting of the registration

Consideration by the Advisory Committee on Biologicals

If an application is to be considered by the Advisory Committee on Biologicals, sponsors should submit with their pre-committee response a tabulation of any serious unexpected adverse events not mentioned in the proposed Australian product documentation or not already submitted.

Between the pre-committee response and ARTG inclusion

Following the pre-committee response, sponsors should report serious adverse events and serious threats to public health according to the same time frame as they would be reported if the product was included in the ARTG. The only difference is that these reports should be sent to the TGA area responsible for blood, tissues and biologicals, not the Pharmacovigilance and Special Access Branch.

Withdrawal or lapse of application

When an application for inclusion of a biological in the ARTG is withdrawn or lapses, section 32DR of the Act provides that the Secretary of the Department of Health may require a sponsor to disclose whether certain information about the product is known to the sponsor and, if that is the case, to provide that information to the Secretary.

Version history

Version	Description of change	Author	Effective date
V1.0	Consultation version	Pharmacovigilance and Special Access Branch and Scientific Evaluation Branch	October 2016

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