Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pharmacovigilance obligations of medicine sponsors

Frequently asked questions

Last updated:
17 October 2022

The information below provides answers to frequently asked questions in relation to the pharmacovigilance obligations of sponsors of medicines on the Australian Register of Therapeutic Goods (ARTG). This information should be read in conjunction with the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/resources/resource/guidance/pharmacovigilance-responsibilities-medicine-sponsors) (the Pharmacovigilance Guidelines).

In the following answers, we refer to the TGA as 'we' or 'us', and to sponsors of medicines in the ARTG as 'you'. We use 'must' or 'required' to describe something you are **legally obliged** to do. We use 'should' to **recommend** an action that will assist you to meet your legal requirements.

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Collecting and reporting adverse drug reactions

Do I have to collect and report adverse reactions to the TGA?

Yes - You must report all **serious** Australian adverse reactions related to your medicine to the TGA, within 15 calendar days of first receipt.

Prior to reporting, you must ensure that the serious adverse reaction report contains:

- an identifiable reporter
- an identifiable patient
- a suspect medicine
- at least one suspect adverse reaction.

As a sponsor of a medicine included in the ARTG, you should have a system in place to collect and record all Australian adverse reactions related to your medicine from all possible sources. These include but are not limited to:

- consumers
- health professionals
- company employees
- internet and social media
- medical literature
- manufacturers
- post-registration studies or initiatives.

Please refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on your responsibilities for collecting and reporting adverse reactions.

What is a serious adverse reaction?

A serious adverse reaction is any medical occurrence in relation to your medicine, that:

- results in death
- is life-threatening
- results in inpatient or prolonged hospitalisation
- results in persistent or significant disability or incapacity

- is associated with a congenital anomaly or birth defect
- is a medically important event or reaction.

It is important that an assessment of seriousness for a medically important event or reaction is based solely on the seriousness of the reported event or reaction, and does not take into account the likelihood that the adverse reaction is associated with the use of the medicine.

Please also refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on seriousness assessments.

Before reporting, do I need to obtain consent to disclose the patient's and reporter's personal information?

Yes - Before reporting serious adverse reactions to the TGA, you must seek explicit consent to disclose the personal information of both the reporter and patient in any submitted report.

This may be in the form of a verbal or written disclaimer, to inform the reporter/patient that the information collected will be recorded and reported in line with Australian regulatory requirements.

Please note that collecting personal information does not override any applicable privacy laws. If the reporter or patient does not wish to provide their details, then you should provide that individual with the option of dealing with you anonymously or by pseudonym. Please refer to the Australian Privacy Principles (https://www.oaic.gov.au/privacy/australian-privacy-principles) (APP) for information on how APP entities can give individuals the option of not identifying themselves, or of using a pseudonym, when collecting personal information.

When reporting a serious adverse reaction to the TGA, you must ensure that the report contains an identifiable reporter, an identifiable patient, a suspect medicine and a suspect adverse reaction. The TGA considers 'identifiable' to mean any information that confirms the existence of a real person (for example a name, set of initials, date of birth, age or gender).

A serious adverse reaction report without an identifiable reporter or identifiable patient still warrants reporting to the TGA within 15 calendar days, if you can confirm the case directly with the reporter at the point of the initial report, and you believe that there is a real patient involved.

How do I report serious adverse reactions to the TGA?

You can submit your serious adverse reaction report to the TGA via the Adverse Event Management System (AEMS) portal, which can be accessed through your TGA Business Services account (https://adfs.tga.gov.au/adfs/ls/?wtrealm=https%3a%2f%2fbusiness.tga.gov.au&wctx=WsFedOwinState%3dHaThYsLB036gWNYK7VUcZnss-S4F9F-jSnui6NTR3asBPGlRvSl_ZZ-QJ4rGi6Hz85nVmVDZhq7sSYKXWacypCJ2MGRE99OiEzapoqfXOGw3pJDRcTGx5cLA332ebn4D&wa=wsignin1.0). Please refer to the AEMS guidance (https://immunisationhandbook.health.gov.au/node/289438) for more information on how to set up and access the AEMS portal.

You can also submit your serious adverse reaction report by setting up an electronic data interchange (https://immunisationhandbook.health.gov.au/node/289398) between your company safety database and the TGA's safety database (Database of Adverse Event Notifications) using the E2B R2 format.

Alternatively, you can submit your serious adverse reaction report via email, by completing a CIOMS form (pdf,107kb) (https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf) and forwarding to adr.reports@health.gov.au (https://immunisationhandbook.health.gov.aumailto:adr.reports@health.gov.au)

Do I have to report special situations (such as cases of medication error, misuse or exposure during pregnancy etc.) which do not report an adverse reaction?

No - You do not need to report cases of overdose, abuse, off-label use, misuse, medication error, occupational exposure, lack of efficacy or exposure during pregnancy and breastfeeding to the TGA, if they do not involve a serious adverse reaction.

However, even if there was no associated adverse reaction, you must collect and record these cases in your safety database for consideration in any ongoing safety evaluation or preparation of aggregate safety reports, such as Periodic Safety Update Reports (PSURs). Upon request, you must be able to provide these cases to the TGA.

Please also refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on your pharmacovigilance responsibilities for reports of special situations.

Do I have to report adverse reactions that do not involve my medicine?

No - For an adverse reaction that does not involve your medicine, you should encourage the patient or reporter to report that adverse reaction to the relevant company or to the TGA (https://immunisationhandbook.health.gov.au/node/287456).

If you have contractual obligations with another company to identify and collect adverse reactions related to their medicine, then you must report these to them within the timeframe stipulated in the contract, so that they can meet the TGA's 15-day timeframe for reporting serious adverse reactions.

Do I have to conduct periodic reconciliation of safety data (including adverse event reports)?

Yes - when transfer of safety data occurs within an organisation or between organisations, there should be a mechanism in place to verify that all data (e.g. adverse events and their key safety data variables) have been received, to ensure the accuracy of company-held safety information.

You should undertake routine reconciliation of safety data, preferably monthly, by producing a summary of adverse events received during the reporting period and checking these against the adverse event reports initially received by the internal department or external organisation.

You should undertake routine reconciliation of safety data even if no adverse event reports were received during the reporting period.

With whom should I have a pharmacovigilance contract? What information should be included in that contract?

You should have a pharmacovigilance contract with any third party that you have engaged to conduct activities on your behalf, who in the course of their work may receive safety information related to your medicine.

Pharmacovigilance contracts should include, but not be limited to, information on:

- the type of safety information to be collected (for example, adverse event reports, special situations, minimum four data elements of a valid report, product quality complaints, significant safety issues)
- roles and responsibilities of pharmacovigilance activities such as safety data collection, case follow up and reporting
- specified timeframes and format of safety data exchange
- timelines and format of reporting to the TGA
- provisions for pharmacovigilance training
- provisions for adverse event reconciliation
- provisions for audit.

Post-registration studies and post-marketing initiatives

What are post-registration studies and post-marketing initiatives? Do I have to report adverse reactions from them?

A post-registration study is any study or supply of your medicine in the post-market setting (for example, post-authorisation safety study) that is not included as part of a Clinical Trials Notification (CTN) (https://immunisationhandbook.health.gov.au/node/287274), Clinical Trials Approval (CTA) (https://immunisationhandbook.health.gov.au/node/287274) or Special Access Scheme (https://immunisationhandbook.health.gov.au/node/288269) (SAS).

Similarly, a post-marketing initiative is any activity conducted by you that has the potential to generate or collect adverse reactions (for example, patient support programs, market research activities) that is not included as part of a CTN or CTA scheme or SAS.

You must report to the TGA, all **serious** Australian adverse reactions related to your medicine, from post-registration studies or post-marketing initiatives, within 15 calendar days of first receipt.

Please refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on your pharmacovigilance responsibilities for post-registration studies and post-marketing initiatives.

For your pharmacovigilance responsibilities related to medicines included in a CTN or CTA scheme, please refer to the Australian clinical trial handbook (https://immunisationhandbook.health.gov.au/node/289564).

For your pharmacovigilance responsibilities related to medicines included in SAS, please refer to Special Access Scheme: Guidance for health practitioners and sponsors (https://immunisationhandbook.health.gov.au/node/289228).

Searching Australian and worldwide medical literature

How often should I be searching Australian and worldwide medical literature?

You should undertake regular (no less than weekly) systematic literature review of widely used reference databases, such as Medline, Excerpta Medica or Embase. Any decision to decrease the frequency of the literature search to less than weekly or to exclude certain databases, should be justified and documented.

This will ensure you capture all Australian adverse reactions related to your medicine in a timely manner, as well as comprehensive and up-to-date safety information, in order to allow to you monitor the ongoing benefit-risk profile of your products.

Please also refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on searching medical literature.

Where can I find more information to assist with my literature search strategy?

Literature search strategies should include the product trade name and all active ingredients. Examples of search strings are available online (see 'Search parameters' on the EMA Medical Literature Monitoring website (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medical-literature-monitoring)).

When searching for active ingredients included in complementary medicines, please also refer to the section 'Scope of the literature search' on page 5 of the TGA document Literature-based submissions for listed medicines and registered complementary medicines (v1.0, May 2020) (https://immunisationhandbook.health.gov.au/node/289507).

Free and reputable biomedical databases, such as PubMed (produced by the National Library of Medicine, USA), can be used to conduct searches of worldwide medical literature, by creating alerts for relevant publications with automatic notifications to your email account.

Please refer to the following links on how to use PubMed, save searches and set up alerts: PubMed Tutorial (https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/cover.html) / Saving Searches (https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/040_015.html) / Creating Alerts (https://www.nihlibrary.nih.gov/resources/subject-guides/keeping-current/creating-alerts-pubmed) / PubMed user guide and FAQs (https://pubmed.ncbi.nlm.nih.gov/help/).

Please also refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more information on searching medical literature.

Identifying and reporting significant safety issues

What is a significant safety issue?

A significant safety issue (SSI) is a new safety issue or validated signal considered by you, in relation to your medicines, that requires urgent attention of the TGA.

This may be because of the seriousness and potential major impact on the benefit-risk balance of the medicine and/or on patients or public health, which could warrant prompt regulatory action and/or communication to patients and healthcare professionals.

SSIs may also include actions taken by comparable foreign regulatory agencies (https://immunisationhandbook.health.gov.au/node/289375) for safety reasons or internal decisions to update company core safety information.

Please also refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for the full definition of an SSI.

Do I have to notify the TGA of significant safety issues?

Yes - Safety issues that meet the definition of a significant safety issue (SSI) must be reported to the TGA, via si.coordinator@health.gov.au (https://immunisationhandbook.health.gov.aumailto:si.coordinator@health.gov.au), within 72 hours of first awareness by any personnel of the Australian sponsor.

If activities related to ongoing safety evaluation are conducted outside of Australia (for example, global headquarters, business partner, global pharmacovigilance vendor), then the TGA expects that Australian-based personnel (the Australian pharmacovigilance contact person or Qualified Person for Pharmacovigilance in Australia) are urgently notified of any safety issue that meets the definition of an SSI. Significant delays are considered unacceptable and pose a risk to public health.

The TGA expects you to use your professional judgement in determining whether a safety issue is significant, thereby warranting notification to the TGA within 72 hours.

The examples outlined in the Pharmacovigilance Guidelines (https://immunisationhandbook.health.gov.au/resources/resource/guidance/pharmacovigilance-responsibilities-medicine-sponsors) are not intended to be an exhaustive list of SSIs. It is up to you to assess each safety issue on a case-by-case basis and evaluate whether they have an impact on the medicine's safety or benefit-risk balance and/or have implications for public health.

Please refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more guidance on the identification and reporting of SSIs.

What is a validated signal? Do I have to notify the TGA of all validated signals?

The TGA adopts the European Medicines Agency's definition (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf) of a validated signal, which is:

> 'A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.'

You do not have to notify the TGA of all validated signals. The TGA expects you to use your professional and clinical judgement in determining whether a validated signal requires urgent attention of the TGA based on the seriousness and/or potential impact on public health.

Please refer to the Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements (https://immunisationhandbook.health.gov.au/node/289370) for more guidance on the identification and reporting of significant safety issues.

Updating Australian Product Information (PI) and Consumer Medicines Information (CMI) documents

What is the timeframe for making a submission to update PI documents?

The TGA expects you to submit safety-related changes to update Australian PI documents within six months of the date that any personnel of the parent company first decided that an update was required (for example, the date of the decision to update company core safety information). This is irrespective of whether your product is currently marketed in Australia or whether the PI document is published on the TGA website.

If you are a sponsor of a generic medicine, it is a condition of registration that you make a submission to the TGA, to align the PI document of your generic product with the Australian innovator PI document, within one month of the date of approval of the safety-related update to the Australian innovator PI document. This is to ensure that safety-related information is consistent in all Australian products containing the same active ingredient, for quality use of medicines by patients and healthcare professionals.

If the Australian innovator product to your generic product is withdrawn from the market, there is no requirement for you continue aligning your PI document with the Australian innovator PI document, as it will no longer exist. The TGA expects you to undertake your own safety monitoring activities (for example, signal detection, routine screening of local and global labelling updates) to identify new safety information relevant to your product, and if required, make a submission to the TGA to update your Australian PI document within six months of the decision date.

What are the timeframes for updating the CMI document, following TGA approval of the PI?

If the CMI document needs to be updated because of an update to the approved PI document, then it is a condition of registration that you must lodge the updated CMI document on the TGA website, within two weeks of the date of the approved PI document. If updates to the CMI are not warranted, then you should document the decision and the date of review.

You do not need to update the 'date of preparation' in the CMI document, to reflect the date the PI document was approved, or the date the CMI document was reviewed, if updates to the CMI were not warranted.

Australian pharmacovigilance contact person and Qualified Person for Pharmacovigilance in Australia (QPPVA)

Do I have to appoint an Australian pharmacovigilance contact person?

Yes - You must nominate an Australian pharmacovigilance contact person and notify the TGA of their name and contact details within 15 calendar days of your first medicine's entry on the ARTG, or within 15 calendar days of a change to the Australian pharmacovigilance contact person or their details.

The Australian pharmacovigilance contact person will be the primary direct contact for all pharmacovigilance correspondence between you and the TGA. They will also be the person responsible for fulfilling your pharmacovigilance reporting and record-keeping

requirements for medicines that you sponsor.

The Australian pharmacovigilance contact person must reside in Australia and should have a sound understanding of the Australian pharmacovigilance reporting requirements. The Australian pharmacovigilance contact person may be different to the QPPVA although ideally, they are the same person.

How do I notify the TGA of the Australian pharmacovigilance contact person?

You can nominate or update the details of your Australian pharmacovigilance contact person through your TGA Business Services account (https://adfs.tga.gov.au/adfs/ls/?wtrealm=https%3a%2f%2fbusiness.tga.gov.au&wctx=WsFedOwinState%3dHaThYsLB036gWNYK7VUcZnss-S4F9F-jSnui6NTR3asBPGlRvSl_ZZ-QJ4rGi6Hz85nVmVDZhq7sSYKXWacypCJ2MGRE99OiEzapoqfXOGw3pJDRcTGx5cLA332ebn4D&wa=wsignin1.0) and assign their role as an 'active' pharmacovigilance contact. This meets the requirement for notifying the TGA of the Australian pharmacovigilance contact person.

You can choose to have more than one person as an active pharmacovigilance contact (for example, a back-up person in the event that the primary Australian pharmacovigilance contact person is unavailable).

For assistance with accessing your TGA Business Services account (https://adfs.tga.gov.au/adfs/ls/?wtrealm=https%3a%2f%2fbusiness.tga.gov.au&wctx=WsFedOwinState%3dHaThYsLB036gWNYK7VUcZnss-S4F9F-jSnui6NTR3asBPGlRvSl_ZZ-QJ4rGi6Hz85nVmVDZhq7sSYKXWacypCJ2MGRE99OiEzapoqfXOGw3pJDRcTGx5cLA332ebn4D&wa=wsignin1.0) please contact TGA Business Services via ebs@health.gov.au (https://immunisationhandbook.health.gov.aumailto:ebs@health.gov.au%20)

Do I have to appoint a QPPVA?

Yes - You should have a qualified person responsible for all pharmacovigilance matters related to the medicines that you sponsor. This person will also be responsible for ensuring that you have an effective pharmacovigilance system in place to be able to comply with Australian pharmacovigilance requirements and guidelines.

Ideally, your QPPVA will also be your Australian pharmacovigilance contact person. The TGA recommends that the QPPVA:

- lives in Australia
- is permanently and continuously available (or at least within the hours of 9am-5pm AEST Monday to Friday), with a back-up person nominated should the primary QPPVA be absent
- is trained and experienced in pharmacovigilance and relevant Australian legislation

- is medically qualified or, if not, has ready access to a medically qualified person for any clinical assessments necessary - we prefer that this medically qualified person reside and be medically registered in Australia so they can address adverse reactions, significant safety issues and the benefit-risk balance of medicines in the Australian context.

Ultimately, the QPPVA should be suitably experienced and qualified in order to monitor the safety of your medicines. The characteristics and skills of the individual QPPVA will be dependent on their specific roles and responsibilities and should ensure that, as a sponsor of medicines on the ARTG, you are able to meet your pharmacovigilance requirements.

Do I have to notify the TGA of the QPPVA if they are different to the Australian pharmacovigilance contact person?

No - You are not routinely required to notify the TGA of the QPPVA if they are a different person to the Australian pharmacovigilance contact person.

However if you wish for them to be an alternative contact to the Australian pharmacovigilance contact person, then you can assign their role as an 'active' pharmacovigilance contact in your TGA Business Services account (https://adfs.tga.gov.au/adfs/ls/?wtrealm=https%3a%2f%2fbusiness.tga.gov.au&wctx=WsFedOwinState%3dHaThYsLB036gWNYK7VUcZnss-S4F9F-jSnui6NTR3asBPGlRvSl_ZZ-QJ4rGi6Hz85nVmVDZhq7sSYKXWacypCJ2MGRE99OiEzapoqfXOGw3pJDRcTGx5cLA332ebn4D&wa=wsignin1.0).

Submission of periodic safety update reports (PSURs) to the TGA

If you are required to submit PSURs to the TGA, the frequency will be outlined as a specific condition of registration under section 28(2B) of the *Therapeutic Goods Act 1989* (http://www5.austlii.edu.au/au/legis/cth/consol_act/tga1989191/s28.html). This may be in the initial product approval letter when the product is included on the ARTG, in the approval letter for major variations or extensions of indication or in a section 28 variation letter (either following a request from the sponsor or initiated by the TGA). These sources should always be referred to for the requirements for individual products.

For products that are approved in the European Union (EU), the TGA will usually align the PSUR reporting requirements and timeframes with those required by the European Medicines Agency (EMA). In this case, the specific condition of registration will state that PSUR reports are to align with the current EU reference date (EURD) lists (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs#submission-requir

ements-and-eu-reference-dates:-the-eurd-list-section), which are published on the EMA website. Sponsors are expected to provide PSURs to the TGA consistent with all elements described in the EURD list, including:

- PSUR submission frequency
- Data lock point
- PSUR submission due date (according to the timelines defined in GVP Module VII, Section A)

The EURD list is frequently updated by the EMA. Therefore, sponsors with this specific condition are expected to have a process for periodically checking the current EURD list to ensure that internally tracked PSUR reporting requirements are updated accordingly.

For more information on PSUR submissions to the TGA, please refer to EMA guideline EMA/816292/2011 Rev 1* (9 December 2013) Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report adopted by the TGA with annotations (https://immunisationhandbook.health.gov.au/products/unapproved-therapeutic-goods/clinical-trials/international-scientific-guidelines-adopted-australia) and Risk management plans for medicines and biologicals Australian requirements and recommendations (https://immunisationhandbook.health.gov.au/resources/resource/guidance/risk-management-plans-medicines-and-biologicals/periodic-safety-update-reports).

Topics:

Safety (https://immunisationhandbook.health.gov.au/safety/safety)

What went wrong? (mandatory)

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