ARTICLE

Pharmacovigilance in Australia: how do adverse event reports from clinicians contribute to medicine and vaccine safety?

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SUMMARY

Reporting adverse events (adverse drug reactions) associated with medicines and vaccines assists with identifying previously unrecognised side effects and other safety concerns.

Reporting adverse events to the Therapeutic Goods Administration is mandatory for sponsors (pharmaceutical companies), and strongly encouraged but voluntary for healthcare professionals and consumers.

Adverse events should be reported even when causality is uncertain, as reports may contribute to identification of a safety signal for new or uncommon events.

Suspected adverse events associated with new medicines and vaccines (registered in the last 5 years), and medicines included in the Black Triangle Scheme, should be prioritised for reporting. For other medicines, serious adverse events and unexpected adverse events should be prioritised.

The Therapeutic Goods Administration analyses adverse event reporting data and uses signal detection methods to identify and evaluate emerging safety signals, which may lead to regulatory actions and communication to address safety issues.

Introduction

Reports of suspected adverse events (adverse drug reactions) from healthcare professionals are an important source of information that helps the Therapeutic Goods Administration (TGA) detect, investigate and take action to improve the safety of medicines and vaccines in Australia (a process known as pharmacovigilance). These reports contribute to the overall body of medicines safety data and can lead to important regulatory actions and communications to reduce the risk of medication harms.

This article explains what happens to reports after they are received by the TGA, how they are used to detect and investigate safety signals, and what actions the TGA may take when a safety issue is detected; it also addresses common misconceptions about adverse event reporting.

Adverse event reporting in Australia

In Australia, adverse event reporting is mandatory for sponsors (pharmaceutical companies), and voluntary but strongly encouraged for healthcare professionals and consumers.[1,2]

In some states and territories, healthcare providers have a statutory obligation to report adverse events following immunisation to their state or territory health department, which then submits them to the TGA.

Adverse event reporting rates for 2014 to 2023 are presented in Figure 1. Reporting increased substantially in 2021 and 2022, largely due to the national rollout of COVID-19 vaccines. Direct reporting by healthcare professionals accounts for around 16% of all adverse event reports for medicines and vaccines. Apart from 2021 and 2022, direct reporting has been steady over the last decade, at approximately 4000 to 5000 reports per year. Additional reports from healthcare professionals are captured indirectly through state and territory health departments and from medicine and vaccine sponsors (Figure 1).

Of the reports received directly from healthcare professionals in 2023, 52% came from pharmacists, 20% from medical practitioners (general practitioners 12%, other medical practitioners 8%), 16% from nurses and 12% from other healthcare professionals.

Barriers and misconceptions about adverse event reporting

There are a number of barriers to adverse event reporting by healthcare professionals, including lack of time, the perception that reporting is not important, and insufficient knowledge and training on what events to report, and how to report them. Two Australian surveys of healthcare professionals found

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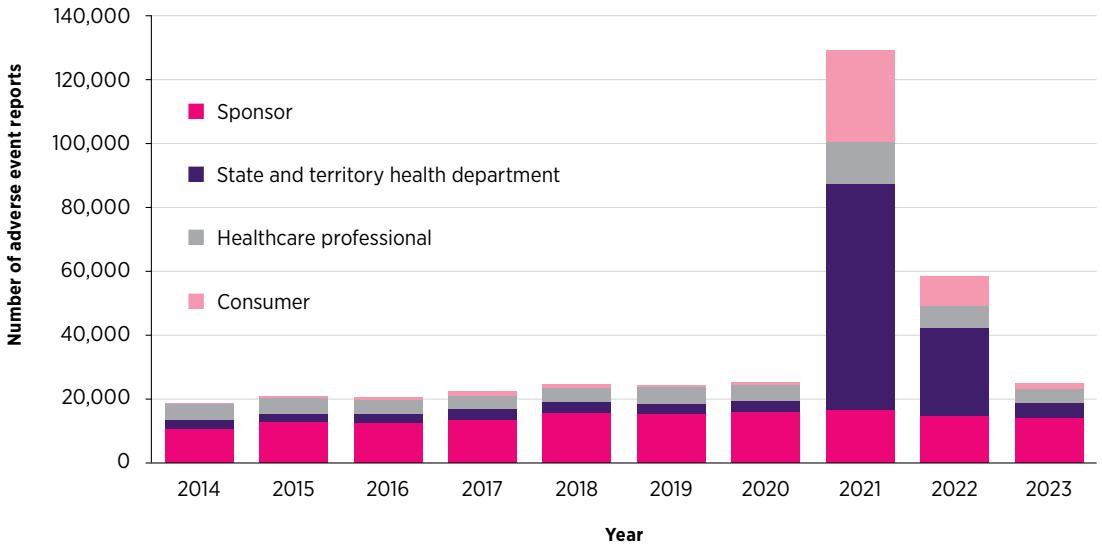
Figure 1 Number of adverse medicine and vaccine events reported to the Therapeutic Goods Administration per year, by reporting group, from 2014 to 2023



they would report more if they were given more training and reporting processes were simplified.[3,4]

There are some misconceptions that may contribute to lack of reporting (Table 1). There is also some confusion about the TGA's regulatory remit. For example, the TGA does not regulate cosmetic products, veterinary medicines, foods or chemicals, and does not provide individual clinical advice to healthcare professionals or consumers.

Why adverse event reporting is important

Reporting of adverse events and subsequent investigation of safety signals are important for public health, but underreporting remains an ongoing issue.[5-7] Healthcare professionals are in a unique frontline position and have the clinical knowledge to detect adverse events during interactions with patients.[8]

Premarket testing and drug trials are done to establish the safety and efficacy of medicines and vaccines before they are used in the wider population. Postmarket surveillance, by regulatory authorities such as the TGA, identifies safety issues that may not have been detected in clinical trials. This is because trials have intrinsic limitations such as relatively small sample sizes and short follow-up periods, and may not represent real-world populations (e.g. may exclude children, pregnant people or those with certain medical conditions).[9,10] Every report contributes to safety monitoring. Even a small number of adverse event reports can help detect a new safety signal and lead to actions to protect the Australian public.

Table 1 Common misconceptions regarding adverse event reporting

Misconception	Truth
Adverse events should only be reported if serious, recurrent or proven.	Any adverse event can be reported, even if there is only a suspicion that it was caused by a medicine or vaccine.
Adverse event reporting is limited to prescribed medicines and vaccines.	Adverse events for any medicine or vaccine can be reported, including over-the-counter and complementary medicines, unapproved medicines obtained through the Special Access Scheme or Authorised Prescriber pathways. Adverse events with medical devices can also be reported.
Only the prescriber of the suspected medicine or vaccine can report.	Anyone can report an adverse event, including healthcare professionals, consumers, family members and carers.
It is hard to know how and where to make the report.	Adverse events can be reported online through the Therapeutic Goods Administration's adverse event reporting website. There is a professional development module on the Australian Commission on Safety and Quality in Healthcare's QUM Learning hub, that provides a step-by-step guide on how to report adverse events. Consumers can report adverse events by calling 1300 MEDICINE (1300 633 424).
A single adverse event is not worth reporting.	All reports are valuable and contribute to the overall body of safety data for a medicine or vaccine. Multiple individual reports makes signal detection possible.

Adverse event reporting also helps to build a detailed safety profile of medicines and vaccines used in Australia.[11]

Prioritising adverse event reports

Although all adverse event reports are important to the TGA, priorities for reporting include:

- suspected adverse events for new medicines and vaccines (registered in the last 5 years)
- suspected adverse events for medicines included in the Black Triangle Scheme. This includes new medicines and medicines recently approved for a new indication or a different population, such as children. These medicines have a black triangle (▼) and accompanying text on their Product Information (PI) and Consumer Medicine Information (CMI) documents, as a reminder for people to report all suspected adverse events, especially serious events and those not listed in the PI and CMI documents[12]
- serious suspected adverse events to any medicine or vaccine, even if the adverse reaction is currently described in the PI (serious events are events that result in hospitalisation, danger to life, disability, birth defects or death)
- adverse events that are unexpected (not mentioned in the PI)
- adverse events that are known, but more severe than expected
- serious drug interactions that are not included in the PI.

How and what to report

To make a report, healthcare professionals and consumers can go to the TGA's adverse event reporting website and fill out the form. It is recommended that healthcare professionals register with the Adverse Event Management System (AEMS), but reports can be submitted without registering. If registered, the user's details will prepopulate in the form and the draft report can be saved. The report can be updated with new information after it is submitted.

Information that should be included in an adverse event report is outlined in Box 1. A basic report takes around 5 to 10 minutes to complete. The reporting process is outlined in an adverse event professional development module for healthcare professionals.

What happens to adverse event reports?

When the TGA receives an adverse event report, it:

- acknowledges receipt and issues a unique case identification number
- checks to see if there is any critical information missing (if so, it may request more information)
- enters the report in the TGA Adverse Event Management System (AEMS)
- codes the adverse event information using the Medical Dictionary for Regulatory Activities (MedDRA)[15]
- assesses individual reports when conducting safety signal reviews (see below).

Two weeks after a report has been entered into the AEMS, a subset of de-identified data is made public in the Database of Adverse Events Notifications (DAEN) for medicines.[16]

Adverse event data is also sent to the World Health Organization's adverse event database and pooled with information from other regulators.[17] This contributes to global pharmacovigilance, which enables identification of rare and unusual events.

How safety signals are detected and investigated

Data from adverse event reports are used to help identify safety signals. The signal may be a previously unrecognised safety issue or an increase in the frequency or severity of reported adverse events.

Box 1 What to include in an adverse event report

There are 4 key parts to an adverse event report:

- **Basic information about the patient:** Patient data must be de-identified. Patient age and sex are required fields. Details about ethnicity can be helpful, including Aboriginal and Torres Strait Islander status, as some adverse events are more prevalent in certain populations.[13,14] Where possible, relevant past medical history should be included.
- **Contact details of the reporter:** The reporter's name, contact details and the type of healthcare professional are helpful. These details are used to send a confirmation with a unique ID, and for the TGA to request more information if required. The unique ID can also be used to update the report if more details about the adverse event become available.
- **Name of the suspected medicine or vaccine:** If more than one medicine, or a combination medicine, was potentially associated with the adverse event, the details of each medicine should be included. Additional information is useful, such as the dose, dates that the medicine was started and stopped, the indication for the medicine, and what other medicines the patient was taking.
- **Details of the adverse event:** Include a brief description of the reaction, along with details of when it began and the outcome (e.g. resolution). More detailed information about the event can be provided later in the report (if using the online form). The report can be updated with more information at a later date.

Adverse events should be reported as soon as practicable, even if all of the information is not available at that time.

Signal detection involves identifying patterns of adverse events associated with a particular medicine (or combination of medicines), through epidemiological and biostatistical analyses, risk assessment and clinical expertise. The TGA utilises specialised programming to perform statistical analysis of disproportional reporting of adverse events to detect safety signals. Advice from specialist advisory committees and expert panels may also be sought.

The TGA also draws on international data and regularly liaises with other regulators to identify safety signals. Safety signals may also be picked up through literature searches, Periodic Safety Update Reports submitted by sponsors, and through other intelligence sources, such as patient advocacy groups, the media and enquiries directly from consumers or through members of parliament. Healthcare professionals can also contact the TGA directly regarding safety issues of particular concern.

Once a safety signal has been detected, it is investigated. This includes, but is not limited to, consideration of causality for individual local cases using the World Health Organization's Uppsala Monitoring Centre system for case causality assessment,[18] international adverse event data, published literature and overseas regulatory information. If the safety signal is confirmed, the following steps occur before regulatory action is considered:

- The impact of the safety issue is weighed against the intended use of the medicine, taking into account clinical significance, severity and frequency of the adverse reaction.
- The reasons why the safety issue occurred, and associated risk factors, are investigated.
- The gathered information is used to decide what type of regulatory action is needed.

If the evidence at the time of the investigation is not sufficient to require regulatory update, routine monitoring is continued to ensure any new information is considered.

Response to safety signals

Actions that can be taken in response to a safety concern include:

- publishing Medicines Safety Updates (for healthcare professionals)[19] and Safety Alerts (for the general public).[19] Summaries of *Medicines Safety Updates* have been published in *Australian Prescriber* since February 2024[20]
- communicating to healthcare professionals via medical colleges and stakeholder groups, or Dear Healthcare Professional Letters from medicine sponsors
- updating the product labelling, or the PI[21] and CMI documents.[22] This may include adding contraindications, warnings, precautions and other new safety information
- limiting the population in which the product can be used
- suspending or cancelling the registration of the product
- recalling a product[23]
- requiring the sponsor to undertake postmarket studies to investigate the safety concern (if more information is needed before taking action).

For the 2023–24 financial year, the TGA completed 202 focused and 26 in-depth signal investigations relating to medicines, and 38 focused and 7 in-depth signal investigations relating to vaccines. This led to the update of 161 PI documents, and their associated CMI documents, and 18 safety publications on the TGA website.

Box 2 and Box 3 outline case studies illustrating pharmacovigilance, from adverse event reporting through to regulatory action – one case is for a registered prescription medicine (Box 2) and the other is for a listed over-the-counter complementary medicine (Box 3).

Conclusion

Pharmacovigilance is a vital process for identifying and addressing emerging safety issues identified in real-world medicine use across diverse patient groups. Every adverse event report helps to build a more complete picture of a medicine's safety profile.

Box 2 Case study: infliximab and mycosis fungoides

In April 2018, a signal was detected via routine pharmacovigilance monitoring after 3 reports of mycosis fungoides in infliximab-treated patients were received from healthcare professionals. Mycosis fungoides is the most common type of cutaneous T-cell lymphoma (CTCL). Warnings about lymphomas and skin cancer were mentioned in the Australian infliximab Product Information (PI), however neither CTCL nor mycosis fungoides were included. Therefore, a signal investigation was started.

The clinical impact of the risk was considered significant and warranted further evaluation. This led to a review of overseas regulator safety labels (which did not include mycosis fungoides), individual case reports received by the Therapeutic Goods Administration (TGA) and the World Health Organization's global adverse event database, published literature identifying case reports and case series, and the sponsor's analysis of the signal which provided additional data.

The TGA concluded there was reasonable evidence of a possible causal association between infliximab and mycosis fungoides that justified including it in the Australian PI. The sponsor was asked to update the Australian PI, and the TGA published a *Medicines Safety Update*[24] in December 2018 to inform healthcare professionals of the risk and its addition to the PI.

Box 3 Case study: vitamin B6 and peripheral neuropathy

The Therapeutic Goods Administration (TGA) received a report of peripheral neuropathy from an individual taking a magnesium supplement, which also contained 41 mg vitamin B6.

Review of the TGA database identified multiple reports of peripheral neuropathy for products containing doses of vitamin B6 below 50 mg/day. In many cases, people were taking multiple products containing vitamin B6 that did not have a warning about this risk on the labels. At the time, only products with vitamin B6 daily doses over 50 mg required a warning about peripheral neuropathy on the label.

The TGA asked for expert advice from the Advisory Committee on Complementary Medicines and conducted a public consultation on proposed regulatory changes.[25] Subsequently, regulatory requirements were updated for listed medicines to strengthen label warnings and reduce the maximum permitted daily dose. The TGA also published a *Medicines Safety Update* for healthcare professionals,[26] and a *Safety Alert* for consumers.[27]

The TGA continues to monitor reports of adverse events related to this issue, including whether the regulatory changes are sufficient to reduce the risk of peripheral neuropathy with vitamin B6.

The TGA is committed to continuous improvements of its pharmacovigilance systems and processes. It is working on streamlining existing pathways for healthcare professionals to report adverse events with the long-term goal of integrating reporting functionality into practice software.[11]

By reporting adverse events, healthcare professionals can support the TGA's pharmacovigilance activities, thereby safeguarding the Australian population. ≺

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Conflicts of interest: all authors are employees of the Therapeutic Goods Administration (TGA), which is part of the Australian Government Department of Health and Aged Care. The TGA is responsible for regulating therapeutic goods including prescription medicines and vaccines in Australia. Fiona Mackinnon was Deputy Editor of Australian Prescriber *from 2006 to 2021.*

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