Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Pharmacovigilance Inspection Program metrics report

January 2022 – December 2022

Version 1.0, February 2025

Contents

Summary

This metrics report covers the period from 1 January 2022 to 31 December 2022, referred to as the 'current reporting period'. This report provides an overview of pharmacovigilance inspection deficiencies, including a comparison of deficiencies identified in the previous reporting periods. Data has been de-identified, aggregated, and aims to assist sponsors with improving their pharmacovigilance systems as well as supporting preparation for pharmacovigilance inspections.

From 1 January 2022 to 31 December 2022, the Therapeutic Goods Administration (TGA) conducted 9 pharmacovigilance inspections of Australian medicine sponsors.

We completed 9 routine, systems-related pharmacovigilance inspections in 2022.

Inspections identified:

- **4** critical deficiencies
- **24** major deficiencies
- **34** minor deficiencies.

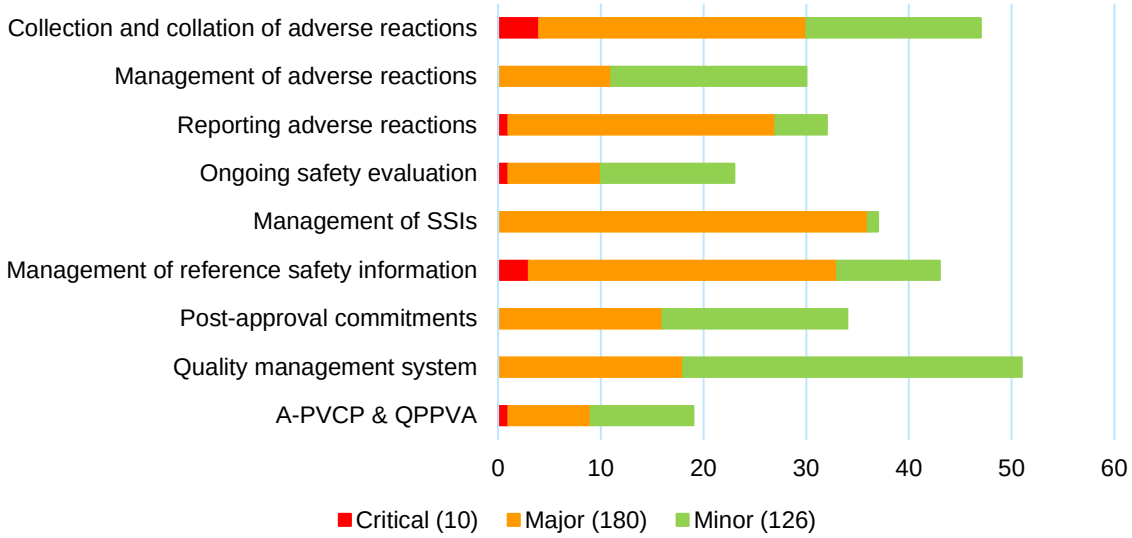
The number and grading of deficiencies by pharmacovigilance topic area is described in *Table 1* (see Appendix I for more detail on each pharmacovigilance topic area). Sponsors developed a Corrective and Preventative Action (CAPA) plan for all identified deficiencies and they have all been rectified.

Table 1: Number and grading of deficiencies by pharmacovigilance topic area in 2022

Topic area	Critical (4)	Major (24)	Minor (34)	Total by topic area (62) n, (%)
Collection and collation of adverse reactions	1	3	5	**9 (14.5%)**
Management of adverse reactions	-	1	7	**8 (12.9%)**
Reporting adverse reactions	1	2	4	**7 (11.2%)**
Ongoing safety evaluation	1	1	1	**3 (4.8%)**
Management of significant safety issues (SSIs)	-	5	1	**6 (9.6%)**
Management of reference safety information	1	2	5	**8 (12.9%)**
Post-approval commitments	-	5	2	**7 (11.2%)**
Quality management system	-	3	6	**9 (14.5%)**
Australian Pharmacovigilance Contact Person (A-PVCP) & Qualified Person Responsible for Pharmacovigilance in Australia (QPPVA)	-	2	3	**5 (8.0%)**

This chart shows the proportion of Critical, Major and Minor deficiencies in each topic area since the commencement of PVIP in 2017 to 2022 (5 year period).

Figure 1: Total deficiencies by topic area since the commencement of the PVIP - 5 year review



In the last five years, we have observed critical deficiencies in the following topic areas: collection and collation of adverse reactions, reporting adverse reactions, ongoing safety management of SSIs and A-PVCP/QPPVA responsibilities. We observed the highest number of critical deficiencies in collection and collation of adverse reactions and management of reference safety information. We observed major findings across all topic areas, with the highest incidence in the areas of management of SSIs, reporting adverse reactions and collection and collation of adverse reactions.

Deficiencies identified in the current reporting period are discussed in more detail in this report (refer to the Deficiencies observed during inspections and Common areas of deficiencies sections).A more detailed review of cumulative inspection outcomes is provided in the Comparison of inspection deficiencies over time section of this report.

Background

Our Pharmacovigilance Inspection Program (PVIP) commenced on 1 September 2017, with the first inspection conducted in January 2018. The PVIP aims to protect public health by strengthening and broadening our post-market monitoring activities and ensuring the continued safety of medicines included on the Australian Register of Therapeutic Goods (ARTG).

Pharmacovigilance inspections enable the TGA to help sponsors to meet their pharmacovigilance obligations. Sponsors are required to create and maintain effective, robust pharmacovigilance systems. The inspections assess the sponsor's compliance with currently applicable Australian pharmacovigilance regulations and guidelines, specifically the:

- *Therapeutic Goods Act 1989* (Subsections 28(5e), 28(5)(ca), 28(2B), 28(3), 29A and 29AA)
- *Therapeutic Goods Regulations 1990* (Regulation 15A)
- *Pharmacovigilance responsibilities of medicine sponsors Australian recommendations and requirements* (v2.2, January 2021) (referred to as the *Pharmacovigilance Guidelines*)
- Conditions – standard and specific, applying to registered or listed therapeutic goods (Section 28 of the *Therapeutic Goods Act 1989).*

In this report we use ‘must’ or ‘required’ to describe a sponsor’s legal obligations. We use ‘should’ to describe actions that assist sponsors to meet their legal requirements.

In a pharmacovigilance inspection, inspectors verify compliance with the mandated reporting and record-keeping requirements in addition to the recommendations set out in the *Pharmacovigilance Guidelines*.

For further information about the PVIP, including how we prioritise inspections and our approach to pharmacovigilance compliance and enforcement, please refer to: *Pharmacovigilance inspection program: Guidance for medicine sponsors*.

Inspections conducted

From 1 January 2022 to 31 December 2022, our PVIP team conducted 9 pharmacovigilance system-related inspections of Australian medicine sponsors. All inspections were routine inspections and targeted in scope (see Appendix II – Inspection types). There were no re-inspections, and all inspections were announced. All 9 inspections were conducted remotely via video conference and the inspection duration ranged 3-4 to business days.

A variety of medicine sponsors including large and small companies were inspected during this period. Whilst there was a risk-based focus on sponsors of prescription medicines, sponsors of the following medicine portfolios were also inspected:

- generic medicines
- biosimilar medicines
- over-the-counter (OTC) medicines
- complementary medicines.

Deficiencies identified during inspections were graded as critical, major, or minor (see Appendix III for definitions of inspection gradings). Comments (observations) are not discussed in this report. We identified deficiencies during all 9 inspections and all inspected sponsors received at least one major and at least one minor deficiency. From the 9 pharmacovigilance inspections conducted during the reporting period, the TGA identified:

- 4 critical deficiencies
- 24 major deficiencies
- 34 minor deficiencies

Each deficiency may comprise multiple separate findings, grouped according to the associated topic area and graded according to the highest-level legislative requirement or according to the cumulative pharmacovigilance impact.

As described in the deficiency grading definitions (refer to Appendix III), we classify deficiencies by the assessed risk level and this may vary depending on the nature of medicine. In some circumstances an otherwise major deficiency may be categorised as critical. The specific nature of the therapeutic good is also a determining factor in the grading of a deficiency.

Deficiencies observed during inspections

Critical deficiencies

We identified 4 critical deficiencies across 2 inspections during the reporting period.

Each of these critical deficiencies represented a serious violation of applicable pharmacovigilance legislation and guidelines or was considered to pose a potential risk to public health. Following the inspections, both sponsors developed CAPA plans, addressing each critical deficiency and proposed actions to mitigate the risk of reoccurrence. We closely monitor all CAPA commitments until they are fully implemented.

The critical deficiencies were categorised identified are presented in Table 2 below.

Table 2: Critical deficiencies per sponsor

Sponsor A	**Pharmacovigilance Topic Area – Critical Deficiency**
Sponsor Type: Medicines/vaccines	Collection and collation of adverse reactions
Sponsor B	**Pharmacovigilance Topic Area – Critical Deficiency**
Sponsor Type: Herbal and Complementary medicine	Reporting adverse reactions
	Ongoing safety evaluation
	Management of reference safety information.

See Appendix I for more information on pharmacovigilance topic areas.

De-identified summaries of the critical deficiencies are provided below grouped by the relevant topic area.

Collection and collation of adverse reactions

The critical deficiency raised under this topic area comprised the following sub-deficiencies:

- failure to perform case collection from our Database of Adverse Event Notifications (DAEN) – medicines
- failure to monitor a sponsor-initiated social media account to collect spontaneous adverse reactions
- failure to develop an Australian website to facilitate the collection of safety information from Australia
- deficiency in the global literature search strategy
- deficiencies in the reconciliation process.

We assigned an overall critical grading to this deficiency due to the significant scale of the actual (and potential) safety information missing from the sponsor's pharmacovigilance system. The consequence of these deficiencies impacted the sponsor's capacity to effectively monitor the quality, safety, and efficacy of the registered therapeutic good as required under Subsections 29A and 29AA of the *Therapeutic Goods Act 1989*.

Our *Pharmacovigilance Guidelines* recommend that sponsors collect adverse event cases from the DAEN – medicines database and online sources that are sponsor funded or managed. These include websites, webpages, blogs, vlogs, social networks, internet forums, chat rooms, health portals and digital media.

The current *Pharmacovigilance Guidelines* recommend regular and routine surveillance of all online forums. Lack of online monitoring may result in a potential deficiency in the ability to sufficiently assess the benefit/risk profile of a therapeutic good. Sponsors are reminded that careful consideration of all pharmacovigilance recommendations in the context of their specific pharmacovigilance system is expected.

Reporting adverse reactions

The critical deficiency raised under this topic area represented a serious violation of applicable legislation and guidelines. The inspectors could not verify any instances in which serious adverse reaction reports had been provided to the TGA within the timeframes set out in the *Pharmacovigilance Guidelines*.

The inspection revealed evidence of multiple examples of non-reporting and late reporting of serious adverse reaction reports to us. Through the investigation process, it was determined that these deficiencies were due to systematic deficiencies in the sponsor's pharmacovigilance system. The sponsor did not identify these examples of non-compliance prior to the inspection and there was no evidence of QPPVA awareness of this non-compliance.

Sponsors' obligations towards reporting of serious adverse reaction reports are described in the *Pharmacovigilance Guidelines* and legislated under Subsection 28(5)(e) of the *Therapeutic Goods Act* and Regulation 15A of the *Therapeutic Goods Regulations 1990*.

In addition, the sponsor did not possess relevant pharmacovigilance records as they did not retain records pertaining to all adverse reaction reports. Therefore, the sponsor failed to comply with the record-keeping obligations described in the *Pharmacovigilance Guidelines* and legislated under Subsection 28(5)(ca) of the *Therapeutic Goods Act* and Regulation 15A of the *Therapeutic Goods Regulations 1990*.

We identified the following non-compliance as part of this critical deficiency:

- failure to include key information in serious adverse reaction reports submitted to the TGA
- deficiencies in the process for submitting serious adverse reaction reports to us and a lack of compliance oversight.

Comparison of source documents and reports submitted to us revealed that submitted reports contained inaccurate or incomplete information. This included examples of non-compliance with the requirement for sponsors to provide the reporter verbatim used to describe the adverse reaction as described in the *Pharmacovigilance Guidelines*.

The inspection team determined that the sponsor did not adhere to the procedure developed for the submission of serious adverse reports to us. Additionally, the processes established by the sponsor did not facilitate compliance with reporting obligations.

Ongoing safety evaluation

An inspection that involved a sponsor with a critical deficiency in this topic area included several identified failures. The sponsor failed to establish any type of pharmacovigilance system including the collation of adverse reactions, any standard operating procedure (SOP) relating to a pharmacovigilance system, the appointment of an A-PVCP, nor any ongoing monitoring, for a period of almost two years. This occurred despite the supply of several medicines in Australia during this period.

This was considered a significant period without a pharmacovigilance system, during which the sponsor was unable to fulfill their mandatory reporting obligations to us. Consequently, the sponsor was unable to detect and investigate any safety issues in a timely manner, which represented a potential risk to public health as the sponsor could not monitor the quality, safety and efficacy of the medicines as required under Subsections 29A and 29AA of the *Therapeutic Goods Act 1989*.

After the sponsor introduced a pharmacovigilance system, multiple examples were identified where adverse reactions from different sources were documented in sponsor records but not collated into the sponsor's safety database for use in ongoing monitoring activities. The sponsor did not therefore comply with the requirement that the pharmacovigilance data they collected, collated, and electronically stored must be available from a single access point within Australia. This impacted on the sponsor's capacity to effectively perform comprehensive ongoing safety evaluation.

Furthermore, there was no evidence of any regular analysis of safety information for the purpose of ongoing safety monitoring. The sponsor failed to proactively identify and manage two signals as an outcome of this failure. The sponsor's written procedures were either not followed or were incomplete in relation to signal detection and management and SSI assessment and reporting.

The following additional sub-deficiencies were also identified in this critical deficiency:

- failure to undertake any regular literature review for case collection and ongoing monitoring purposes
- failure to monitor for safety-related actions taken or requested by comparable overseas regulators (CORs)
- deficiencies in the sponsor's safety database which limited the sponsor's ability to perform systematic critical analysis and evaluation of cumulative cases to identify potential safety issues.

There was an overall failure to record information in a structured way in the sponsor's database used to collate safety information for ongoing monitoring purposes. Examples included incomplete records of cases such as missing adverse reaction terms, missing special situation terms and missing patient demographics, summary rather than verbatim information recorded, and no recorded causality assessments.

Management of reference safety information

The inspection with a critical deficiency in this topic area involved multiple and systematic breaches of paragraph 9A(4)(a) of the *Therapeutic Goods Act 1989* and Regulation 10 of the *Therapeutic Goods Regulations 1990* in relation to label compliance for medicines.

The sponsor had failed to implement three mandatory warning statements for one medicine. The investigators classified two of the reports as serious and represented a significant risk to public health. If the mandatory warnings had been included on the label, the physicians managing these patients may have had the patients cease or not have commenced treatment. This compliance breach therefore presented a serious violation of applicable regulations, which adversely affected the rights, safety, and well-being of patients.

A review of labels of other sponsor medicines in the inspection provided evidence of further examples of breaches of paragraph 9A(4)(a) of the *Therapeutic Goods Act 1989* and Regulation 10 of the *Therapeutic Goods Regulations 1990* via a failure to implement:

- mandatory warning statements in line with the TGO 92 requirements (multiple examples)

- an indication in line with the Therapeutic Goods (Permissible Indications) Determination (one example).

The deficiency in this topic area also concerned a lack of alignment of reference safety information on the sponsor website compared to the current information on the medicine labels. Providing inaccurate information relating to a medicine on a website may lead to confusion and misuse of the medicine by the public.

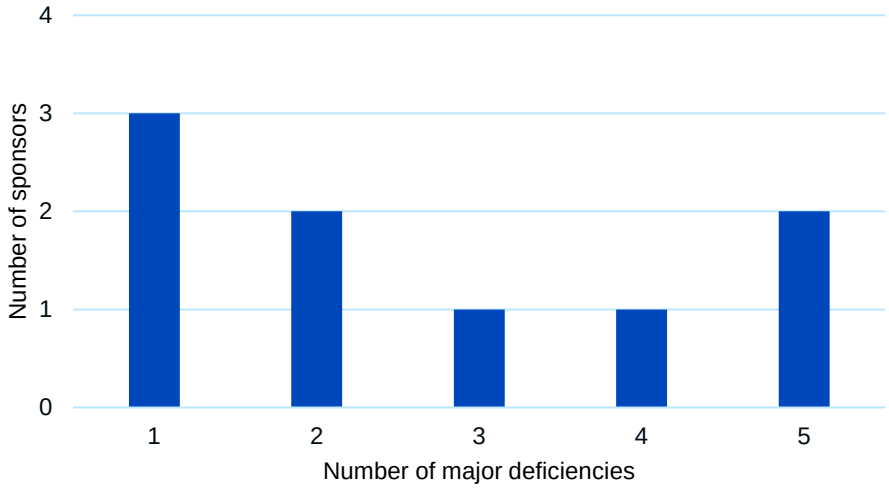
The sponsor did not implement any written procedures for the management of reference safety information, including the creation of a label and the variations of an existing label for medicines. There was nil evidence presented regarding training of relevant staff on this element of the pharmacovigilance system. The inspectors deemed that the lack of sufficient training may have contributed to the overall critical deficiency.

Major and minor deficiencies

During this reporting period, at least one major deficiency and one minor deficiency was identified in every inspection conducted.

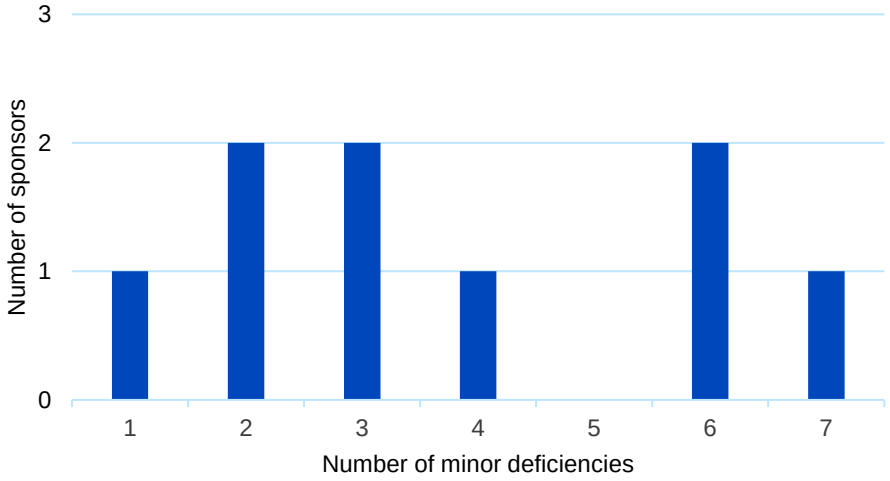
A total of twenty-four 24 major deficiencies were identified (see *Figure 2*).

Figure 2: Number of major deficiencies per sponsor



There were 34 minor deficiencies identified from the 9 inspections conducted (see *Figure 3*).

Figure 3: Number of minor deficiencies per sponsor



Deficiencies identified during the reporting period have been grouped according to the overarching topics across the pharmacovigilance system. Each topic area is comprised of various sub-topics (see Appendix I).

A summary of the topic areas in which major and minor deficiencies were most frequently identified is provided in *Table 3*. Of note, two topic areas, collection and collation of adverse reactions, and the quality management system, appeared across both gradings.

Table 3: Summary of most frequently identified major and minor deficiencies by pharmacovigilance topic area.

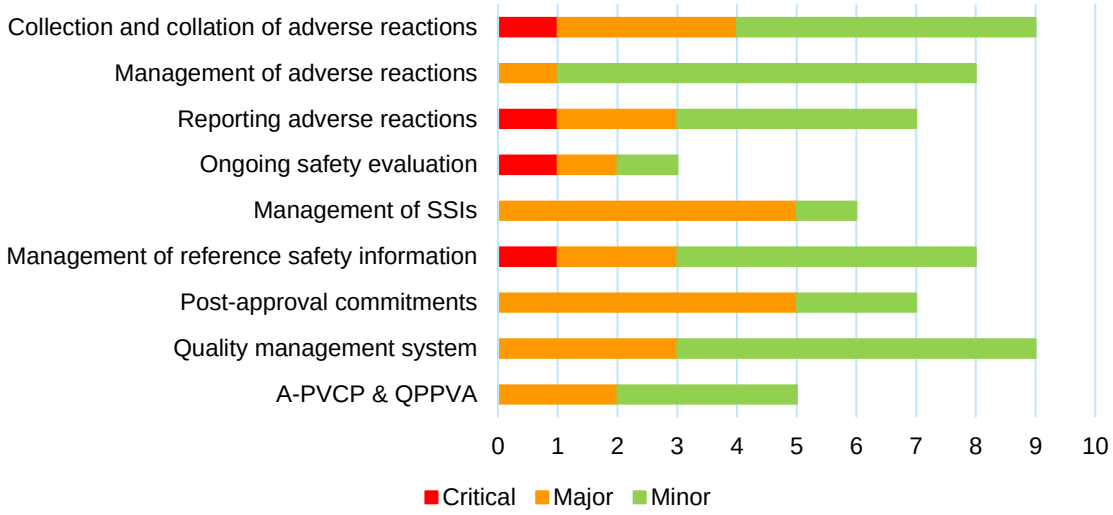
Deficiency grading	Total deficiencies	Topic areas with deficiencies most frequently identified (number of inspections)
Major	24	Management of SSIs (5) Post-approval commitments (5) Collection and collation of adverse reactions (3) Quality management system (3)
Minor	34	Management of adverse reactions (7) Quality management system (6) Collection and collation of adverse reactions (5) Management of reference safety information (5)

Common areas of deficiencies

The most common deficiencies were observed in 2 areas of investigation, collection and collation of adverse reactions and quality management systems (*Figure 5*). Similarly, these 2 topic areas had the most common deficiencies in the previous reporting period.

The number and grading of all deficiencies by pharmacovigilance topic area is presented in *Figure 4*.

Figure 4: Number and grading of deficiencies by topic area for 2022



An overview of the non-compliance across the inspection topic areas is discussed below.

Collection and collation of adverse reactions

We identified a deficiency in collection and collation of adverse reactions in every inspection conducted during the reporting period. Grading of deficiencies ranged from minor to critical. Refer to the section Critical Deficiencies in this report for a detailed discussion of the critical deficiency for this topic area.

Deficiencies were identified in the following processes:

- failure to collect safety information from medical information enquiries, product quality complaints, company-sponsored websites and social media, local and international medical literature, internal company departments (including any platforms used to record interactions with customers), business partners, the TGA DAEN – medicines, records of telephone calls (voicemail) and post-registration programs including patient support programs, product familiarisation programs, market research programs and registries
- failure to include relevant safety reporting provisions in all third-party contractual agreements prior to the service commencing (for over-the-counter (OTC) medicines, this included agreements with retail partners and social media influencers)
- failure to implement timeline for reporting of safety information by company personnel
- failure to reconcile safety information with all possible (relevant) sources or delays with conduct of reconciliation
- inadequate identification, collection and collation of special situation reports including lack of efficacy and off-label use

- failure to establish access to safety data from a single access point in Australia
- deficiencies in literature search strategy including scope of search terms, frequency of searches and exclusion of non-marketed medicines
- failure to collect and record consent to follow up for additional information and patient ethnic origin including Aboriginal and/or Torres Strait Islander origin status
- failure to record invalid reports (e.g., drug-event pairs) in the pharmacovigilance system and perform follow up on these reports for additional information.

Sponsors should maintain a pharmacovigilance system that allows them to identify, collect and collate all information related to safety of their medicine from all possible sources. It is recommended that sponsors encourage consumers and health professionals to submit safety information by providing adverse reaction reporting forms and contact details on the company website.

Sponsors should develop written procedures that describe the roles, responsibilities, and timelines for the collation of accurate and complete reports of adverse reactions and special situation reports from all identified sources. Appropriate QPPVA oversight of all potential reporting channels is expected. Furthermore, it is recommended that the sponsor considers monitoring and routine testing of externally published contact channels (e.g., phone, email, webforms and fax) to ensure the ongoing effectiveness of this part of the pharmacovigilance system.

Where the sponsor uses a vendor for the delivery of a post-registration program, the sponsor needs to ensure their awareness of how the program is structured. Specific consideration should focus on what potential reporting channels may be available for safety information and what formats of source documents may be created. The sponsor needs to ensure that written procedures and agreements adequately describe these aspects of case collection including quality assurance activities to minimise the risk of unreported safety information.

Many inspections identified a lack of due diligence in case collection from medical information enquiries. This comprised unidentified safety information (including valid, invalid, AE and special situation reports) as well as enquiries where it was not clear whether an actual patient had experienced an event. Sponsors are reminded that it is incumbent upon the sponsor to conduct sufficient follow up procedures to confirm involvement of ‘a patient’. Care should always be taken to determine if an enquiry involves an adverse event.

We require sponsors to collect and record invalid reports containing drug-event pairs from all sources. Additionally, sponsors should exercise due diligence in following up invalid reports to collect missing data elements. However, if a report cannot be validated it must be retained and recorded in their pharmacovigilance system and included in ongoing safety evaluation activities.

Sponsors are advised that individual cases of suspected lack of efficacy must be collected, retained, considered in ongoing monitoring activities, and provided to us upon request. When identifying and collecting special situation reports such as off-label use, the sponsor should always consult the current locally approved PI due to the potential difference between the locally approved PI and other reference safety information such as the Company Core Safety Information (CCSI).

In accordance with the *Pharmacovigilance Guidelines*, pharmacovigilance data collected, collated, and electronically stored must be available from a single access point within Australia. For sponsors where this pharmacovigilance data is collated in a global safety database, or data is collected by global organisations e.g., via a global literature search, the QPPVA must be able to demonstrate ready access to this Australian pharmacovigilance data from Australia.

Quality management system

We identified a major or minor deficiency in the sponsor's quality management system in all 9 inspections conducted during the reporting period.

Most deficiencies associated with the quality management system could be categorised under one of the four areas discussed below.

Pharmacovigilance procedures

All 9 inspections conducted included a deficiency relating to pharmacovigilance procedures. Inadequacy of pharmacovigilance procedures or their management was consistently one of the most frequently cited sponsor root cause analyses for inspection deficiencies. Sponsors should establish a quality management system that supports their pharmacovigilance system to meet their Australian pharmacovigilance requirements. It is noted that robust standard operating procedures underpin a quality management system.

Sponsors are expected to have an effective pharmacovigilance system in place and make provisions for regular review for improvements to the system where required. Audits or other quality assurance methods can facilitate this as well as regular reviews of standard operating procedures.

Deficiencies were identified with the following aspects of sponsor pharmacovigilance procedures:

- failure to monitor for TGA updates or updates to internal processes, assess the impact on pharmacovigilance standard operating procedures and implement required updates in a timely manner
- inadequate version control of pharmacovigilance procedures
- failure to incorporate the recovery of the pharmacovigilance system in the event of a disaster or disruption should be included in the sponsors business continuity plan and procedures.

Furthermore, there were examples of the sponsor conducting pharmacovigilance activities that had not been documented in a written procedure. Consequently, no associated training records were available, and it was not possible to verify that these activities would be conducted in a consistent, systematic way. In addition, there was no evidence staff undertaking these activities understood the associated requirements and timelines.

Pharmacovigilance training

We identified a deficiency in pharmacovigilance training in all 9 inspections conducted during this reporting period.

Pharmacovigilance awareness training should be conducted for all company personnel (including contractors) at induction of employment, preferably within the first month. Annual refresher training is recommended at a minimum for all relevant staff.

Failures to complete or delayed completions of initial and refresher company pharmacovigilance training were identified across multiple inspections. In some instances, an absence of training records meant inspectors could not verify compliance.

Records of pharmacovigilance awareness training should be retained indefinitely for the life of the medicine, in line with the TGA recommendations in the *Pharmacovigilance Guidelines.* Failure to develop a procedure to outline how the sponsor identified personnel who required training and subsequently delivered timely initial and refresher pharmacovigilance awareness training was a deficiency in multiple inspections.

It is recommended that the sponsor verifies understanding of pharmacovigilance awareness training via a test set to a 100% pass mark, to set the expectation that the staff are familiar with all (rather than some) pharmacovigilance responsibilities.

Deficiencies in the content of the pharmacovigilance awareness training were also identified in inspections from this reporting period whereby training material either did not align with the TGA requirements and recommendations in the *Pharmacovigilance Guidelines* or key aspects regarding the pharmacovigilance responsibilities of personnel were not addressed.

Other aspects of pharmacovigilance training, including training on pharmacovigilance procedures, was reviewed as part of the inspection process and the following deficiencies were identified during this reporting period:

- failure to identify, define and allocate for training, the relevant procedures for pharmacovigilance staff
- failure to record QPPVA and back-up QPPVA training on relevant TGA pharmacovigilance guidance documents and company procedures (this deficiency was identified in pharmacovigilance systems where the role of the QPPVA was fulfilled by sponsor personnel as well as where the role was outsourced to a vendor).

Third-party agreements

Seven out of 9 inspections conducted in this reporting period included deficiencies regarding a contracted third party, the content of the executed agreement and sponsor oversight of the third party. Deficiencies included:

- failure to develop a procedure for systematic assessment of sponsor agreements to ensure contractual pharmacovigilance provisions were implemented for relevant activities
- failure to implement a pharmacovigilance agreement in a timely manner upon engagement with business partners with delays identified of more than 600 days
- failure to maintain agreements, including for example, up-to-date sponsor contact details and alignment of clauses with any updates to the sponsor or the TGA requirements
- omission of important pharmacovigilance requirements and responsibilities from relevant third-party agreements
- deficiencies with the version control and maintenance of sponsor templates for pharmacovigilance agreements and clauses
- failure to initiate or conduct audits of third-party service providers or business partners to ensure pharmacovigilance responsibilities were fulfilled
- lack of pharmacovigilance oversight of agreements and third parties.

The agreements reviewed involved third parties undertaking pharmacovigilance activities on behalf of the sponsor (pharmacovigilance vendors, parent companies or business partners) or activities with an impact or potential impact on the pharmacovigilance system, e.g., patient support programs.

Sponsors must ensure pharmacovigilance responsibilities are met when the pharmacovigilance system includes contractual arrangements with other external organisations. External companies should be appropriately trained and be managed under sufficient oversight by the sponsor. Audits or other quality assurance methods can facilitate this.

Pharmacovigilance record-keeping

A deficiency in pharmacovigilance record-keeping was observed in 6 out of 9 inspections conducted during this reporting period.

Under Subsection 28(5)(ca) of the *Therapeutic Goods Act 1989*, records pertaining to the reporting requirements and safety for your medicine(s) must be retained for the life of the medicine and for an additional 5 or 10 years after removal from the ARTG for listed and registered medicines respectively. These timelines are set out in the *Pharmacovigilance Guidelines* alongside further information about the types of pharmacovigilance records that sponsors must consider. The *Pharmacovigilance Guidelines* also set out record-keeping recommendations for specific types of records.

Deficiencies included:

- non-alignment of record retention periods to TGA requirements
- failure to provide inspectors with requested pharmacovigilance records, required or recommended to be retained, including invalid reports, reference safety information, pharmacovigilance training records and literature reviews
- failure to develop procedures regarding access to pharmacovigilance records
- failure to define records that should be identified as source documents and managed as adverse event records
- failure to describe record-keeping responsibilities and describe sponsor access to pharmacovigilance records in pharmacovigilance agreements with business partners
- failure to establish defined, secure document retention systems to trace all data entry, modification, and deletion for electronic pharmacovigilance records
- inadequate storage and access to paper pharmacovigilance records.

As a part of the quality management system, sponsors should identify all records that are relevant to their pharmacovigilance system and clearly document how these will be managed. Specific activities incumbent upon the sponsor includes sufficient management of record retention, access, and retrieval. All pharmacovigilance records (both electronic and hard copy) should be secured with appropriate confidentiality and accessibility controls.

The sponsor record-keeping system should support the timely retrieval of pharmacovigilance records upon request by the TGA. Sponsor inspection-related responsibilities include providing the inspectors, within the given deadline, any information or records needed to conduct the inspection. These responsibilities may extend to other organisations in Australia or overseas who are involved in sponsor pharmacovigilance activities.

Sponsors are reminded that record-keeping requirements also apply to records created and/or maintained overseas for sponsor medicines included in the ARTG, and responsibilities towards pharmacovigilance records must be addressed in relevant agreements.

Management of reference safety information

A deficiency related to the management of reference safety information was identified in 8 out of 9 inspections conducted. Five of these deficiencies were graded as minor, 2 major and 1 critical. Please refer to the section Critical Deficiencies of this report for a detailed discussion of the critical deficiency for this topic area.

To ensure the safe use of medicines, all reference safety information documents made available by the sponsor to healthcare professionals, consumers and sponsor personnel need to be current and maintained.

Sponsor written procedures should facilitate timely submission of variations and implementation of any approved changes to ensure there is no undue delay in updating the PI and CMI. Furthermore, any other sponsor materials that are relied upon by prescribers and patients to make decisions relating to the safe and effective use of medicinal products should be maintained. It is recommended to sponsors to maintain the currency of the PI irrespective of whether the product is marketed or supplied in Australia or whether the PI document is published on the TGA website.

Deficiencies in this topic area comprised multiple findings related to delays in updating the Australian PI, CMI, product packaging leaflets, minimum PI and related materials with new or revised safety information. Examples are outlined below.

Timelines applicable for the maintenance of the reference safety information

Sponsors should have procedures in place to ensure compliance with regulatory timeframes and procedures should incorporate appropriate quality checks. Procedures should also describe record-keeping practices to ensure the retention of evidence to verify compliance with sponsor obligations and regulatory timelines. Sponsor tracking of due dates and completion dates of regulatory timeframes and internal updates may facilitate compliance and oversight, including oversight by the QPPVA.

Deficiencies with the following timelines were identified during this reporting period:

- delayed submission to the TGA of safety-related variations to the Australian PI, beyond six months of company decision date
- failure to lodge the updated PI on the TGA eBS within two weeks of our approval of the safety-related variation.
- failure to lodge the updated CMI on the TGA eBS within two weeks of our approval of the safety-related variation/PI.

The sponsor should ensure that procedures of their global organisation facilitate timely communication of safety-related updates to be incorporated into Australian reference safety information.

Standard procedures following safety-related variations

The following deficiencies were identified in relation to sponsor procedures after our approval of a revised PI:

- failure to provide evidence to substantiate a sponsor assessment of CMI consistency with the PI
- failure to communicate changes and availability of updated reference safety information to relevant staff and third parties
- delayed alignment of the Minimum (abridged) PI with the complete PI
- delayed revision and implementation of the updated product insert
- failure to define timeframes, conduct a timely impact assessment and make necessary updates to all relevant company-sponsored material (consequently, the following types of ‘current’ materials were identified during inspections which referenced an outdated PI:

externally facing educational materials, and internal materials used by medical information staff to respond to medical enquiries).

It is expected that as part of our record-keeping recommendations, sponsors hold evidence of a CMI impact assessment, to document the timely decision about whether a CMI revision was warranted following approval of a safety-related variation. Ongoing consistency of the CMI with the PI is a sponsor obligation imposed as a condition of registration.

We recommend that the PI and CMI are consistently accessed via our website. During the inspection reporting period, deficiencies were identified where the sponsor failed to ensure that the PI and CMI published on other platforms (that the sponsor funded, managed or were responsible for, e.g., company-owned websites), were in line with the version published on our website.

The sponsor should be aware of all repositories under their control used to access the PI and CMI, both internally and externally. Additionally, the sponsor should ensure that there is a written procedure to ensure a minimal delay in alignment across platforms following any updates. The same awareness and procedures should extend to all other types of materials shared by the sponsor via online platforms and following safety-related updates. These materials need to be reviewed, aligned, and updated on those platforms.

The sponsor should identify all stakeholders that require notification of an update to reference safety information based on their role and responsibilities. Deficiencies in the access to updated reference safety information for internal staff (e.g., medical information team) as well as third-party personnel (e.g., sponsor-initiated patient support programs) were identified during the reporting period. The sponsor is responsible for ensuring that any contracted third-party personnel have access to the current reference safety information. Ideally this should be documented in the agreement with third parties for the avoidance of confusion, including how reference safety information will be accessed and how the third party will be informed of any important updates e.g., safety-related changes.

Updating reference safety information for generic medicines

Sponsors of generic medicines must comply with the condition of registration to align PI and CMI within one month of a safety-related update to the innovator's PI when this condition is imposed by the TGA. A delay of more than 1 year and 10 months was identified through inspection in the current reporting period.

Another deficiency concerning examples of non-submission of safety-related updates for non-marketed generic medicines was identified. Sponsors are reminded that the supply or marketing status of a medicine does not affect the responsibility of a sponsor of a generic medicine to submit on time updates to the PI of the generic medicine to the TGA.

Sponsor procedures should describe a process for identification of the innovator product and routine review of the innovator PI on the TGA website to identify safety-related updates. Furthermore, the timeframe for this review must enable compliance for the timing of the subsequent submission to the TGA of any required variations to the generic medicine PI.

Management of adverse reactions

Deficiencies in the management of adverse reactions were identified in 8 out of 9 inspections conducted during the reporting period comprising 1 major deficiency and 7 minor deficiencies.

Deficiencies in this area have a potential impact on serious adverse reaction reporting to the TGA and ongoing safety evaluation activities.

A broad range of non-compliance was identified for this topic area in this reporting period as summarised below, with a more detailed discussion also provided for the areas of non-compliance identified most frequently across inspections:

- deficiencies in seriousness assessments
- incorrect classification of valid reports as invalid
- inconsistencies with the recorded report type categorisation
- deficiencies in the electronic data management of adverse reaction records
- failure to retain complete source documents including follow-up attempts
- deficient or lack of quality control and quality assurance processes related to the management of electronic safety information including validation of electronically recorded information against source documents
- deficiencies with the recording of reporter causality, sponsor causality and sponsor expectedness assessments of Australian reports as recommended in the *Pharmacovigilance Guidelines* or outlined in sponsor procedures
- inconsistencies with the MedDRA coding of event terms including failure to identify, accurately record and code all event terms from reports within the pharmacovigilance system
- failure to manage special situation reports within the sponsor's pharmacovigilance system
- incorrect record of Day 0 for case reports in the sponsor safety database/pharmacovigilance system
- deficiencies in the follow-up of adverse reaction, special situation and invalid reports including those from consumers and identified from the medical literature
- roles, responsibilities, and timelines for case management activities, including those listed above, should be defined in a company procedure and trained upon by those with an associated responsibility.

Seriousness assessments need to be based on the adverse event alone, independent to the medical evaluation, causality, and validity of the case report. Assessments are expected to be conservative when event outcomes or treatment information is not available.

The TGA definition of a valid case may differ from other jurisdictions e.g., in relation to what constitutes an identifiable patient, and sponsors must ensure that company procedures for the management of Australian case reports are in line with the *Pharmacovigilance Guidelines*.

Electronic data management of case reports and source documents

Sponsors are reminded that our recommendations for the management of electronic data are included in the *Pharmacovigilance Guidelines*. These steps ensure the integrity of the safety information collated by the sponsor (e.g., accuracy and traceability of all data entry including modification and deletion), assist with sponsor record keeping, reporting and ongoing monitoring obligations, and include the implementation of:

- internal processes to identify and manage duplicate cases
- an audit trail for electronic data

- strict access controls to documents and databases to ensure pharmacovigilance data remains secure and confidential across the complete data path
- quality control procedures and quality assurance auditing to verify the accuracy of stored data for initial and follow-up reports against the original data
- retention and easy access to source data (e.g., letters, emails, records of telephone calls and written notes that include details of an event) or an image of the source data to facilitate quality control and quality assurance processes.

Management of special situation reports

Sponsors must record all special situation reports. Examples of a special situation report includes reports of overdose, abuse, off-label use, misuse, medication error, exposure during pregnancy and breastfeeding or occupational exposure. Special situation reports should be included in ongoing monitoring, even if there is no association with an adverse event.

Follow up

Sponsors are expected to extend reasonable effort to follow up, where possible, on all adverse events received to obtain missing information and/or validate a case. The additional information and further supplementary data may be significant to supporting the clinical evaluation (i.e., seriousness and causality) of the case.

For consumer reports, this includes seeking voluntary informed consent to contact the treating doctor for medical confirmation of the adverse reaction and any additional relevant information. The consumer may also be able to provide valuable information (e.g., discharge summaries or laboratory results) and so their contribution to the monitoring of medicines safety should not be overlooked. Where consent for follow up with a consumer's treating doctor is not available, we expect that follow up should be performed with the consumer for relevant cases.

Additionally, the *Pharmacovigilance Guidelines* recommendations on follow up of special situation reports (regardless of whether there is an associated adverse event) should be followed.

Reporting adverse reactions

A deficiency in reporting adverse reactions to the TGA was identified in 7 out of 9 inspections. Of those 7 deficiencies, 1 was graded as critical, 2 were graded as major and 4 were graded as minor.

Minor deficiencies were assigned where no adverse effect to the rights, safety or well-being of patients would be expected because of the deficiency. In practice, this presented as a low volume of late reports where the lateness was not attributable to any systematic non-compliance. To resolve the deficiency, the sponsor had proactively identified the non-compliance ahead of the inspection and implemented an associated CAPA Plan as a part of their routine quality management system.

Deficiencies identified in this topic area included:

- failure to report and/or delayed reports of serious adverse reaction reports to us (identified in all 7 inspections)
- deficiencies in reporting rules applied to determine the reportability of safety information
- deficiencies in management of follow up information to serious adverse reaction reports

- deficiencies in record keeping of serious adverse reaction report submissions.

As a requirement for all sponsors, serious adverse reactions must be reported to us within 15 calendar days of first receipt by any company personnel. Sponsors should ensure that robust procedures, and where relevant agreements, are in place to facilitate prompt reporting of all safety information from all sources to achieve compliance with the 15-day reporting timeframe.

Where sponsors rely on pharmacovigilance agreements for the exchange of safety information – including the assessment of adverse reactions for onward reporting to us – responsibilities and timelines need to be clearly outlined and followed.

Where sponsors rely on automated reporting rules, it is important to verify the compliance of those against the legislative requirements for Australia. Furthermore, where E2B reporting has been implemented, the sponsor needs to retain appropriate oversight of report submissions.

The QPPVA is expected to demonstrate awareness of compliance with this reporting obligation, including any late reports. The sponsor is expected to investigate any known incidences of late reports to identify the required improvements for an effective pharmacovigilance system.

Sufficient record-keeping obligations apply to adverse reaction reports and the sponsor must be able to produce records to verify compliance with the reporting obligation for serious adverse reactions to us upon request.

Post-approval commitments

A deficiency in compliance with post-approval commitments was identified in seven out of nine inspections, comprising five major deficiencies and two minor deficiencies.

Deficiencies identified in this topic area included:

- failure to access all approval letters and Section 28 letters applicable to products on the ARTG and implement processes to verify ongoing compliance with all post-approval commitments imposed
- failure to produce records to verify fulfillment of post-approval commitments
- delayed Periodic Safety Update Report (PSUR) submissions
- failure to implement the correct reporting period and/or submission frequency of PSURs as specified in the approval letter
- failure to notify, or delayed notification to, the TGA of the commencement of supply
- delays in the submission of an updated Risk Management Plan (RMP) / Australian Specific Annex (ASA) to the TGA e.g., following the European Medicines Agency (EMA) approval of removal or reclassification of safety concerns.

Sponsors must comply with all conditions of registration as set out in the approval letter or any subsequent amendments and compliance will be assessed in an inspection. Conditions of registration relevant to the pharmacovigilance system may include but are not limited to: notification to us of the date of commencement of supply of supply, implementation of the Black Triangle Scheme requirements, preparation, and timely submission of PSURs, maintenance of RMPs and ASAs and compliance with RMP commitments. Additional conditions may include the submission of safety data from clinical studies or registries.

Company procedures should be developed, and staff trained on the specific roles and responsibilities for management and execution of all post-approval commitments.

If sponsorship of a medicine was transferred, the current sponsor is expected to have access to the original TGA approval letter(s) for complete oversight of conditions of registration relating to pharmacovigilance. Further information regarding the obligations of a new sponsor, including record keeping, can be found on the TGA website.

Company procedures should require prompt communication of updates that impact the ASA. This includes communication of RMP updates from global staff to the sponsor, to ensure that the RMP-ASA is maintained in a timely manner. The ASA should be submitted as an update to us within the recommended three months of the change being accepted by the EMA. Where the responsibility for the EU-RMP or Core-RMP lies with a global business partner, the responsibilities for the timely management and communication of changes should be specified within the pharmacovigilance agreement.

Management of SSIs

A deficiency in the management of SSIs was identified in 6 out of 9 inspections. Of these, 5 deficiencies were graded as major and 1 as minor.

Deficiencies in this topic area comprised multiple findings related to the:

- failure to identify SSIs
- failure to report SSIs to the TGA within 72 hours of first (local) awareness
- delayed communication of safety issues from the global company to the local sponsor, including validated signals identified internally and safety-related actions taken by CORSs
- failure to include relevant timelines and responsibilities for the management of SSIs in pharmacovigilance agreements with business partners
- failure to develop standard procedures for the assessment of safety issues as SSIs and the subsequent management and notification of SSIs including the documentation of decisions relating to SSI notification to us
- failure to retain records relating to management of safety issues including evidence of the receipt of the issue, sponsor assessment and the justification of the decision for, or against, an SSI notification to the TGA
- failure to conduct SSI assessment of safety issues for non-marketed medicines.

Delays in the receipt of information about potential SSIs from a parent/global organisation, including business partners, are considered unacceptable and a risk to public health.

Sponsors should have robust procedures in place to ensure that internally validated signals and suspected or confirmed medicine quality defects are promptly received and assessed against the *Pharmacovigilance Guidelines*.

We also consider SSIs to include safety-related actions taken by CORs. Therefore, sponsors should have procedures in place to ensure their timely awareness of such safety-related actions. This may include regularly screening safety-related information published by CORs or ensuring that any COR requests for safety-related actions are sent to the sponsor in a timely manner from a parent/global organisation.

Sponsors are reminded that relevant third-party contractual agreements should include safety reporting provisions that outline responsibilities and timelines related to the identification, management and reporting of SSIs. Examples include pharmacovigilance agreements with business partners who maintain the global safety database and are assigned the primary responsibility for signal detection.

Care should be taken to ensure that the correct definition of a SSI is included in procedures and agreements, particularly where global templates are utilised.

The sponsor must ensure that pharmacovigilance obligations, including compliance with the *Pharmacovigilance Guidelines*, are fulfilled for all medicines registered or listed to the sponsor on the ARTG regardless of their Australian marketing/supply status.

A-PVCP & QPPVA

A deficiency of any grading related to the A-PVCP and QPPVA topic area was identified in 5 out of 9 inspections. Specifically, 2 major deficiencies and 3 minor deficiencies were identified for this topic area.

Deficiencies in this topic area were related to:

- failure to notify us of the name and contact details of the A-PVCP within 15 calendar days of the first medicine's entry on the ARTG
- failure to notify us of any changes to the name and/or contact details of the A-PVCP within 15 calendar days
- inadequate experience and knowledge of pharmacovigilance by A-PVCP
- inadequate experience and knowledge of pharmacovigilance by QPPVA
- inadequate oversight of the pharmacovigilance system by the QPPVA
- deficiency in pharmacovigilance training of the sponsor appointed back-up A-PVCP and back-up QPPVA.
- deficiency in availability and suitability of medically qualified person to the sponsor.

Sponsors are reminded that they must nominate an A-PVCP who will be responsible for fulfilling their pharmacovigilance reporting requirements. The nominated A-PVCP must reside in Australia and should have a sound understanding of Australian pharmacovigilance reporting requirements and this training and experience should be recorded and retained.

The A-PVCP is required to be nominated through the TGA eBS. Any changes to the A-PVCP or their details must be notified via an update in the TGA eBS within 15 calendar days. Evidence to demonstrate compliance with these reporting requirements should be available during an inspection and retained in accordance with sponsor pharmacovigilance record-keeping requirements.

The sponsor's appointed QPPVA should ensure that the sponsor has an effective pharmacovigilance system in place to comply with Australian pharmacovigilance requirements. A lack of QPPVA oversight of the following aspects of the sponsors pharmacovigilance system was identified in inspections conducted in this reporting period:

- agreements with third parties
- pharmacovigilance responsibilities assigned to third parties.
- implementation of safety updates to reference safety information

- management of post approval commitments.

The sponsor should be able to provide evidence of how the QPPVA achieves ongoing oversight of the pharmacovigilance system and how the effectiveness of the pharmacovigilance system is measured. Sponsor written procedures should facilitate QPPVA oversight, including aspects of the pharmacovigilance system that are not the direct responsibility of the QPPVA, such as commercial agreements.

Where the sponsor has a relationship with a global company, the QPPVA needs to have adequate understanding of the global pharmacovigilance processes that are relevant to the Australian pharmacovigilance system to allow them to have effective oversight of the entire pharmacovigilance system.

The QPPVA should be suitably experienced and qualified and needs to have adequate understanding of the Australian and (if applicable) global pharmacovigilance processes to fulfill their role. Evidence of QPPVA training and understanding of pharmacovigilance, relevant Australian legislation and sponsor processes and medicines should be documented and records of this documentation retained in accordance with sponsor pharmacovigilance record-keeping recommendations.

Ongoing safety evaluation

A deficiency of any grading in ongoing safety evaluation was identified in 3 out of 9 inspections conducted during the reporting period. Specifically, 1 critical, 1 major deficiency and 1 minor deficiency were identified for this topic area.

Additionally, the major and minor deficiency which pertained to inspections of a sponsor of innovator medicines and a sponsor of generic medicines involved:

- non-compliance with record-keeping recommendations and requirements for ongoing monitoring activities and information surrounding SSIs respectively
- deficiencies with the database/system used by the sponsor for ongoing safety evaluation activities
- delayed communication of validated signals from global organisation to the sponsor for assessment as an SSI
- failure to develop a standard operating procedure for ongoing safety monitoring and evaluation activities
- failure to monitor for safety-related actions taken or requested by CORs.

Safety monitoring activities should include a documented review of cumulative cases to allow for a comprehensive review of potential safety issues. This process should be described in a written procedure to ensure a standardised approach within the sponsor's pharmacovigilance system. The process should describe the methodology of detection and investigation of such issues in a timely manner including the assessment of the safety issue against the requirements in the *Pharmacovigilance Guidelines* and notification of SSIs to us.

All steps associated with signal detection and management are expected to be well documented to verify the actions taken, the timeframes of these actions and the justification for any decisions taken.

The system used to monitor the ongoing benefit-risk profile of sponsor medicines needs to have adequate functionality to critically analyse and evaluate collated safety information. The inspection deficiency regarding the sponsors database/system used for these activities concerned incomplete records of cases and inconsistent methodology of how information such as MedDRA terms and patient demographics was recorded. Summary rather than

verbatim information was recorded and there was an overall failure to record comprehensive case information in a structured and systematic way to facilitate reliable signal detection.

Where safety monitoring activities are conducted by a parent company or by a third party or partner the sponsor and specifically the QPPVA needs to have adequate understanding of the processes to allow them to have effective oversight of the entire pharmacovigilance system.

Comparison of inspection deficiencies over time

From the commencement of the PVIP on 1 September 2017 to 31 December 2022 we conducted 44 pharmacovigilance inspections of Australian medicine sponsors. A breakdown of inspections conducted per reporting period is presented in *Table 4*.

Table 4: Overview of pharmacovigilance inspections and average number of deficiencies each year

Inspection period	Number of inspections conducted (44)	Average number of deficiencies per inspection (all gradings)	Average number of critical deficiencies per inspection	Average number of major deficiencies per inspection	Average number of minor deficiencies per inspection
01-Sep-17 to 31-Dec-18	10	7.7	0	5	2.7
01-Jan-19 to 31-Dec-19	10	7.7	0.1	4.2	3.4
01-Jan-20 to 31-Dec-20[1]	6	7.5	0.3	4.5	2.7
01-Jan-21 to 31-Dec-21	9	6.1	0.3	4.1	1.7
01-Jan-22 to 31-Dec-22	9	6.9	0.4	2.7	3.8

Inspection deficiency topic areas

The number and distribution of all critical, major, and minor deficiencies across inspection topic areas since the commencement of the PVIP are shown in *Figure 5, 6*, and *7*, respectively.

Consistent with the observed trends in the last reporting period, case collection and collation remained the topic area for which the largest number of critical deficiencies have been identified over time. Additionally, management of SSIs followed by management of reference safety information remain the topic areas for which the largest number of major deficiencies have been reported since the commencement of the PVIP.

[1] Fewer inspections were conducted in 2020 as a result of a four-month pause on inspections in response to the COVID-19 pandemic.

The number of major deficiencies identified in some topic areas such as reporting of adverse reactions and management of reference safety information decreased in the current reporting period (see *Figure 6*). However, this was accompanied by an increase in minor deficiencies identified in these topic areas, as shown in Figure 7, indicating that less serious examples of non-compliance were identified in these topic areas in comparison to previous years.

Figure 5: Total number of critical deficiencies by topic area for all reporting periods

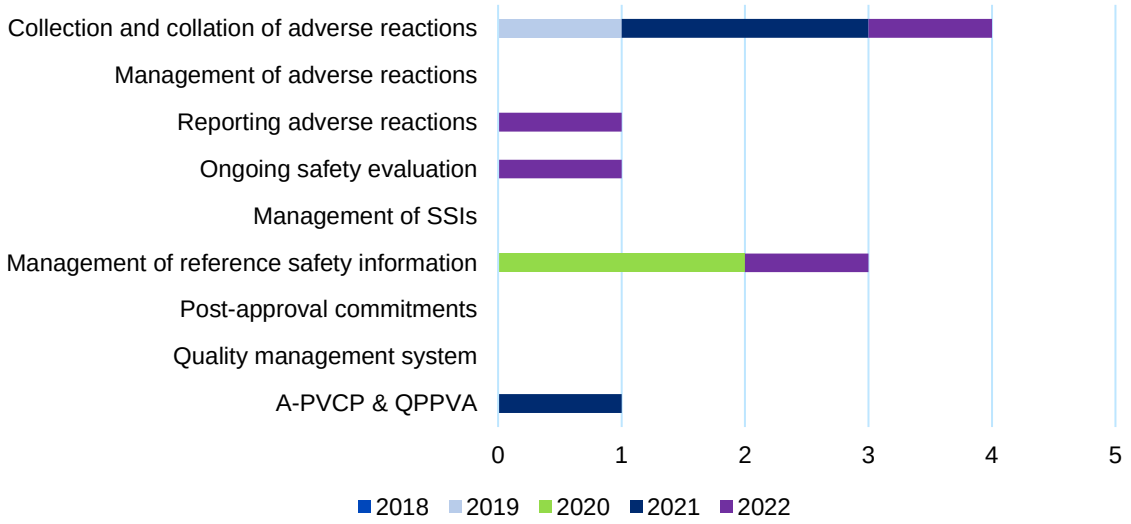


Figure 6: Total number of major deficiencies by topic area for all reporting periods

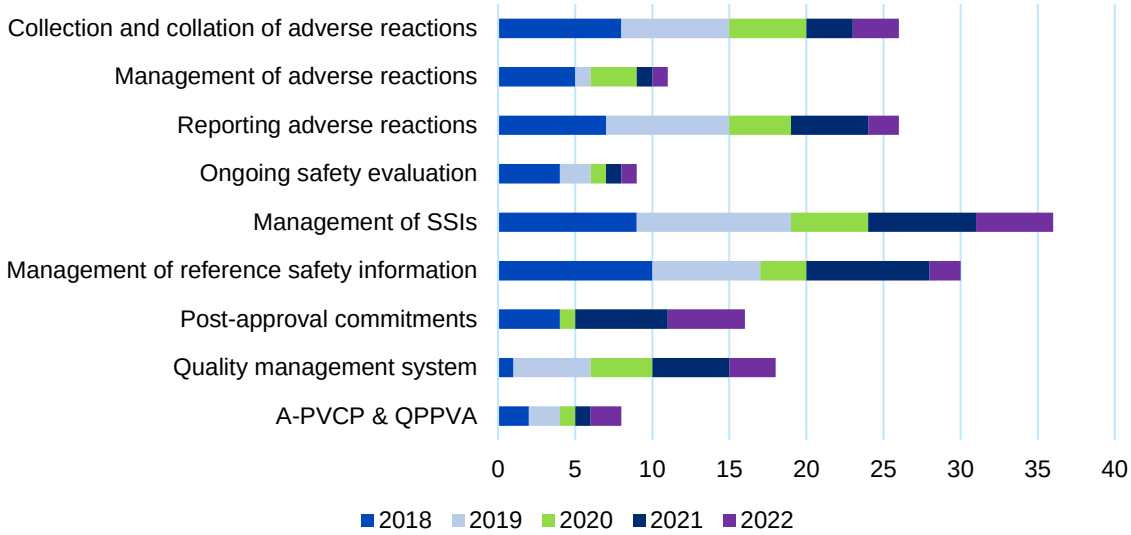
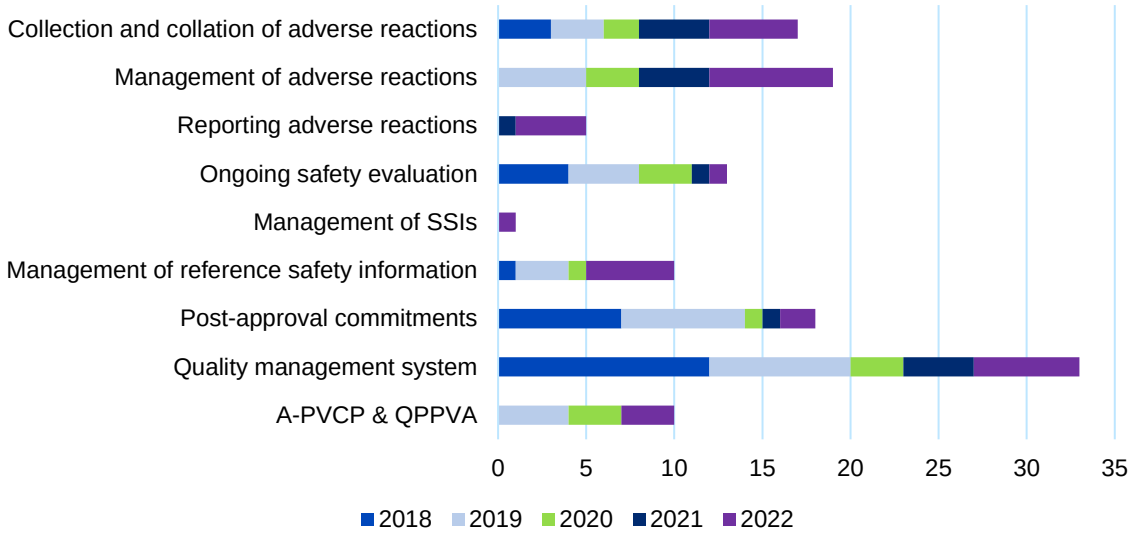


Figure 7: Total number of minor deficiencies by topic area for all reporting periods



Appendix I: Pharmacovigilance inspection topic areas

Topic area	Sub-topic
Collection and collation of adverse reactions	Spontaneous sources of safety data, including medical information, product quality complaints, medical literature, company personnel (e.g., sales representatives, social/digital media etc.)
	Solicited sources of safety data, including patient support or market research programs, post-registration studies etc.
	Safety data exchange agreements, pharmacovigilance agreements and pharmacovigilance clauses in other agreements[2]
Management of adverse reactions	Case processing, including data entry, quality control and assurance, coding, causality and seriousness assessment, and follow-up and management of invalid and special situation reports
Reporting adverse reactions	Reporting serious adverse reactions within 15 calendar days
Ongoing safety evaluation	Signal detection and management
	Production of PSURs
Management of SSIs	Identification of SSIs
	Recording of assessment of safety issues as SSIs or the decision not to notify the safety information as an SSI
	Reporting SSIs within 72 hours
Management of reference safety information	Maintenance of CCSI (if applicable)
	Maintenance of Australian PI, CMI, product packaging leaflets and product labelling
	Maintenance of safety-related information in company-sponsored material (e.g., educational, or promotional items)
	Communication of updated safety-related information to internal and external stakeholders

[2] this sub-topic may instead be categorised under the Quality management system topic area, depending on the specific nature of the non-compliance identified in the inspection.

Topic area	Sub-topic
Post-approval commitments	Submission of PSURs
	Maintenance and submission of RMPs/ASAs
	Compliance with RMP commitments
	Oversight of and compliance with other pharmacovigilance related conditions of registration
Quality management system	Management and retention of pharmacovigilance records
	Pharmacovigilance training
	Management of pharmacovigilance procedures
	Audit and deviation management
	Safety data exchange agreements, pharmacovigilance agreements and pharmacovigilance clauses in other agreements
	Oversight of vendors
Role of the A-PVCP & QPPVA	Notification of the A-PVCP including updates within 15 calendar days
	QPPVA oversight of the pharmacovigilance system including involvement and awareness of product-specific issues

Appendix II: Types of inspections

From 2021, the PVIP implemented the risk-based stratification of routine inspections into targeted or comprehensive inspections. Targeted scope inspections focus primarily on a review of the local pharmacovigilance system implemented by the sponsor. Comprehensive scope inspections follow the previous approach to inspections, which includes a review of local systems and those undertaken by overseas companies and counterparts without differentiation.

This risk-based method aligns with the overall approach we take to scheduling pharmacovigilance inspections. Risk factors that are considered include the sponsor's products, their pharmacovigilance system, their compliance history, their PVIP Risk Assessment Survey score and their recent history of inspections by CORs.

The following is an excerpt from the *Pharmacovigilance inspection program: Guidance for medicine sponsors*.

Please note the TGA is referred to as 'we' or 'us', and sponsors as 'you'.

Routine inspections

Routine pharmacovigilance inspections are scheduled as part of the inspection program. There is no specific trigger for these inspections, although we take a risk-based approach to prioritising them. These inspections are usually system-related inspections, but one or more products may be selected as examples to verify the implementation of the system and provide practical evidence of its functioning and compliance.

'For cause' inspections

'For cause' inspections are undertaken in response to specific triggers where a pharmacovigilance inspection is the appropriate way to examine the issues. 'For cause' inspections generally focus on specific aspects of the sponsor's pharmacovigilance system or examine identified compliance issues and their impact on a specific product. However, we may also inspect the sponsor's entire pharmacovigilance system as a result of a trigger. Significant public health concerns or identified noncompliance are expected to be the most common triggers.

System-related inspections

Pharmacovigilance system-related inspections review the procedures, systems, personnel and facilities in place and determine whether your system meets your regulatory pharmacovigilance obligations. As part of this review, product-specific examples may be used to determine how the pharmacovigilance system operates and whether it complies with requirements.

Product-related inspections

Product-related pharmacovigilance inspections primarily focus on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than reviewing the system overall. They are likely to be 'for cause' inspections to investigate a specific product issue. Some aspects of the wider system may be examined during a product-related inspection (that is, the system used for that product).

Announced and unannounced inspections

We anticipate most inspections will be announced – that is, we will notify you of them in advance to ensure the relevant personnel will be available for the inspection. However, it may sometimes be appropriate to conduct unannounced inspections or to perform an inspection at short notice (for example, when an announcement could compromise the objectives of the inspection or when prompt inspection is required due to urgent public health concerns).

Re-inspections

We may re-inspect the sponsor's pharmacovigilance system as part of our routine inspection program. We prioritise re-inspections by assessing risk factors. If a previous inspection identified a high level of compliance this may increase the time between re-inspections. More frequent re-inspections may occur:

- where we have identified significant noncompliance
- to verify sponsors have taken action to address deficiencies observed during inspection
- to evaluate the sponsor's ongoing compliance with their obligations and evaluate changes to their pharmacovigilance system
- when a previous inspection finds, a sponsor had failed to take appropriate corrective and preventative action in response to prior inspections.

Remote inspections

These are pharmacovigilance inspections of the sponsor's premises (or the premises of a firm contracted to help fulfil the sponsor's pharmacovigilance activities) that we perform remotely using communication technology such as the internet or video/tele conferencing. If the remote inspection reveals issues that require onsite inspection, or the inspection objectives could not be met remotely, we may visit the inspection site.

Appendix III: Inspection deficiency gradings

Excerpt from the *Pharmacovigilance inspection program: Guidance for medicine sponsors*.

Critical deficiency:

A deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a sponsor is observed to have engaged in fraud, misrepresentation or falsification of data.

Major deficiency:

A deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor deficiency:

A deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Note:

- Deficiencies are classified by the assessed risk level and may vary depending on the nature of medicine. In some circumstances an otherwise major deficiency may be categorised as critical.
- A deficiency reported after a previous inspection and not corrected may be given higher classification.
- Comments (observations) may be included in the inspection report and are not discussed here in this report. Comments are not deficiencies but might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Appendix IV: Acronyms

The following acronyms were used in this report:

A-PVCP	Australian Pharmacovigilance Contact Person
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
CAPA	Corrective and Preventative Action
CCSI	Company Core Safety Information
CMI	Consumer Medicines Information
COR	Comparable Overseas Regulator
DAEN	Database of Adverse Event Notifications
EMA	European Medicines Agency
NCE	New Chemical Entity
OTC	Over the counter
PI	Product Information
PSUR	Periodic Safety Update Report
PVIP	Pharmacovigilance Inspection Program
QPPVA	Qualified Person for Pharmacovigilance in Australia
RMP	Risk Management Plan
SSI	Significant Safety Issue
TGA	Therapeutic Goods Administration
TGA eBS	TGA eBusiness Services System
TGO	Therapeutic Goods Order

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Pharmacovigilance Compliance and Clinical Trials Section Pharmacovigilance Branch	February 2025

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference: D25-470429