Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Targeted consultation: Reporting requirements for safety issues

Proposed changes to *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements*

Version 1.0, October 2022

TGA Health Safety Regulation

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Introduction

Reporting of significant safety issues (SSI) forms part of the pharmacovigilance responsibilities for all sponsors of medicines listed or registered on the Australian Register of Therapeutic Goods (ARTG). Sponsors' pharmacovigilance responsibilities are set out in the Therapeutic Goods Regulations 1990 (the Regulations) at s15A *Conditions of registration and listing of medicines*:

> For the purposes of paragraphs 28(5)(ca) and (e) of the Act, a person in relation to whom a medicine is registered or listed must comply with the record-keeping requirements (if any) and the reporting requirements (if any) set out in the document published by the Therapeutic Goods Administration titled *Pharmacovigilance Responsibilities of Medicine sponsors*, as in force from time to time.

Version 2.2 of the *Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements* guidance document (the PV Guidelines) outlines the current reporting requirements for SSIs.

It is widely acknowledged, both by the Therapeutic Goods Administration (TGA) and medicine sponsors, that the PV Guidelines do not clearly explain SSI reporting requirements. As a result, the TGA often receives safety notifications lacking key information or for issues that are not truly significant. This introduces unnecessary 'noise' into the system and increases the risk that truly urgent safety issues will not receive appropriate, timely attention.

This targeted consultation seeks feedback from key stakeholders on the clarity, suitability and practicality of proposed changes to the PV Guidelines, with respect to the definition of, and reporting requirements for, safety issues.

The aim of these changes is to support timely responses to new safety information by the TGA. The proposed changes to the PV Guidelines are not intended to lessen the current requirements for reporting of safety issues, but to better define which issues are to be notified urgently, and to allow more time for the appropriate review of all other safety issues. This should increase the quality of notifications and enable the TGA to act on all safety issues in a timeframe proportionate to the risk to public health.

Prior consultation

Work to redevelop the definition and reporting requirements of SSIs was initially undertaken by the Signal Investigation Unit of the Pharmacovigilance and Special Access Branch (now Pharmacovigilance Branch (PB)) in 2020. This work was placed on hold in 2021 due to the additional resource requirements of COVID-19 vaccine pharmacovigilance. During the prior consultation, the Advisory Committee for Medicines were supportive of changes to the PV Guidelines in relation to SSI reporting. Preliminary discussions on the topic were also held with Medicines Australia in August 2020.

Pharmacovigilance Branch has recently recommenced work on this topic. All prior feedback has been considered in the development of this paper.

Scope

In the interest of transparency, proposed changes to the current PV Guidelines, including major formatting and other significant editorial changes are provided in a marked-up attachment to this paper. A table summarising the major changes between the current and proposed versions is also provided.

For the purposes of this targeted consultation, feedback is only sought on changes to the PV Guidelines that specifically relate to the definitions of, and reporting requirements for, safety issues. These are also provided in a separate document.

Background

Current definition and reporting requirements

The current PV Guidelines defines an SSI as:

> …a new safety issue or validated signal considered by you in relation to your medicines that requires urgent attention of the TGA. This may be because of the seriousness and potential major impact on the benefit-risk balance of the medicine and/or on patient or public health, which could warrant prompt regulatory action and/or communication to patients and healthcare professionals. (p 9)

To assist medicines sponsors in determining whether an identified safety issue meets the definition of an SSI, a range of examples are then provided, including:

- safety-related actions by comparable international regulatory agencies such as:
  - the withdrawal or suspension of the medicine's availability
  - the addition or modification, for safety reasons, of a contraindication, warning or precaution statement to the product information or label
  - the modification or removal, for safety reasons, of an indication.
- changes in the nature, severity or frequency of known serious adverse reactions which are medically significant
- detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction that may impact on the safety or benefit-risk balance of the medicine
- series of reports of similar or linked adverse reactions reported at the same time (that is, a cluster) assessed to suggest a quality defect issue that may have implications for public health
- an unusual and significant lack of efficacy occurring in or outside Australia that may have implications for public health
- major safety findings from a newly completed non-clinical study, post-registration study or clinical trial that may impact the benefit-risk balance of the medicine on the ARTG
- a signal of a possible teratogenic effect or of significant hazard to public health
- safety issues related to any raw materials used in the medicine that may impact the safety of the medicine and/or have implications for public health
- safety issues due to misinformation in the product information or label that may impact the safety of the medicine
- safety issues related to use outside the approved indication or intended use that may impact the safety or benefit-risk balance of the medicine. (p 9)

Sponsors must report all significant safety issues related to their ARTG-listed or registered medicines within 72 hours of awareness. The PV Guidelines advise sponsors to use professional judgement in determining whether a safety issue is significant but go on to instruct, ‘If in doubt about a safety issue, treat it as significant’.

Problems with current definition and reporting requirements

The following issues have been identified by both sponsors and the TGA as contributing to the inconsistent interpretation of SSI definition and reporting requirements:

Unclear guidance on what safety issues require reporting

The definition in the current PV Guidelines restricts reporting requirements to safety issues requiring the urgent attention of the TGA. However, this definition is followed by many examples, some of which contain subjective language. This leads to variable interpretation of which issues are reportable as SSIs.

Safety issue notifications reported too early and lacking detail

Due to the unclear guidance, many safety issues are notified to the TGA before enough information is known about the impact of the issue. The following are common examples of these types of notifications:

Safety issues:

- notified at the point of signal validation irrespective of the impact on the benefit-risk balance of the medicine
- notified before actions have been recommended by a comparable overseas regulator
- notified before actions have been proposed by the innovator sponsor
- that have not yet been analysed in the Australian context.

This results in notifications lacking key pieces of information and necessitates further communication between the TGA and sponsors.

Single category with 72-hour reporting timeframe

Sponsors have indicated that the 72-hour reporting timeframe for SSIs is difficult to achieve, particularly over weekends, given that internal sponsor processes often require liaison with global colleagues.

The 72-hour reporting timeframe is problematic for the TGA as it is another cause for the submission of incomplete notifications.

Multiple sponsors reporting the same safety issue

To adhere to their pharmacovigilance reporting requirements, sponsors only report safety issues with respect to their ARTG-listed or registered products. Where there are generic products available or it is a class-wide safety issue, the TGA will often receive multiple notifications regarding the same issue.

Conservative approach to reporting of significant safety issues

The current PV Guidelines encourage a conservative approach to reporting safety issues as SSIs. The instruction on page 10, 'If in doubt about a safety issue, treat it as significant' coupled with the previously described unclear guidance leads to the overreporting of safety issues.

These problems contribute to an increased risk of the system becoming saturated by less urgent information. This then leads to the risk that truly significant safety issues won't receive appropriate timely attention.

Proposed changes to the PV Guidelines

The TGA has reviewed the current PV Guidelines with respect to the definition and reporting requirements for SSIs. The proposed changes outlined in this paper are intended to improve the quality of safety notifications, not to lessen sponsors' requirements to report safety issues. The proposed changes aim to overcome the problems described above by:

- redeveloping the definition of SSI to be clearer and narrower
- providing fewer SSI examples requiring less subjective interpretation
- clarifying the point at which safety notifications should be received by the TGA
- providing a safety issue reporting form to streamline and ensure complete, correct safety issue reporting
- introducing a second reporting category for less urgent safety issues, with a timeframe proportionate to the risk to public health.

The document containing proposed changes to safety issue reporting requirements should be read and referred to when answering the consultation survey.

A tiered reporting system

Under the proposed changes to the PV Guidelines different safety issues will have different timeframes for reporting, depending on the urgency of the issue.

We are proposing 2 categories of safety issues: 'Significant Safety Issues (SSIs)' and 'Other Safety Issues (OSIs)'.

Significant Safety Issues

The proposed definition and examples of SSIs are closely aligned with the European Medicines Agency's definition of Emerging Safety Issue and related examples. This change will result in a much smaller number of safety issues meeting the definition of an SSI.

Under this proposal SSIs must continue to be reported within 72 hours, as they have a potential major impact on the benefit-risk balance of the medicine and on public health and are likely to require rapid action by the TGA.

Examples of SSIs include:

- the following major safety-related actions by other overseas regulators:
  - the withdrawal or suspension of the medicine's availability
  - the addition of a boxed warning, modification or removal of an indication (for safety reasons) or addition of a contraindication to the product information or label.
- major safety findings from a newly completed non-clinical study, post-registration study or clinical trial that are likely to impact the benefit-risk balance of the medicine e.g. an unexpected increase in the rate of fatal or life-threatening adverse events
- major safety issues identified through spontaneous reporting or published literature, which may lead to the addition of a contraindication, restriction of the use of a medicine, or its withdrawal from the market.

Other Safety Issues

Safety issues that are unlikely to alter the benefit-risk balance of the medicine but will still require action by the TGA must be reported as OSIs. Many of these types of safety issues are already being reported by sponsors as SSIs under the current PV Guidelines.

Examples of OSIs include:

- internally identified signals that have undergone a signal assessment and identified a new or changed risk.

This includes any signal identified through a sponsor's internal pharmacovigilance system. The TGA requires notification of these signals only after an internal signal assessment is completed if the signal is *not* refuted.

- safety-related changes by overseas regulators to the product information documents or labels (that do not meet the definition of SSIs).

This includes, but is not limited to, any safety-related change to the *Warnings and Precautions*, *Interactions*, *Fertility, Pregnancy and Lactation* and *Adverse Effects* or equivalent sections of the product information documents or labels.

- safety issues due to incorrect or out-of-date information in the product information document
- safety issues related to established use outside the approved indication or intended use (off-label use).

This includes any safety issue identified from any source relating to established off-label use.

- changes in the severity or frequency of a known serious adverse reaction
- identification of clinically significant risk factors for the development of a known adverse reaction.

Other safety issues must be reported to the TGA within 30 calendar days of establishing that a safety issue exists. The reporting timeclock begins (as Day 0) on the day that the internal safety assessment is completed by the sponsor.

Safety issue reporting form

At the time of publication of the revised PV Guidelines, a safety issue reporting form will be introduced as the standard method of reporting safety issues to the TGA. A form previously provided in feedback by Medicines Australia has informed the development of this form.

To submit a safety issue, either SSI or OSI, sponsors will be required to download a *Microsoft Word* version of the form directly from the TGA website (link to be determined). We hope in future to have online reporting capabilities, but these are yet to be developed.

One single form will be available for the submission of both SSIs and OSIs, and for initial and follow up safety notifications. Sponsors will be required to select which type of safety issue they are reporting, and whether the notification is an initial or follow up notification.

If an SSI is being reported, sponsors will be required to complete as many fields as possible within the 72-hour timeframe. Due to the urgent nature of SSI notifications, incomplete forms *will* be accepted as valid notifications.

If an OSI is being reported, sponsors will be required to complete ALL information fields in the form. Incomplete OSI notification forms *will not* be accepted as valid notifications.

Implementation of this safety issue reporting form will encourage complete and correct reporting of safety issues and assist the TGA in upholding a consistent reporting process. Following an initial 3-month transition period, it will be mandatory to submit safety issues using this form.

Completed forms should be emailed to the Signal Investigation Coordinator at si.coordinator@health.gov.au. A response acknowledging receipt will be provided as confirmation.

A copy of the proposed form is included for review along with this consultation paper.

Safety issue reporting decision tree

A decision tree for the notification of SSIs and OSIs is included as Appendix A to the revised PV Guidelines. This has been developed to aid sponsors in the decision-making process about whether a safety issue should be notified to the TGA, and if so, at what point it should be notified.

How to respond

The TGA is requesting your feedback with the following questions, to be submitted via the online survey.

Participation and feedback received during this consultation is greatly appreciated.

Questions

1. What is your name?

2. What is your email address?

3. What is your organisation?

4. Do you believe the proposed two-tiered reporting system for safety issues is suitable and practicable? *Y/N*

   If you answered no, please indicate why and provide comment regarding a possible alternative system.

5. Do you have any concerns with the two-tiered reporting system not addressed at the previous question? *Y/N*

   If you answered yes, please outline these.

6. With reference to the information on SSIs in the 'Proposed changes to the PV Guidelines, version 2.2: Changes to safety issue reporting requirements' document:
   Are the definitions and reporting requirements for SSIs clear and comprehensive? *Y/N*

   If you answered no, please indicate why.

   Are the provided examples of SSIs sufficiently clear? *Y/N*

If you answered no, please comment including any additional examples that you feel should be included.

Do you agree with the proposed timeframe for the reporting of SSIs? *Y/N*

If you answered no, please indicate why.

Please include any comments or suggestions regarding SSI reporting requirements not captured elsewhere.

7. With reference to the information on OSIs in the 'Proposed changes to the PV Guidelines, version 2.2: Changes to safety issue reporting requirements' document:
Are the definitions and reporting requirements for OSIs clear and comprehensive? *Y/N*

If you answered no, please indicate why.

Are the provided examples of OSIs sufficiently clear? *Y/N*

If you answered no, please comment including any additional examples that you feel should be included.

Do you agree with the proposed timeframe for the reporting of OSIs? *Y/N*

If you answered no, please indicate why.

Please include any comments or suggestions regarding OSI reporting requirements not captured elsewhere.

8. With reference to the draft safety issue reporting form:
Is this form clear and practical? *Y/N*

If you answered no, please indicate why.

Would you prefer a single form (with options for SSI or OSI notification) OR separate forms for each type of safety issue?

Would you prefer a single form (with options for initial or follow-up notification) OR separate form for each type of notification?

Do you think 3 months is an acceptable transition period, following which time the form will become mandatory for reporting safety issues? *Y/N*

If you answered no, please indicate why.

Please include any comments or suggestions regarding the safety issue reporting form not captured elsewhere.

9. With reference to the safety issue reporting decision tree:
Is the decision tree a useful addition to the PV Guidelines? *Y/N*

If you answered no, please indicate why.

Is the decision tree clear and easy to follow? *Y/N*

If you answered no, please indicate why.

Please include any comments or suggestions regarding the decision tree not captured elsewhere.

10. Would you be interested in attending any TGA workshops on safety issue reporting/PV Guidelines updates following publication of the revised PV Guidelines? *Y/N*

11. Do you have any final comments or suggestions on the proposed updates to the safety issue reporting requirements or the PV Guidelines?

Next Steps

This consultation will run for a period of 6 weeks, from **Monday 24 October 2022** until **11:59pm on Monday 5 December 2022.**

Following consideration of responses, the final revised version of the PV Guidelines will be published as version 3.0. This is expected to occur in early 2023.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medicines – Surveillance and Targeted Review, Medicines and Vaccines Investigation and Surveillance, Pharmacovigilance Branch	October 2022

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Reference/Publication #