



Frequently asked questions

Identifying and reporting safety issues – PV Guidelines (version 3.0)

The information below provides answers to frequently asked questions in relation to updates to the [Pharmacovigilance responsibilities of medicine sponsors: Australian recommendations and requirements](#) (the PV Guidelines) with respect to identifying and reporting safety issues.

SIGNIFICANT SAFETY ISSUES (SSIs)

Are all contraindication updates to a product label considered to be SSIs?

Generally, the addition of a contraindication is considered an SSI, however professional judgement should always be exercised. If you determine that an update to the contraindication section of a label is not an SSI and do not report it to the TGA, you should document a justification for this decision. We may ask you to provide this documentation at any time.

OTHER SAFETY ISSUES (OSIs)

Does the TGA expect the sponsor of an innovator product to report a company decision to update company labelling (CCDS) as an OSI prior to submission of a safety related request (SRR)?

Yes – where the decision to update company labelling has been informed by the outcome of an internally assessed safety issue.

Should a safety-related change to non-serious adverse events (AEs) (such as changes in the nature, severity and frequency of non-serious AEs), be reported as an OSI?

Yes – a safety-related change to a non-serious adverse event which increases the previously known risk of the medicine would be considered an OSI.

Is a comparable overseas regulator (COR)-requested label update required to be reported to the TGA?

Yes – a safety-related label update request by a COR is considered reportable. This should be reported within 30 days of completion of the company assessment of the label update request.

Which label updates by CORs require reporting as OSIs?

Any safety-related update to the equivalent sections of the Australian Product Information (PI), sections 4.4-4.9, including non-serious adverse events. However professional judgement should always be exercised, as a safety-related update to another section of the label may also constitute an OSI.

Do update requests from CORs refuted by the sponsor require reporting to TGA?

Yes – *all* safety-related changes requested by CORs to the product label that are classified as OSIs require submission to the TGA, regardless of whether you agree with the conclusions or recommendations of the regulator. This is outlined on page 17 of the PV Guidelines. Any justification for no further action in Australia should be included with the OSI notification to the TGA.

Is a confirmed safety issue an example of an OSI?

Yes – bearing in mind that confirmed safety issues can either be SSIs or OSIs, depending on the nature of the safety issue. Professional judgement should always be exercised, and you should always document the rationale for your assessment.

What if we do not know at the time of reporting an OSI whether the Australian PI will be updated, which is a mandatory field on the electronic form?

Planned risk mitigation strategies must be included in the assessment and notification form. Therefore, the assessment is not completed until this has occurred. Do not submit an OSI until you know whether or not you propose to update the PI.

Does internally assessed mean at the end of the full signal assessment process? i.e., not at validation stage.

Yes – this is correct for OSIs.

How does the TGA define ‘subsequent risk mitigation strategies’ as outlined in the definition of OSI?

Subsequent risk mitigation strategies are the actions you propose to take to mitigate the risk of the safety issue to the Australian public that has been identified with your medicine. This may include updating the medicine’s PI document, issuing a Dear Healthcare Professional Letter, or proposing additional pharmacovigilance activities. For more information, please refer to [International scientific guideline: GVP module XVI – Risk minimisation measures: selection of tools and effectiveness indicators \(Rev 2\)](#) – which has been adopted by the TGA with annotations.

Should all out-of-specifications (OOS) that do not qualify as SSIs be reported as OSIs?

No - an OOS is a medicine defect and should be reported as such. Not all medicine defects are also safety issues. Professional judgement should be exercised to determine if an OOS also involves a safety issue and if so, whether the safety issue qualifies as an SSI or OSI.

GENERAL**At what point are safety issues identified by a COR considered reportable to the TGA?**

At the point that a safety issue has an associated safety-related action (i.e. regulatory outcome) from a COR, the issue becomes reportable to the TGA (unless the safety issue is deemed significant and requires the urgent attention of the TGA).

For example, a US FDA Newly Identified Safety Signal (NISS) or safety issue noted by EMA PRAC for discussion or investigation are NOT considered reportable until planned actions have been requested (e.g. update to product label) and your company’s internal assessment is complete.

If a COR recommends the addition of a 'precautionary warning' to the product label, is this classified as an OSI?

Generally, the addition of a warning or precaution to the product labelling is classed as an OSI. An exception to this is a COR-request for the addition of a boxed warning – this is considered an SSI, as described on page 16 of the PV Guidelines.

Professional judgement should always be exercised. If, after initial assessment an identified safety issue is determined to have potential major impact to the benefit-risk balance of the medicine and/or public health then it must be notified to the TGA as an SSI.

Do these safety issue reporting requirements apply to products supplied through a clinical trial?

The requirement to report safety issues as described in the PV Guidelines only applies to clinical trials where the medicine is being used in line with the Australian approved indications as per the PI. For all other clinical trials, follow the [clinical trials](#) reporting guidelines.

Do these safety issue reporting requirements apply to listed medicines?

Yes – the PV Guidelines apply to all medicines registered or listed on the Australian Register of Therapeutic Goods (ARTG).

Is the reporting of SSIs and OSIs required for unapproved products supplied under the Special Access Scheme (SAS)?

No – the PV Guidelines only apply to medicines registered or listed on the ARTG. Sponsor reporting requirements for unapproved medicines supplied under the SAS are outlined in [Special Access Scheme: Guidance for Sponsors](#).

What are the safety issue reporting requirements for products under application with the TGA?

The PV Guidelines apply to medicines already registered or listed on the ARTG. For further information on reporting requirements between application submission and prior to inclusion in the ARTG, please refer to page 34 of the PV Guidelines.

Do similar regulatory safety actions from second (and subsequent) CORs require notification to the TGA?

Yes – similar regulatory safety actions from subsequent CORs still require notification to the TGA. This is because actions taken by different regulators often differ. Also, there is a cumulative effect of multiple regulator action which may impact the TGA's assessment of the safety issue.

Where do the PV Guidelines stand in comparison to the *Therapeutic Goods Act 1989*, regulations and rules? Do they have the same legal implications?

The PV Guidelines have legislative underpinnings – please refer to pages 16 and 32 of the PV Guidelines for more information.

Is there a link between TGA PV Guidelines and EU Good Pharmacovigilance Practices (GVP)?

Yes – however, whilst the safety issue reporting requirements changes were informed by GVP Module IX, this guideline has not been adopted by the TGA and *sponsors must comply with the requirements and are expected to comply with the recommendations set out in the TGA PV Guidelines*. Sponsors need to be aware of the processes in place at their global organisations (whether they are aligned to GVP Module IX or not) to ensure expedited/timely communication of safety issues to the sponsor.

Where the global organisation is an external organisation, you must still ensure you meet your pharmacovigilance responsibilities. You should have a detailed pharmacovigilance contract or agreement in place with them that stipulates the explicit roles and procedures to ensure you can comply with your reporting obligations.

Is a regular CCDS update rolled out to the Australian PI classified as a safety issue (either SSI or OSI) that requires reporting?

A CCDS update which results in an Australian PI update may or may not be classified as a safety issue, depending on the origin and scope of the update. Professional judgement should be exercised. However, if determined to be a safety issue, a notification should be submitted separate to and in advance of a submission to update the PI.

If a communication is published by a COR regarding a safety issue which is already included in the label (e.g. "discontinue if rash develops"), and no new 'action' is taken by regulator or sponsor, does this require reporting?

It would depend on what prompted the regulator to publish such communication. Has there been a change in reporting which may prompt the TGA to consider publishing a similar communication? Such a reminder is unlikely to constitute an SSI but may constitute an OSI. Professional judgement should be exercised, and sponsors should err on the side of reporting if unsure.

If a sponsor reports an SSI, but on receipt the TGA deems it was an OSI, how will it be processed?

The sponsor will be notified by the TGA that the issue does not meet the definition of an SSI and will be asked to resubmit the safety issue as an OSI upon assessment completion.

TIMEFRAMES**What is considered 'day 0' for the 72-hour SSI reporting clock?**

The SSI clock starts (as day 0) as soon as personnel from the Australian sponsor (including any third parties, vendors or partners that have been delegated pharmacovigilance responsibilities) become aware of the safety issue (i.e. receipt/awareness). The reporting clock restarts when you receive additional clinically or medically relevant information related to a previously reported SSI.

What is considered 'day 0' for OSIs?

Day 0 for OSIs is the day that any personnel of your Australian sponsor (including any third parties, vendors or partners that have been delegated pharmacovigilance responsibilities) are made aware of a safety issue for which the assessment has been completed – this includes an assessment against OSI criteria in the Australian context.

OSIs must then be notified to the TGA within 30 calendar days. The notification should include a description of the safety issue, the source and any available evidence, an assessment of the risk and potential impact of the safety issue, any action proposed for Australia (e.g. PI update) – or justification for no further action.

When does the 3-calendar day *global to Australia* timeframe for SSIs start?

The 3-calendar day timeframe for notification of an SSI from global to the Australian sponsor begins when global personnel first become aware of the SSI.

This is defined in the PV Guidelines as the *date of global awareness*. Your global procedures should clearly define day 0 for the 3-calendar day timeframe in line with your company processes. You must keep records of communications including dates when global and local personnel were notified of SSIs and reasons for any delays in communication.

Where the global organisation is an external organisation, you must still ensure you meet your pharmacovigilance responsibilities. Day 0 for the 3-calendar day timeframe is the date of awareness of the external global organisation. You should have a detailed pharmacovigilance contract or agreement in place with them that stipulates the explicit roles, procedures and timelines for exchange of information to ensure you can comply with your reporting obligations.

Why does it need to be 3-calendar days from global to affiliate, why not keep it as 72 hours?

The timeframe for notification from global to the Australian sponsor is defined as 3-calendar days to differentiate this from the timeframe for reporting from Australian sponsor awareness to the TGA (72 hours).

What is meant by a ‘substantial and inappropriate delay’ with regards to timelines for OSIs notified from global to Australian sponsor?

Sponsors are expected to have clearly documented internal procedures and/or agreements in place to ensure timely communication of OSIs from global personnel to your relevant Australian personnel for reporting. Sponsors should exercise professional judgement to implement timelines reflective of the risk profile of the medicine and safety issue. It is expected that communication will occur more rapidly for more serious safety issues. During an inspection, a sponsor’s justification for their timelines and procedures will be reviewed and it will be determined whether there are substantial or inappropriate delays.

Does day 0 differ when a partner company is involved? – i.e., a contractual partner or third-party distributor.

Day 0 begins as soon as personnel of the party that has delegated pharmacovigilance responsibilities in Australia becomes aware of the safety issue.

Where you have contractual arrangements with a third-party organisation, you should have a detailed pharmacovigilance contract or safety data exchange agreement (SDEA) in place with them that stipulate the explicit roles, procedures and timelines for collecting and reporting safety information to ensure you can comply with your reporting obligations.

NOTIFICATION OF COR-IDENTIFIED SAFETY ISSUES BY SPONSORS OF GENERIC MEDICINES

What is meant by ‘timely submission’ for generic PI updates to align with the innovator PI?

A timely submission to update the generic product PI following innovator update to PI is considered to be one month. Please also refer to the [FAQ, “What is the timeframe for making a submission to update PI documents?”](#)

Does this alternative pathway for reporting of COR-identified safety issues apply to sponsors of biosimilar medicines?

No – biosimilars are not generic medicines, they are regulated as new chemical entities. Therefore, this method for reporting does not apply to sponsors of biosimilar medicines. Sponsors of biosimilar medicines must follow the standard SSI/OSI reporting of COR-identified safety issues as described in the PV Guidelines.

How do generic sponsors ensure they are compliant with reporting timeframes (72 hours for SSI and 30 days for OSI)?

Where the safety issue source is a *COR-action or request*, and a generic medicine sponsor is waiting for the innovator PI update to occur, the reporting timeframes for SSIs and OSIs do not apply. Please refer to page 17 of the PV Guidelines for more information.

In addition, generic medicine sponsors are expected to have clearly documented internal procedures, including timelines, in place to ensure:

- Sponsor identification and reporting to the TGA of safety issues from COR actions or requests when there is no Australian innovator product to your generic product, or when the Australian innovator product has been withdrawn from the ARTG
- Sponsor identification and reporting of safety issues to the TGA from any other source (e.g. internal ongoing analysis of the benefit-risk balance of the medicine).

Is a generic sponsor required to report SSIs or OSIs if they have already updated the PI and CMI to align with the innovator?

Sponsors of generic medicines have their obligation to report any such safety issue fulfilled with the submission of an application to align their generic PI document with the Australian innovator PI document, within one month of the date of the TGA approval of the safety-related update to the Australian innovator PI document.

MEDICINE SAFETY ISSUES – ELECTRONIC NOTIFICATION FORM

What action should be taken if the electronic online notification form is not available?

In this situation, sponsors should contact the Signal Investigation Coordinator via email (si.coordinator@health.gov.au) to alert the TGA of the problem. If required, sponsors will be able to notify the TGA of safety issues via a standard email to the Signal Investigation Coordinator to ensure that required timeframes are adhered to.

Is it mandatory to use the notification form for reporting SSIs/OSIs?

It is strongly encouraged to use the notification form for reporting safety issues during the implementation period.

From 1 February 2024 it will be mandatory to use the notification form to report safety issues.

Is it possible to have a smart form that links to eBS/ARTG so the system downloads the required ARTG name/AUST R versus typing them in every time?

No – the current form and ARTG do not have this capability.

Will I receive a copy of the full notification submitted online?

At the point of submission, you will receive a copy of the submitted notification via the supplied email address.

Does a separate notification form need to be completed for each product for the same safety issue (e.g., mono, combination products containing the same active ingredient)?

No – only one notification needs to be submitted where the safety issue concerns more than one product containing the same active ingredient. There is provision in the form to list all products concerned.

Can the form be saved in draft for internal review prior to submission?

No – the current form does not have this capability.

Can multiple email addresses be added to the form to receive the submission acknowledgement from the TGA?

Not currently, however, we are working to determine if this functionality is possible in future.

The notification form requires ARTG number, but one product may have many unique ARTG numbers. Which one do we include on the form?

Any ARTG number that identifies the sponsor product involved in the safety issue can be included. However, if multiple different products containing the same active ingredient are involved (e.g., single ingredient products and combination products) these should be listed separately.

How can I provide attachments if direct upload to web forms is restricted in my company?

In this situation, please provide any necessary attachments to a safety notification by replying to the submission acknowledgement email which will send to the Signal Investigation Coordinator.

If we receive follow up information after an OSI has already been reported via the online form, do we submit another report?

Yes – you can select ‘Follow up’ as type of notification in the Medicine safety issues – Electronic notification form.

EXAMPLE SCENARIOS**Examples of significant safety issues (SSIs):**

Example SSI 1: Health Canada contacts the Canadian affiliate of your company announcing their intention to withdraw all formulations of *Drug A* from the Canadian market due to an unfavourable change in the benefit-risk balance of the drug. You are the Australian innovator sponsor of Drug A.

Your global headquarters are made aware of this request in line with company procedures. Your global headquarters must then notify your Australian affiliate of this COR-safety related request within 3 calendar days of global headquarters awareness. Day 0 begins as soon as any personnel of your Australian affiliate (including any third parties, vendors or partners that are delegated pharmacovigilance responsibilities) becomes aware of this Health Canada request. SSI notification to the TGA must occur within 72 hours of Australian awareness.

Example SSI 2: The US FDA requests the modification of the contraindication section of the US label for *Drug B* to include *Condition C* in the existing list of conditions in which patients should not be administered Drug B.

You, the Australian innovator sponsor of Drug B, have a licencing agreement with a separate global organisation to supply Drug B to the Australian market. The global organisation is made aware of this FDA request in line with company procedures. This global organisation must then notify you, the Australian sponsor, of this COR-request within 3 calendar days of the global organisation’s awareness. Day 0 begins as soon as any personnel of the Australian sponsor (including any third parties, vendors or partners that are delegated pharmacovigilance responsibilities) becomes aware of this FDA request. SSI notification to the TGA must occur within 72 hours of Australian awareness.

Examples of other safety issues (OSIs):

Example OSI 1: The EMA’s PRAC recommends an update to include the risk of *Condition E* in sections 4.4 and 4.8 of the EU SmPC for *Drug D*.

You are the Australian innovator sponsor of Drug D. Your global headquarters are made aware of this PRAC request in line with company procedures. Your global headquarters conduct an internal assessment which concludes that there is insufficient evidence for a causal association between Drug D and Condition E. Your global headquarters provides you with the internal assessment,

without substantial or inappropriate delay. To complete the assessment, you assess the risk and potential impact of the safety issue in the Australian context and propose no further action. Day 0 is the day this internal assessment is completed. You have 30 days from day 0 to report this safety issue to the TGA.

Example OSI 2: Your company is the Australian innovator sponsor of Drug F. There is no global organisation and all safety issue detection and assessment is conducted in Australia by a third party organisation with delegated pharmacovigilance responsibilities with whom you have a contractual agreement (the PV organisation). Following periodic internal review of the published literature by the PV organisation, a potential safety issue – *Condition G* with *Drug F* is identified.

The PV organisation conducts an internal assessment – which includes a description of the safety issue (*Condition G* with *Drug F*), the source (published medical literature) and any available evidence for or against the safety issue. The outcome of this assessment is that this safety issue is a confirmed risk. To complete the assessment, the PV organisation assesses the risk and potential impact of the safety issue in the Australian context and proposes to update section 4.8 of the Australian PI with information about post-marketing cases of *Condition G* occurring in patients who have been treated with *Drug F*. Day 0 is the day this internal assessment is completed. This safety issue must be reported to the TGA within 30 days of day 0.

Examples of situations/safety issues that do not need to be reported:

Example 1: You are the Australian generic sponsor of *Drug H*. Your company's internal pharmacovigilance system identifies a spike in local reports of *Condition I* in patients being treated with *Drug H*. Immediately following identification, it is determined that this safety issue does not require the urgent attention of the TGA. The rationale for this decision is documented.

An internal assessment is then conducted by your company which concludes there is insufficient evidence for a causal association between *Condition I* and *Drug H*. The safety issue is refuted.

As this safety issue was internally identified and subsequently refuted, it does not need to be reported to the TGA.

Example 2: Following receipt of three case reports of *Condition K* occurring in patients being treated with *Drug J*, Swissmedic conducts an investigation of the safety issue which concludes that no evidence of a causal link has been found to date. The outcome of their investigation is published in *Vigilance News*, available publicly on Swissmedic's website.

As no regulatory action is recommended by Swissmedic, this safety issue does not need to be reported to the TGA.

Example 3: Following discussion at the most recent PRAC meeting, the European Marketing Authorisation Holder of *Drug L* has been requested by PRAC to assess cases of *Condition M* associated with *Drug L* treatment in the next PSUR.

As no major safety-related actions or safety-related changes to the EU SmPC have been requested, this safety issue does not need to be reported to the TGA at this time.

Example 4: The Pharmacovigilance Programme of India (PvPI) has published a Monthly Drug Safety Alert, identifying the adverse drug reaction *Condition O*, in association with *Drug N*.

As the PvPI is not a COR, this safety issue does not need to be reported to the TGA.