



Australian Government

Department of Health

Therapeutic Goods Administration

Consultation: Strengthening monitoring of medicines in Australia

Enhanced medicines vigilance

Version 1.0 March 2017

TGA Health Safety
Regulation

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Purpose and scope

The Therapeutic Goods Administration (TGA) is seeking comments on the implementation of a range of enhancements to the existing Medicines Vigilance Framework. These enhancements are designed to proactively minimise, detect and address medicine safety-related issues.

About the TGA

The TGA is responsible for ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose. These include goods Australians rely on every day, such as vitamin tablets and sunscreens, through to goods used to treat serious conditions, such as prescription medicines, vaccines, blood products and surgical implants.

The TGA regulates the supply of:

- medicines prescribed by a doctor or dentist
- medicines available from behind the pharmacy counter
- medicines available in the general pharmacy
- medicines available from supermarkets
- complementary medicines, these include vitamins, herbal and traditional medicines
- medical devices, from simple devices like bandages to complex technologies like heart pacemakers
- products used to test for various diseases or conditions (in vitro diagnostic devices), such as blood tests; and
- vaccines, blood products, and other biologics

and the manufacturing and advertising of these products.

The TGA mandate is to regulate medicines, medical devices and biological products throughout their lifecycle. The TGA is focusing on implementing changes to ensure a greater emphasis on transparency of regulatory decision-making processes, a continuing focus on business process reform and a more strategic approach to the use of information technology to support regulatory operations for the monitoring of medicines once they are marketed in Australia.

Background

In 2015, a review of [Medicines and Medical Devices Regulation](http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation)¹ (MMDR) was undertaken by an Expert Panel. It identifies ways to improve access to therapeutic goods for consumers and remove unnecessary red-tape for industry whilst maintaining the safety of therapeutic goods in Australia. The Expert Panel made a number of recommendations including those aimed at enhancing the post market monitoring processes currently undertaken by the TGA.

¹ <<http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation>>

These recommendations were made predominantly in Recommendation 27, where the Expert Panel proposed that the Government undertake:

1. Better integration and timely analysis of available datasets, including analysis of matched de-identified data from the Pharmaceutical Benefits Scheme, Medical Benefits Scheme, eHealth records, hospital records, private health insurance records and device and other relevant registries and datasets;
2. Establishment and maintenance of registries for all high-risk implantable devices;
3. Implementation of a scheme to alert practitioners and consumers that a drug is newly registered and to encourage reporting of any adverse events;
4. Provision for electronic reporting of adverse events; and
5. Enhanced collaboration with overseas National Regulatory Authorities to share information relating to safety or efficacy.

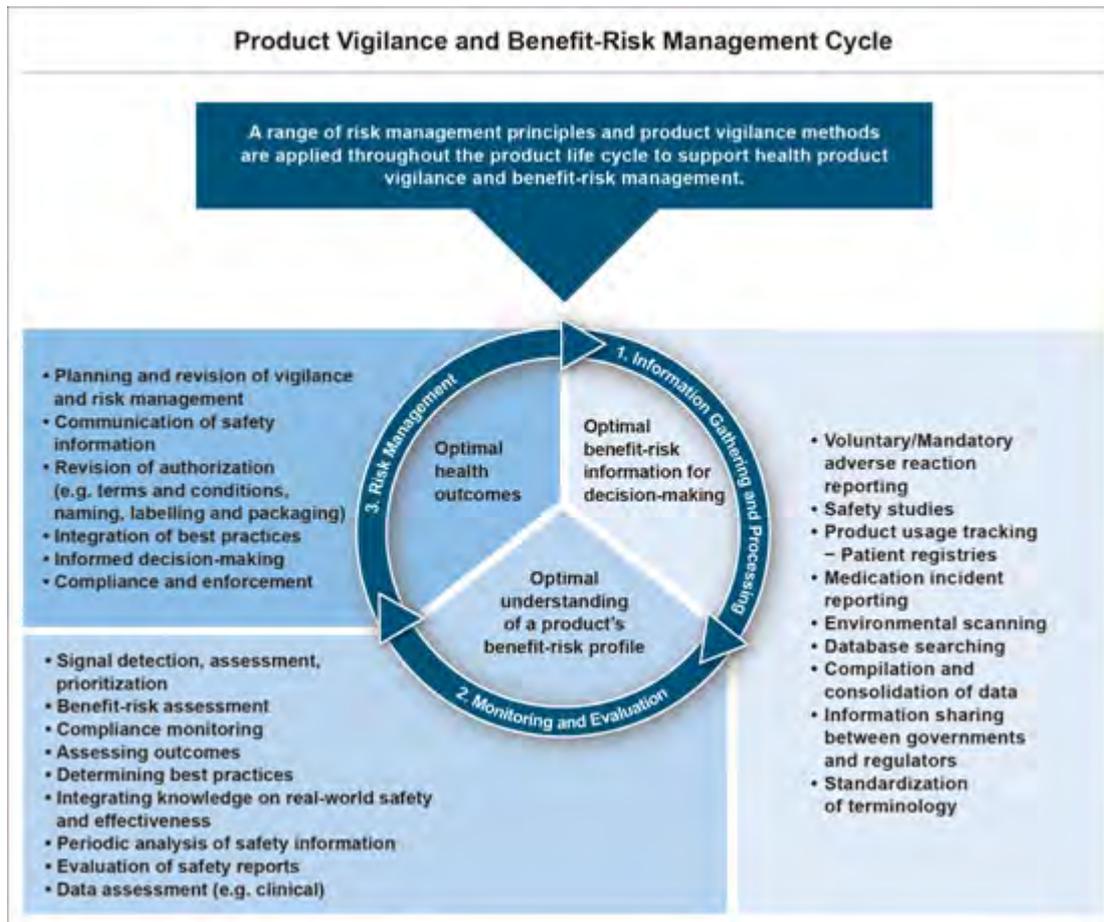
On 15 September 2016 the Australian Government Response to the Review of Medicines and Medical Devices Regulation was released. In it, the Government accepted the recommendations made, with the caveat that Recommendation 27.2 will be deferred until other work is undertaken. Now, as a result of the Government's acceptance, we are undertaking extensive enhancement to the safety monitoring of medicines in Australia.

The scope of our post-market monitoring activities extends across listed and registered complementary, over-the-counter and prescription medicines, as well as vaccines, biologicals and the different classes of medical devices. Post-market monitoring is a collaborative activity that TGA shares with medicine sponsors, health professionals, consumers and overseas medicines regulators.



For the purposes of this consultation paper, the focus is on medicines, which includes vaccines and biological medicines.

Our current medicines vigilance tools, aligned to international best practice, are detailed below:



(Source: [Health Canada](#))

These tools are able to manage a range of medicine safety profiles, from New Chemical Entities (NCEs) that are first in pharmacological class, to listed complementary medicines. They will continue to be used and applied with the introduction of [provisionally registered medicines](#) in order to characterise risks associated with these medicines, and to require the sponsor to collect and submit post-registration clinical data to substantiate the medicine's efficacy and safety.

The existing medicines vigilance tools are applied to products using a risk-based approach. An assessment of the risk posed by the medicine involves consideration of a number of factors, such as:

- How much do we know about the medicine and its safety profile?
- What is the likelihood that the medicine is responsible for adverse events and whether these events are serious in nature?
- What is the population in which the medicine is used (such as in children, pregnant women, otherwise healthy patients)?
- What is the context in which the medicine is used (is it available for use over the counter or prescribed by a medical practitioner, is it used for serious or non-serious medical conditions?)

An example of how the existing Medicine Vigilance Framework is applied

A sponsor of an immunosuppressant drug sought registration on the Australian Register of Therapeutic Goods (ARTG). During the RMP evaluation it was identified that pharmacovigilance activities were required to better characterise a potential safety concern. As a result, the sponsor was required to undertake a range of specific risk management activities.



A year later we detected a potential safety signal; patients taking this medicine were reporting a re-activation of an underlying infection not listed as a contraindication in the Product Information (PI) or Consumer Medicines Information (CMI).

The result of investigations by the TGA determined that the re-activation of the infection was related to use of the drug. We worked with the sponsor to widen the contraindications information in the PI and CMI and included an article in TGA's *Medicines Safety Update* to alert health professionals to this new issue.

The full details regarding the pharmacovigilance requirements for sponsors of Australian medicines are available on the TGA website via the following link:

<<https://www.tga.gov.au/australian-requirements-and-recommendations-pharmacovigilance-responsibilities-sponsors-medicines>>.

Further information regarding Risk Management Plans (RMP) can be found on

<<https://www.tga.gov.au/publication/risk-management-plans>>.

Enhancements

In addition to the vigilance tools listed above, the following enhancements will be made to the existing Medicines Vigilance Framework.

Adverse event reporting

Black triangle scheme



We will introduce the Black Triangle Scheme in order to alert health professionals and consumers to the fact that a particular medicine is newly available and to request they report adverse events associated with the medicine. At the time of registration, medicines will have undergone a range of studies to measure the safety and efficacy of the medicine. While these medicines have been well studied, it is not always possible to predict all adverse events from clinical trial data. Rare adverse events may not be detected in clinical trials, and since there is variation between individuals in the way they respond or react to medicines, there is the potential for previously unknown adverse events to occur at any time. The implementation of a Black Triangle Scheme is intended to act as a reminder to health professionals and consumers that they can help by informing the TGA about the effects a new medicine might be having on a consumer.

Black Triangle Schemes are currently in operation throughout the member states of the European Union (EU). The triangle is displayed on their PI and CMI equivalents next to the name of the medicine, with an explanation that the product is subject to additional monitoring and a request to report suspected adverse events. The symbol does not appear on product labels or other packing in Europe.

The Black Triangle is also displayed next to the name of the medicine in a number of reference texts, such as the British National Formulary. In the EU the types of products for which it is mandatory to display the triangle include, for example: new chemical entities, products for which a post-authorisation safety study was requested at the time of registration and products registered with specific adverse event reporting obligations. There are approximately 300 products currently required to display the Black Triangle in the EU.

We are proposing that prescription medicines for which registration is being sought will be included in the scheme if the product is:

- a new chemical or biological² entity
- a medicine with provisional registration, including where an extension of indication is provisionally registered.

Other types of registered medicines, aside from those listed above, may be included in the scheme if we assess that the following circumstances apply:

- during the registration evaluation process, evaluation of the medicine indicates a suspected concern about the safety profile of the product which the TGA assesses as needing prioritised monitoring; OR
- the new medicine is an extension of indication where there is limited international experience in the same indication or a similar indication such that the safety profile in the population for which it is indicated in Australia is not well established; OR
- a new and significant safety concern arises with an established, registered medicine, which TGA assesses requires prioritised monitoring

Where a component of a fixed dose combination product is subject to additional monitoring under the Scheme, the combination product will also be included in the Scheme.

Consistent with the European approach we are proposing that the symbol will appear in:

- Approved Product Information (PI) and Consumer Medicine Information (CMI);
- Advertising, promotional and educational materials produced by the sponsor for health care professionals;
- Relevant texts such as Australian Medicines Handbook (AMH) and MIMS; and
- Prescribing and dispensing software.

Product Information (PI) reformat

In addition to the Black Triangle scheme, the TGA will work with sponsors to reformat the PI to ensure important prescribing information (such as indications, contra-indications, precautions and adverse event information) is easily accessible to the prescriber, thereby enhancing the ability of health professionals to minimise the occurrence of adverse events occurring in their patients.

² Biological in this context means biological medicine, such as a vaccine (except for seasonal flu vaccines) or a medicine derived from plasma (blood).



Questions

- Do the proposed criteria for inclusion in the Black Triangle Scheme appropriately target new medicines for which adverse event reports should be sought?
- What information, communication and education activities would assist health professionals and consumers to understand the Black Triangle Scheme and the importance of reporting adverse events for these medicines?
- Are the proposed changes to the Product Information (PI) leaflet useful for health professionals?
- What support will sponsors need to comply with the new format and what are achievable timelines for implementation of the new format?

Compliance

Pharmacovigilance (PV) inspection program

As a requirement of registration, sponsors of medicines must collect and report on relevant adverse events; and provide TGA with information on significant safety issues or any other information that is relevant to the balance of benefits and risks associated with their product. Reporting of [serious adverse events](#) is mandatory and it is incumbent upon the sponsor to have robust processes in place for collecting, analysing and reporting on issues related to their products. While this process currently results in data flowing from sponsors to the TGA, the TGA has no established pharmacovigilance inspection program and compliance with existing pharmacovigilance requirements by Australian sponsors is not formally assessed. To verify Australian sponsors' compliance with existing pharmacovigilance requirements we will implement a system of inspection audits.

Pharmacovigilance inspections are legislated in the European Union (EU) where risk based inspections of sponsors occur. In the USA 'for cause' and routine inspections occur.

In 2016 we completed a pilot PV Inspection Program with ten volunteer companies that ranged across large multinational companies, Australian owned and based companies, smaller biotechnological companies to complimentary/herbal medicine companies; and involving an array of product types, such as topical, oral and IV products. There were no critical deficiencies identified as a result of the pilot, but it did identify areas for improvement, such as the timeliness with which adverse event reports were submitted to TGA.

We will implement a PV Inspection Program to enable TGA to proactively ensure companies have appropriate pharmacovigilance systems in place and are compliant with legal responsibilities.

All sponsors of listed and registered medicines will fall within scope of the PV Inspection Program. It is proposed that the following factors will be considered when determining which sponsors to target and prioritise for inspection:

- the types of medicines the sponsor is responsible for, specifically medicines with uncertainty about their risk profile (new medicines and provisionally registered medicines);

- products with known safety concerns;
- evidence that the sponsor is or has been non-compliant with other TGA regulatory requirements – such as, RMP activities;
- data analysis which identifies potential non-compliance with pharmacovigilance requirements under the *Therapeutic Goods Act 1989*– for example evidence of failure to submit adverse event reports within required timeframes;
- information from prior inspections in Australia and overseas.

The PV Inspection Program will use a risk based approach that includes a component of random inspections as well as the targeted inspections initiated through the established criteria.

Sponsors of provisionally registered medicines will be prioritised for the PV Inspection Program. We will place a greater focus on these sponsors to ensure that robust pharmacovigilance systems are in place to support the necessary reporting required by the RMP.

Where an inspection results in critical or a significant number of major findings, the sponsor would be prioritised for a follow up inspection to confirm that deficiencies have been rectified and adequate preventative measures are in place.

Where deficiencies are identified through the pharmacovigilance inspection process, we will, in the first instance, work with the sponsor to address the deficiencies, such as providing the sponsor with education, guidance, tools that can be used and examples of best practice, where available.

A regulatory response may be considered in instances where:

- a sponsor has a continuous history of non-compliance despite efforts by the TGA in line with the [TGA Regulatory compliance framework](#);
- major deficiencies remain unaddressed by the sponsor; or
- an inspection identifies critical findings posing high risk to public safety.

If our attempts to work with the sponsor to achieve compliance are unsuccessful, we will consider taking regulatory action.

We will publish statistics on our PV Inspection Program activities on a six monthly basis.



Question

- What activities could TGA undertake to assist sponsors in complying with their pharmacovigilance requirements?

Risk Management Plan (RMP) compliance monitoring

We currently require Risk Management Plans (RMP) to be provided with applications for new chemical entities, new biological entities and applications to change the registration of existing medicines where the change might introduce a new safety concern due to the addition of a new population group such as children or the elderly. The RMP sets out the required actions a sponsor must undertake to characterise and reduce the risk posed by the medicine. The RMP forms an agreed plan of action between the TGA and the sponsor. Activities required as part of

the RMP might include conducting additional studies, undertaking education activities with health care practitioners or other activities deemed necessary to collect additional safety data regarding the medicine or reduce risks associated with the use of the medicine.

Relevant details from RMPs are included in the Australian Public Assessment Reports for prescription medicines (AusPARs). AusPARs are intended to provide transparency regarding the registration process and scientific rationale for the registration of a specific medicine. An AusPAR is generally prepared for submissions for products containing new chemical and biological entities, biosimilar medicines, major variations and extensions of indications. In addition, an AusPAR will be published if the information is considered to be in the interest of the Australian public. See: Table 1. Summary of AusPAR required by application category and types in the [Australian Public Assessment Report \(AusPAR\) guidance document](#).

Further details regarding AusPARs can be found on the TGA website at <https://www.tga.gov.au/auspars-questions-answers>.

The TGA may review past RMP requirements as sponsors submit revisions to their agreed RMP or seek to vary the approved registration of a medicinal product, providing an opportunity for the TGA to evaluate past compliance. However, to enhance the RMP process we will now focus on a proactive approach of monitoring to ensure that activities are completed within the agreed time frames, that sponsors have reported when necessary and that they seek agreement with the TGA to make any changes to the RMP. To achieve this we will implement RMP Compliance Monitoring to verify compliance with these additional activities.

In the first instance, we will work with sponsors to ensure that agreed requirements have been met. Where a sponsor fails to meet their obligations as outlined in the RMP we will follow up with the sponsor to ensure their action. If our attempts to work with the sponsor to achieve compliance are unsuccessful, we will consider taking regulatory action.

We will publish updates on the progress of confirmatory efficacy studies for provisionally registered medicines as they are monitored through the RMP Compliance Monitoring process.

Questions



- Is the information regarding RMP requirements included in the AusPARs sufficient to inform you of the risk minimisation and pharmacovigilance commitments that have been made by the sponsor?
- What activities could we undertake to assist sponsors in complying with their RMP requirements?

Improved collection and use of data

As part of the revised Medicines Vigilance Framework, we will be enhancing our data analytics capabilities to better support pharmacovigilance monitoring and compliance activities. This will be achieved through better data collection, linking of health datasets and implementation of analytic IT software.

As one example of improved data linkages, the existing datasets held by the Australian Government Department of Health have the potential to contribute to the evidence base TGA uses to investigate whether a medicine causes an adverse event. This could be achieved by linking the following datasets: Pharmaceutical Benefits Scheme (what medicine the patient was

taking), Medicare Benefits Schedule (MBS) (what procedure the patient had) and hospital (why the patient had the procedure or why they were admitted).

The TGA has a number of projects currently underway that will establish the feasibility of advanced data linkage. These projects will support the TGA to fully employ linked, de-identified data sets to support medicines safety investigations in the future.

Adverse Events Management System (ADRS)

We are implementing a new IT system – the Adverse Events Management System – that will replace the existing Adverse Drugs Reporting System (ADRS). The new system will improve and streamline the way sponsors, health professionals, state and territory health departments and consumers submit adverse event reports electronically to TGA. In particular, the new system will make it easier for sponsors to meet their mandatory reporting requirements as the new IT system will use the same electronic reporting standards sponsors use for reporting adverse events to overseas regulators.

International information sharing

We continuously look for opportunities to improve how we collaborate with our international counterparts to proactively minimise, detect and address medicine safety-related issues.

Consistent with the approach taken in MMDR we will identify opportunities to strengthen our use of overseas reports.

The new AEMS will enhance our capacity to share more complete adverse event data with the World Health Organisation (WHO) and thereby facilitate international regulatory collaboration and make a stronger contribution to international pharmacovigilance endeavours.

Conclusion

We are introducing a range of changes to strengthen the safety monitoring for Australian registered medicines by enhancing TGA's post-market monitoring capability. These changes include:

- verifying sponsors have complied with additional risk minimisation and pharmacovigilance activities in their RMP;
- verifying sponsors have complied with their pharmacovigilance requirements through a new on-site inspection program;
- encouraging adverse event reporting for newly registered medicines and making it easier for sponsors to report adverse events; and
- contributing more comprehensive adverse event data to international medicines vigilance.

Whilst these new capabilities will be directed at the full breadth of medicines which fall within the scope of the post-market monitoring program, provisionally registered medicines, as higher risk medicines, will be amongst those medicines prioritised for being subject to these new or enhanced capabilities.

Next steps

Feedback from this consultation will be used to inform how we implement the Medicines Vigilance Framework. The implementation of these programs will occur between September 2017 and January 2018.

Appendix

Definitions	
Adverse Event Reporting	<ul style="list-style-type: none"> • Reports on harmful and unintended responses to medicines, vaccines, biologicals and medical devices marketed in Australia or in clinical trials. • Expedited reporting of serious unexpected clinical trials adverse events. • Reports regarding deficiencies in labelling, instructions or packaging, defective components, performance failures, poor construction or design of medical devices marketed in Australia.
Australian Public Assessment Report (AusPAR)	<p>An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.</p> <ul style="list-style-type: none"> • AusPARs are prepared and published by the TGA. • An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time. • A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA
Biological medicines	<p>Biological medicines are therapeutic goods that are derived from biological sources and are regulated as registered medicines. They include proteins and polysaccharides such as:</p> <ul style="list-style-type: none"> • Vaccines • Products of the fermentation of recombinant cell-lines; • Medicines derived from the fluids and tissue of humans (where specified in the Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011) and animals • Bacterially-derived proteins; • Animal-derived polysaccharides like heparin. <p>Biological medicines do not include antibiotics and small peptides or molecules <2500 Da.</p> <p>Biological medicines are distinct from 'biologicals' which are human cell and tissue products.</p>

Definitions	
Consumer Medicine Information (CMI)	A document for patients with that gives a plain-English explanation of the prescription medicine product
Critical deficiency	<p>A deficiency in pharmacovigilance practise or processes that has, or may significantly adversely affect the 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.</p> <p>Also occurs when it is observed that the sponsor has engaged in fraud, misrepresentation or falsification of data.</p>
Listed medicines	<p>Listed medicines are assessed by the TGA for quality and safety but not efficacy.</p> <ul style="list-style-type: none"> · Some over-the-counter medicines are listed. · Most complementary medicines are listed.
New chemical entity (NCE)	<ol style="list-style-type: none"> a. A chemical, biological or radiopharmaceutical substance that has not previously been included in the ARTG; or b. an isomer, mixture of isomers, complex, derivative or salt of a registered chemical substance that, having previously been included in the ARTG, differs from the registered substance in having different safety or efficacy properties; or c. a biological substance that, having previously been included in the ARTG, differs from the registered substance: <ol style="list-style-type: none"> i. in having a different molecular structure; or ii. in deriving from source material of a different nature or from a different manufacturing process; or d. a radiopharmaceutical substance that <ol style="list-style-type: none"> i. is a radionuclide or ligand that has not previously been included in the ARTG; or ii. has a coupling mechanism, linking the molecule and radionuclide, that has not previously been included in the ARTG; or e. a fixed combination of active substances that have not previously been included in the ARTG as that fixed combination.
Pharmacovigilance	The monitoring and prevention of adverse effects of medicines after they have been approved for use.

Definitions	
Product Information (PI)	<p>Product information is defined in s3 of the Therapeutic Goods Act 1989 to mean:</p> <p>'in relation to therapeutic goods, information relating to the safe and effective use of the goods, including information regarding the usefulness and limitations of the goods'.</p> <p>The PI is used by health professionals.</p>
Provisionally registered medicine	<p>A provisionally registered medicine is a medicine granted a time-bound registration on the basis of early clinical data on efficacy and safety, where the potential benefit of earlier availability of the medicine outweighs the risk that additional data are still required. Given the higher risk, such medicines will be subject to prioritised monitoring by the TGA as well as additional registration requirements such as the submission of confirmatory clinical data on efficacy and safety.</p>
Registered medicine	<p>Registered medicines are assessed by the TGA for quality, safety and efficacy.</p> <ul style="list-style-type: none"> · All prescription medicines are registered. · Most over-the-counter medicines are registered. · Some complementary medicines are registered.
Risk Management Plan (RMP)	<p>Summary of the known important safety information about the therapeutic product (safety specifications).</p> <p>Plans to identify and characterise known or potential safety concerns (pharmacovigilance plan) and to minimise any identified or potential safety risk (risk minimisation plan).</p> <p>High-risk medicines may require an assessment of benefit.</p>

Definitions	
Serious adverse event	<p>An adverse event for which one or more of the following is true</p> <ul style="list-style-type: none"> · results in death · is life-threatening · requires inpatient hospitalisation · prolongs existing hospitalisation · results in persistent or significant disability or incapacity, including permanent impairment of a body function or permanent damage to a body structure · necessitates medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure · is a congenital anomaly or birth defect · is a medically important event
Sponsor	<p>In relation to therapeutic goods, means:</p> <ol style="list-style-type: none"> a. a person who exports, or arranges the exportation of, the goods from Australia; or b. a person who imports, or arranges the importation of, the goods into Australia; or c. a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere).

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Reference # R16/805152