Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Minor variations to registered prescription medicines

Biological medicines

Version 1.2, May 2013

TGA Health Safety Regulation

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About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

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Version history

Version	Description of change	Author	Effective date
V1.2	Original Publication	Management and Coordination Section/Office of Scientific Evaluation	May 2013

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Abbreviations and acronyms

ARTG	Australian Register of Therapeutic Goods
ARGPM	*Australian Regulatory Guidelines for Prescription Medicines*
BP	*British Pharmacopoeia*
CPD	certified product details
CTD	common technical document
EMA	European Medicines Agency
GMP	good manufacturing practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Ph. Eur.	*European Pharmacopoeia*
PI	product information
PMF	Plasma Master File
TG Act	*Therapeutic Goods Act 1989*
TGA	Therapeutic Goods Administration
TGO	therapeutic goods order
TSE	transmissible spongiform encephalopathy
USP	*United States Pharmacopeia – National Formulary*
WCB	working cell bank
WSL	working seed lot

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Part 1
General information

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1.1 What is a biological medicine?

Biological medicines are therapeutic goods that are derived from biological sources and are regulated as registered prescription medicines. Biological medicines are distinct from the therapeutic goods that are regulated as 'biologicals' (as defined in the *Therapeutic Goods Act 1989*[1] [TG Act] and its amendments) and are therefore not regulated under the Biologicals Regulatory Framework. Biological medicines are not regulated as 'biologicals' because they are specified in the Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011. This determination declares several broad classes of products to be therapeutic goods but not to be biologicals. Biological medicines within these broad classes include:

- vaccines
- antivenoms
- bacterial derived toxins
- immunoglobulins
- monoclonal antibodies (including modified monoclonal antibodies)
- allergens
- radiolabelled biological medicines
- plasma-derived products, for example immunoglobulins and clotting factors
- hormones such as insulins, growth hormones, gonadotropins, calcitonins (non-synthetic) and somatropin, but not steroid hormones and synthetic peptides of less than 32 amino acids
- enzymes such as pancreatins, streptokinase, hyaluronidase, alteplase and urokinase
- cytokines, growth factors and interleukins such as interferons, erythropoietin and thrombopoietin, but not urinary-derived proteins
- heparins, low–molecular weight heparins, enoxaparins and anti-thrombins
- products of recombinant DNA technology
- peptides that are from natural sources and not synthetically derived.

1.2 About this document

All prescription medicines available for general marketing in Australia are registered in the Australian Register of Therapeutic Goods[2] (ARTG). Section 2.5 of the *Australian Regulatory Guidelines for Prescription Medicines*[3] (ARGPM) sets out the kinds of applications that can be made to enter medicines into the ARTG. Different processes, forms, timeframes and fees apply, depending on the type of application and category.

[1] <http://www.comlaw.gov.au/Series/C2004A03952>
[2] <http://www.tga.gov.au/industry/artg.htm>
[3] <http://www.tga.gov.au/industry/pm-argpm.htm>

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This document provides guidance for making minor variations to existing ARTG entries.

Scope

Prescription medicines are medicines that require an authorised health professional's written instruction (prescription) before they can be obtained from a registered pharmacist. The types of therapeutic goods that are regulated as prescription medicines are listed in Part 1 of Schedule 10 of the Therapeutic Goods Regulations 1990[4]. Most prescription medicines are contained in Schedules 4 and 8 of the *Standard for the Uniform Scheduling of Medicines and Poisons*[5].

This document provides guidance for minor variations to registered prescription medicines that are **biological medicines**. These include vaccines, natural peptides, monoclonal antibodies and other recombinant products. It does not cover products that are defined as biologicals and regulated under the Biologicals Regulatory Framework. Further information on biologicals can be found in the *Australian Regulatory Guidelines for Biologicals*[6]. If sponsors are unsure whether their product is a biological medicine or a biological, they should contact the Therapeutic Goods Administration.

All other registered prescription medicines contain chemical entities. These medicines include antibiotics, short-chain synthetic polypeptides and some hormones. Guidance for minor variations to chemical entities is provided in *Minor Variations to Registered Prescription Medicines: Chemical Entities*.

Guidance for other types of variations to prescription medicines (that is, variations administered in the Streamlined Submission Process[7]) is located in the ARGPM.

This document applies only to minor variations to registered prescription medicines (biological medicines). It has six parts:

- **Part 1 (General information)** provides an overview of the legislation that governs minor variations to registered prescription medicines, including the types of variations that can be made under each part of the TG Act. It also includes information about making changes to the approved product information (PI) that relates to minor variations to ARTG entries of registered prescription medicines.
- **Part 2 (Requesting a correction to an incorrect or incomplete entry in the ARTG)** describes the process for correcting errors in the ARTG entry or the PI for prescription medicines, such as spelling or grammatical errors.
- **Part 3 (Making a safety-related request to vary an entry in the ARTG)** describes the process for requesting minor variations to ARTG entries that relate to the safety of the medicine, by reducing the patient population that can receive the medicine (for example, by

[4] <http://www.comlaw.gov.au/Series/F1996B00406>
[5] <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>
[6] <http://www.tga.gov.au/industry/biologicals-argb.htm>
[7] <http://www.tga.gov.au/industry/pm-ssp.htm>

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removing an indication or limiting the use of the medicine) or by adding a warning or precaution (for example, a warning about an adverse effect or interaction).

- **Part 4 (Requesting a variation that does not reduce quality, safety or efficacy)** describes the processes for requesting minor variations to ARTG entries that are not related to the safety of the medicine (as described in Part 3) and do not create a separate and distinct good (for example, a change in the shelf life of the product). Some of these variations can be self-assessed, and some require data to be submitted to the Therapeutic Goods Administration (TGA) for evaluation before the request can be approved or rejected.
- **Part 5 (Applying for a variation that creates a separate and distinct good)** describes the processes for applying for minor variations to ARTG entries where the variation creates a new therapeutic good (for example, a change in container type). These changes are not 'safety-related', as described in Part 3. Some of these variations can be self-assessed, and some require data to be submitted to the TGA for evaluation.
- **Part 6 (Changes that do not require prior approval)** explains the few types of changes that the TGA does not need to be notified about at all, as well as changes that the TGA does not need to approve before the change is implemented. These processes cannot be used if a variation will require a change to the PI.

1.3 Overview of the legislative basis for varying products

The standard conditions of registration, which apply to all registered prescription medicines, state that:

> Changes or variations in respect of any information concerning the registered or listed therapeutic goods, being information that would have been relevant to a decision to register/list the goods in the ARTG, including information on the formulation of the registered/listed goods or other aspects of their manufacture, and the labelling of the goods, shall forthwith be notified to the Secretary, or the Secretary's delegate appointed for the purposes of section 28 of the *Therapeutic Goods Act 1989* and where necessary, the change or variation shall not be implemented until approved by the Secretary.[8]

This means that once a medicine is entered in the ARTG, the information cannot be changed (apart from limited exceptions) without the approval of the Secretary.

Throughout this document, 'the Secretary' refers to the Secretary of the Australian Government Department of Health and Ageing, or the Secretary's delegate in the TGA.

Variations to existing ARTG entries can be made under s. 9D of the TG Act or, if the variation will result in the creation of a separate and distinct good, under s23. Some exceptions are listed in Part 6 of this document, 'Changes that do not require prior approval'.

Section 9D has three subsections that are relevant for making variations for prescription medicines:

[8] Conditions—Standard and Specific—Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989 <http://www.tga.gov.au/pdf/dr4-appendix-04.pdf>

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- Subsection 9D(1) allows sponsors to request an update to an ARTG entry that is incomplete or incorrect (see Part 2). The Secretary can also make corrections under s. 9D(1), if necessary, without the sponsor needing to make a request.
- Subsection 9D(2) allows sponsors to request safety-related variations to an ARTG entry (and consequential changes to the PI). A variation is safety-related if it reduces the patient population (such as by removing an indication), or has the effect of adding a warning or precaution (such as an adverse effect or interaction).
- Subsection 9D(3) allows sponsors to request other variations to an ARTG entry that do not have the effect of creating a separate and distinct good under s. 16(1) of the TG Act, provided that the change does not reduce the quality, safety or efficacy of the medicine.

If the variation creates a separate and distinct good, sponsors must apply to the TGA under s. 23 of the TG Act for approval of a new registered medicine under s. 25.

Separate and distinct goods

Under s. 16(1) of the *Therapeutic Goods Act 1989*[9], a medicine is a separate and distinct good from a registered medicine if it has:

- a different formulation, composition or design specification; or
- a different strength or size (disregarding pack size); or
- a different dosage form or model; or
- a different name; or
- different indications[10] or
- different directions for use; or
- a different type of container (disregarding container size).

Pathways for making minor variations to registered prescription medicines are shown in Figure 1.1.

[9] <http://www.comlaw.gov.au/Series/C2004A03952>
[10] Except for variations to indications under s. 9D(2) of the Therapeutic Goods Act 1989, as described in s. 9D(2A).

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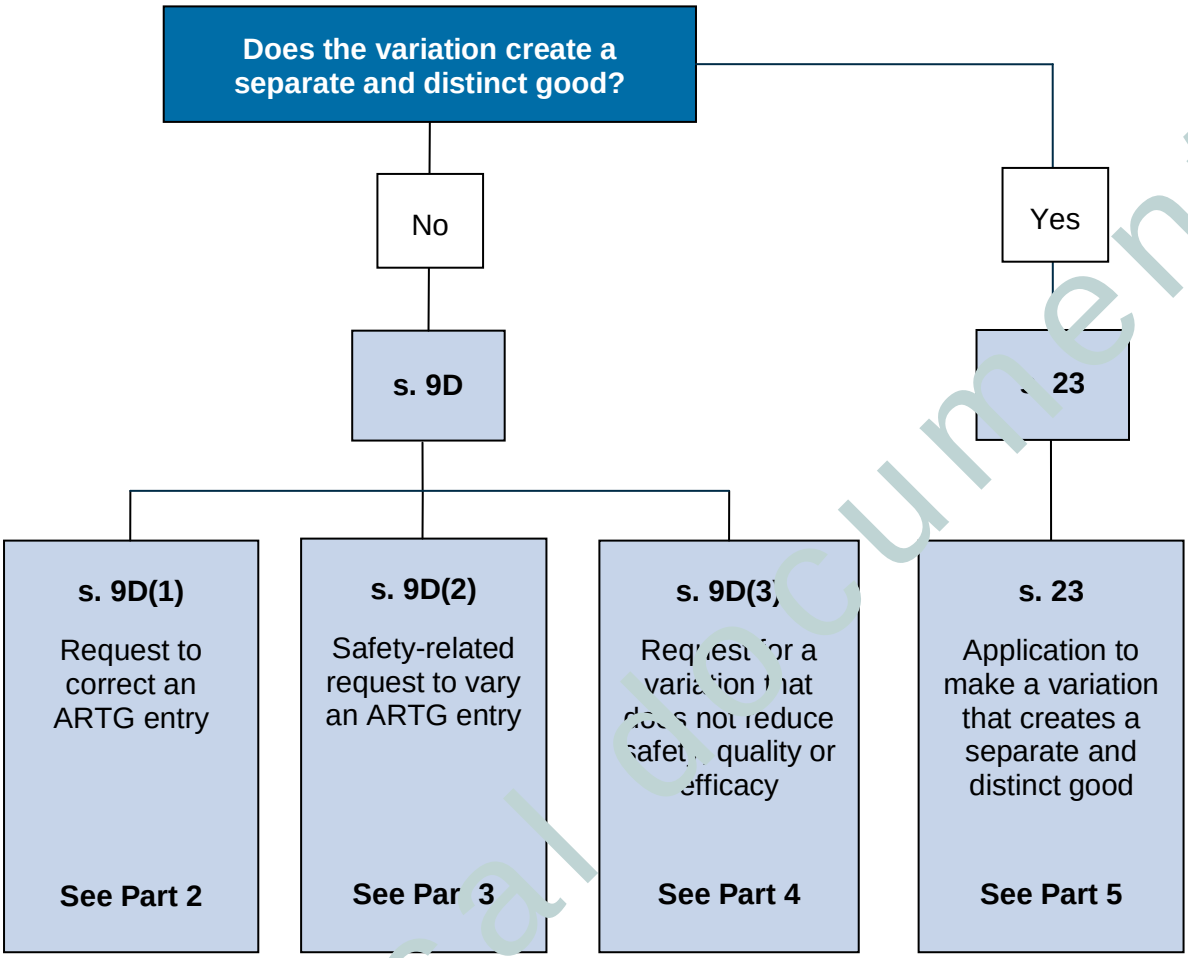
Figure 1.1 Pathways for requesting variations to, or making applications for, registered prescription medicines



ARTG = Australian Register of Therapeutic Goods
Note: sections refer to the *Therapeutic Goods Act 1989*

Other than for the few exceptions specified in Part 6, it is a breach of condition of registration to implement a variation before the Secretary has approved it. Penalties may apply,[11] including suspension or cancellation of registration.[12] It is therefore important that sponsors follow the correct procedure when making variations to registered medicines to avoid breaching the provisions of the TG Act. If sponsors do not understand which procedure to follow, they should contact the TGA.

[11] See s. 21A of the Therapeutic Goods Act 1989
[12] See s. 30(2)(c) of the Therapeutic Goods Act 1989

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Categories and timeframes

The TGA takes a risk-based approach to assessing variations to prescription medicines. This means that the higher the risk associated with the variation, the greater the level of assessment required by the TGA for a decision to be made. There are three levels of assessment made by the TGA for variations:

- major variations, which require evaluation of a full dataset, or any combination of quality, nonclinical, clinical and bioequivalence data (Category 1 and Category 2 applications administered in the Streamlined Submission Process[13]). These variations are not discussed in this document
- variations that only require evaluation of quality-related data (Category 3 applications)
- lower risk variations for which the sponsor can provide an assessment of their own data for the TGA to verify (known as self-assessable requests).

The ARGPM has more details about different categories of applications.

The Therapeutic Goods Regulations 1990[14] specify statutory processing times for requests and applications relating to prescription medicines. The specified timeframe is known as 'the clock'. The length of time depends on the level of assessment required—for example, evaluation of clinical, nonclinical, bioequivalence and quality data (that is, a Category 1 or 2 application) has a longer timeframe (255 or 175 working days) than an assessment of quality data only (Category 3 application) or verification of a self-assessable request (45 working days). Requests for variations to ARTG entries under s. 9D(1) (corrections) or s. 9D(2) (safety-related requests) have no statutory timeframes.

TGA requests for further information

The TGA may need to request extra information about a proposed variation, or to clarify information provided. This can be done as a request for additional information under s. 31 of the TG Act, as described in Section 3.4.2 of the ARGPM. Requests made under s. 31 are usually requests for existing information or documents relating to specific aspects of the product, the quality, presentation or safety or efficacy for their intended use. This is the most common type of request for further information made by the TGA.

Alternatively, the TGA may raise an objection to a request or application under regulation 16F. An objection usually means that the Secretary will ask the sponsor questions about the product or the proposed variation (to which the sponsor must respond) that are necessary for a decision to be made about the request before a decision is made. An objection would usually be raised if the TGA had a particular concern about the proposed variation, and would like to provide the sponsor with the opportunity to provide additional information. An example of such an objection would be if the TGA believed that clinical data may be required to support the proposed variation—in this case, an objection would be raised and the sponsor would be asked to justify why they felt that supporting clinical data were not required.

If the Secretary raises an objection, the clock will stop from the time the Secretary raises the objection until the TGA receives the response from the sponsor. The Secretary then has 30 working days from the day on which the response to the objection is received, to notify the

[13] <http://www.tga.gov.au/industry/pm-ssp.htm>
[14] <http://www.comlaw.gov.au/Series/F1996B00406>

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sponsor of the decision. If the Secretary does not meet this 30–working day deadline after an objection is raised, the application or request is deemed to have been approved. The clock also stops at any time the Secretary is waiting for a response to a s. 31 request for information.

Fees and submission types for minor variations

Schedule 9 of the Therapeutic Goods Regulations 1990 (the 'Regulations') outlines the range of fees for services that the TGA provides, including fees for making minor variations to registered prescription medicines.

Fees for registered prescription medicines are calculated on a 'per submission' basis. The term 'submission' is defined in Part 1 of Schedule 9 of the Regulations. If a sponsor is making more than one application or request **simultaneously**, that falls under one of the categories listed in the Regulations, and as long as all of the medicines in the applications contain the same active ingredient, they are considered to be making a single submission. This does not include applications for multiple ARTG entries that contain the active ingredient alone as well as in combination with other active ingredient(s). The different types of minor variations and the corresponding submission types are described in Table 1.1. For example, simultaneous requests for multiple different quality-related variations from one sponsor, all requiring evaluation of quality data (that is, multiple Category 3 applications) are considered a single submission under Item 2B of Schedule 9. A simultaneous or concurrent application from, or on behalf of, another applicant is a separate submission.

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Table 1.1 Relevant submission types for minor variations

Submission[1]	Part of Act	Type of application[2]	Level of TGA assessment
2A(a)	s. 9D(1)	Correction of an ARTG entry	Verification of summary provided by sponsor
	s. 9D(2)	Safety-related request (SRR)	
	s. 9D(3)	Self-assessable request (SAR)	
2CA	s. 9D(2)	Safety-related request (SRR) with data	Evaluation of (usually clinical) data
2B	s. 9D(3)	Category 3 application	Evaluation of quality data
2(a)[3]	s. 23	SAR (that creates a separate and distinct good)	Verification of summary provided by sponsor
2(bj) and 4(h)	s. 23	Category 3 application (that creates a separate and distinct good)	Evaluation of quality data

[1]The numbers listed correspond to the relevant item number in Schedule 9 of the Regulations.
[2]The different types of applications are discussed in subsequent sections of this document.

[3]Included for completeness. This application type is not listed as a kind considered to be a submission in Part 1 of Schedule 9 of the Regulations

Importantly, the concept of a submission is only relevant for the purposes of calculating the fees payable, reflecting the fact that it is easier for the TGA to process more than one very similar type of application or request at the same time than if they were received separately. As an example, a sponsor may wish to change the shelf life of a prescription medicine that is sold as three different strengths (and therefore has three separate ARTG entries). The TGA evaluation of these requests will be very similar, if not identical, for each ARTG entry. A sponsor can submit all three requests to the TGA as Category 3 applications at the same time, and will only pay one fee under item 2B of Schedule 9 of the Regulations.

Corrections to ARTG entries, safety-related requests (SRRs) and self-assessable requests (SARs) that do not require TGA evaluation of data (that is, requests under s. 9D(1), s. 9D(2) and s. 9D(3)) can be lodged as a single submission for the purposes of calculating fees payable (Table 1.1). The TGA administrative processes for each of these types of applications are distinctly different, including different processing timeframes, different forms and different information requirements. These application types should therefore be submitted to the TGA as separate application dossiers with separate application forms; a single cover letter linking the three requests can also be provided. However, sponsors will only need to pay a single fee, as long as the separate applications are lodged with the TGA simultaneously and meet the relevant requirements of a submission.

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For example, if a sponsor wants to submit a SAR at the same time as requesting a correction to the same ARTG entry, they should submit two separate forms, with the relevant required information for each application type as separate dossiers. These requests will be processed as appropriate for each type of variation, and two separate decisions will be made. However, only a single fee under item 2A of Schedule 9 of the Regulations will be payable.

Please note that safety-related variations (see Part 3) submitted as stand-alone requests, without any other different request types, will help the TGA process any urgent requests as quickly as possible.

Making an appeal

Decisions made under s. 9D(1), s. 9D(2), s. 9D(3) and s. 25 are 'initial decisions' within the meaning of s. 60 of the TG Act. This means that a person whose interests are affected by the decision can request a review by the Minister for Health and Ageing. A request must be made in writing within 90 days of when the person first notices the decision and should be sent to:

The Parliamentary Secretary to the Minister for Health and Ageing
Parliament House
CANBERRA ACT 2600

The letter should be headed 'Request for reconsideration under section 60 of the *Therapeutic Goods Act 1989*'.

Any request for internal review should contain a clear description of what is wrong with the initial decision and give the reasons. The person making the request should include all the information that they would like the Minister's delegate undertaking the review to consider. Under s. 60(3A) of the TG Act, the Minister's delegate cannot consider any other information provided after the request is made, unless the delegate has asked for the additional information, or the additional information indicates that the safety, quality or efficacy of the product is unacceptable. The appeal will normally be handled by the one of the Minister's delegates within the Australian Government Department of Health and Ageing (that is, at the TGA).

The delegate can confirm or revoke the initial decision, or revoke the initial decision and substitute a new decision. If a person has not received a response within 60 calendar days of making the request, the initial decision is taken to be confirmed.

If the person is not satisfied with the decision, they can appeal to the Administrative Appeals Tribunal (AAT; subject to the *Administrative Appeals Tribunal Act 1975*[15]). Applications to the AAT must be made within 28 calendar days of the Minister's decision following an appeal. The AAT may affirm the decision, vary it, set it aside, substitute a new decision or refer the decision back to the original decision maker.

[15] <http://www.comlaw.gov.au/Series/C2004A01401>

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Variations to multi-component products

Most registered prescription medicines are presented as a product that contains a single component (for example, a blister pack that contains one type of tablet—although this tablet may contain more than one active ingredient), but some prescription medicines contain multiple components in the same pack. The regulatory requirements for these multi-component products depend on the nature of the individual components in the pack.

The most common multi-component packs are composite packs, kits, and system or procedure packs. Kits and composite packs are defined in the legislation under s. 7B of the *Therapeutic Goods Act 1989*[16]. System or procedure packs are defined in s. 41BF—these are regulated as medical devices (see the *Australian Regulatory Guidelines For Medical Devices*[17] on the TGA website). Variations to the medicine components of kits and composite packs are regulated in a similar way to any other prescription medicine.

Composite packs contain two or more therapeutic goods, but do not contain therapeutic devices or medical devices that are included in the ARTG. They are used for a single treatment or a single course of treatment, and the components are either combined before treatment or administered in a particular sequence. The composite pack itself is regulated as a separate and distinct good and must have its own unique AUST R number. Individual components within the pack may or may not have separate registrations or listings. Examples of composite packs are a blister pack that contains several different types of tablets, for example oral contraceptives, or a vial of medicine that is a lyophilised powder that is packaged with an ampoule or vial containing a diluent.

Kits are therapeutic goods that contain multiple components to be used as a unit. A kit may consist of registered medicines, listed medicines, exempt medicines, biologicals or exempt biologicals. Kits may include other items or 'articles' that are normally regarded as medical devices when supplied on their own, but due to their nature and intended use are regulated as part of a prescription medicine product. The legislative basis for this is the Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2010[18]. In this order, the medicine and the other item form a single integral product that is intended exclusively for use in the given combination and is not reusable (although it may be multi-dose). An example of a kit is a cream or ointment supplied with a purpose-built applicator.

1.4 Changes to the product information

As described in Appendix 8 of the ARGPM, a draft PI must be lodged, in a form approved by the Secretary under s. 7D of the TG Act, as part of an application under s. 23 to enter a 'restricted

[16] <http://www.comlaw.gov.au/Series/C2004A03952>
[17] <http://www.tga.gov.au/industry/devices-argmd.htm>
[18] <http://www.tga.gov.au/industry/legislation-devices.htm>

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medicine' (for example, a registered prescription medicine) in the ARTG. The form for providing product information[19] is available on the TGA website. All PI documents must be approved by the TGA before a medicine can be registered. Sponsors will be advised in the decision letter from the TGA about when changes to the PI will come into effect.

The PI may need to be changed as a result of a variation to an ARTG entry, as described below, or a change to the PI may be the only variation to an ARTG entry that is requested.

Consequential changes to the product information that result from variations to an ARTG entry

Some variations to ARTG entries will require the PI to be updated. For example, changing the product description will require the 'Presentation' section of the PI to be updated accordingly. Changes to the PI are considered at the same time as the rest of the request or application. If the variation to the ARTG entry is approved, the necessary changes to the PI will also be approved.

- For variations requested under s. 9D—including 9D(1), 9D(2) and 9D(3)—approval of a change to the PI is made under s. 25AA(4).
- For variations applied for under s. 23 (variations that create separate and distinct goods), approval of a new PI is made under s. 25(4) and s. 25AA(1).

If a variation to an ARTG entry means that the PI must be altered, the request or application for the variation should include:

- a clean copy (not marked-up) of the currently approved PI for the relevant registered medicine containing the proposed changes
- a copy of the currently approved PI for the relevant registered medicine, with changes clearly marked
- a table explaining how each of the changes relates to the request, preferably including references to any data submitted in support of each change
- an assurance that the PI provided is the most recent approved version
- an assurance that all of the proposed changes to the PI relate to the requested changes to the ARTG entry, and no other unidentified changes have been proposed or made.

For products with more than one registered trade name, only one representative marked-up copy of the complete PI is required, but sponsors should still submit one clean copy of the PI for each registered trade name. These requests should also include an assurance that all PI documents for all trade names will be changed in the same way, and at the same time, once the changes have been approved by the TGA.

Format for marked-up product information

This section provides guidance on how PI documents can be marked up to identify proposed changes. This is not a mandatory requirement, but following this guidance will assist with the decision-making process by the TGA. Table 1.2 provides details of the suggested types of marking up. Figure 1.2 shows an example of a marked-up PI. All marked-up text should be in a

[19] <http://www.tga.gov.au/industry/legislation-pi-form.htm>

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different colour(s) from the currently approved, unchanged PI text. Sponsors should ensure that the information in the entire PI is consistent with the proposed changes. Proposed changes in the text of the PI relating to different changes, requests or applications should be clearly identified by using different coloured fonts. Where applicable, reasons for specific proposed changes can also be provided in comment boxes in the margins.

Table 1.2 Guidance for preparing marked-up product information

Change to product information	Mark-up
Text to be deleted	Use strikethrough font. Text that is proposed to be deleted should be shown in its current position, not in comment boxes in the margins. However, explanatory comments added in the margins may be useful.
Text to be inserted	Use underlined font.
Text to be moved	Use strikethrough font to show where the text is being moved from, and underlined font to show where it is being moved to. Comment boxes in the margin may be useful at both the current and proposed locations to indicate that the text is to be moved, and to specify the section it is being moved to. Including page numbers in comment boxes to cross-reference between the current and proposed locations is encouraged, particularly for long PIs.
Multiple requests in one submission (for example, several changes under the same part of the Act)	Proposed changes in the text of the PI relating to different changes, requests or applications should be clearly identified by using different coloured 'track changes' fonts or by identifying them in comment boxes. Figure 1.2 provides an example of two different kinds of changes proposed under s 9D(3), marked up in different colours and with explanatory comments in the margin.

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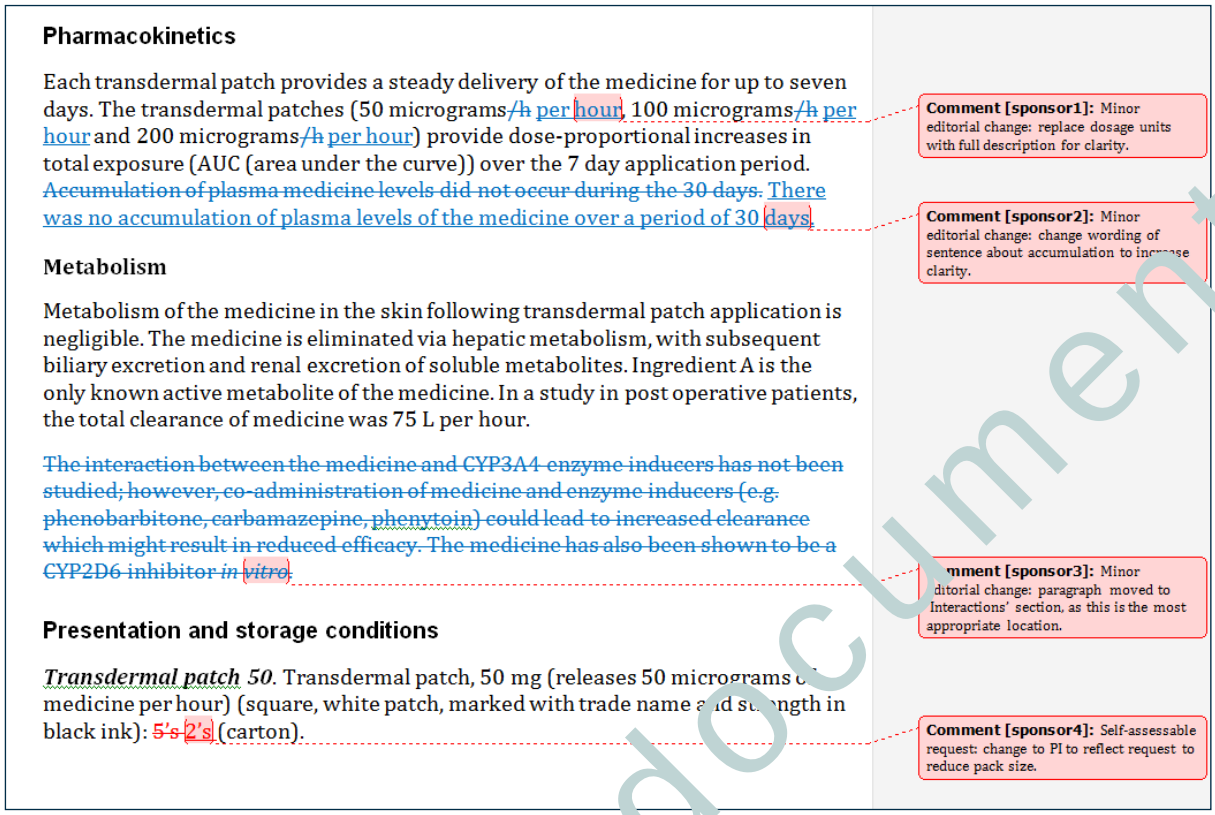
Figure 1.2 Example of marked-up product information



Note: This figure shows inserted text (underlined) and text to be deleted or moved (strikethrough font). All proposed changes are shown in their current or proposed position, and not in comment boxes in the margins. The marked up text shows proposed changes to the product information corresponding to two separate variations being requested under s. 9D(3)– minor editorial changes to increase clarity (blue text) and a change to reflect a self-assessable request to reduce the pack size of the product (red text). Clearly distinguishing between PI changes corresponding to different types of variations that have been submitted simultaneously to the TGA will aid the decision-making process, as different types of changes may be assessed by different TGA delegates.

Other changes to the product information

In some cases, the only proposed variation to an ARTG entry is a change to the PI. Most of these changes do not meet the criteria of a safety-related request (see Part 3) and are requested under s. 9D(3). The type of request depends on the level of assessment required by the TGA to make a decision. One example of this is a 'minor editorial change to the PI' (see below). Most other examples of where the only variation to an ARTG entry is a change to the PI require supporting clinical, nonclinical or bioequivalence data, and should be submitted as a Category 1 request in the Streamlined Submission Process[20]. These types of changes to the PI are not discussed in this document.

See the *Australian Regulatory Guidelines for Prescription Medicines*[21] (ARGPM) for more information about Category 1 and Category 2 applications.

[20] <http://www.tga.gov.au/industry/pm-ssp.htm>
[21] <http://www.tga.gov.au/industry/pm-argpm.htm>

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Minor editorial changes to the product information under s. 9D(3)

Some quality-related variations made under s. 9D(3) will also require a change to the product information (PI). However, in some cases, the only proposed variation to an ARTG entry being requested under s. 9D(3) is a change to the PI.

An example of this is a change to the PI that meets the criteria of a 'minor editorial change', as described below. Minor editorial changes to the PI can be made as a self-assessable request under s. 9D(3).

Minor editorial changes are intended to improve the quality and readability of the PI, and must not alter the context or meaning of the information provided. No new or amended information relating to the quality, safety or efficacy of the product should be proposed as a minor editorial change. All PIs must comply with the specified form for providing product information[22] for a restricted medicine.

Examples of minor editorial changes to the PI include:

- changing the sentence structure to improve clarity (for example, changing 'The pharmacokinetics of multiple doses of product X showed that no accumulation of drug occurred after multiple dosing' to 'No accumulation of product X occurred after multiple doses in pharmacokinetics studies')
- some cases of moving text within the same section of the PI, without changing any text
- changing the text about whether or not a particular presentation is marketed
- amending headings to comply with the latest approved form for the PI.

The same requirements apply for included information and format of the marked-up PI as for variations that result in a consequential change to the PI.

Sponsors wanting clarification about which procedure to follow should contact the TGA.

1.5 Implementing approved variations

Variations to registered prescription medicines cannot be made without approval from the Secretary. Sponsors are encouraged to advise the TGA of any unusual circumstances related to the planned approach for implementing a variation (particularly quality-related variations). Examples of this include any periods when the ARTG entry has been updated to reflect the approved change but product prepared under previous conditions is still on the market, or in certain cases, periods when 'old' and 'new' product are being supplied concurrently.

[22] <http://www.tga.gov.au/industry/legislation-pi-form.htm>

Historical document

Sponsors who no longer intend to implement an approved change should inform the TGA in writing as soon as possible to determine the requirements to request a new change the ARTG entry under s. 9D(3) (see Section 4.2).

On rare occasions, some changes beyond the sponsor's control may need to take place before the TGA can approve them (for example, a change to the name of an overseas supplier). In these cases, sponsors should submit a request to the TGA as soon as they become aware of the change, so that the ARTG entry can be updated as appropriate.

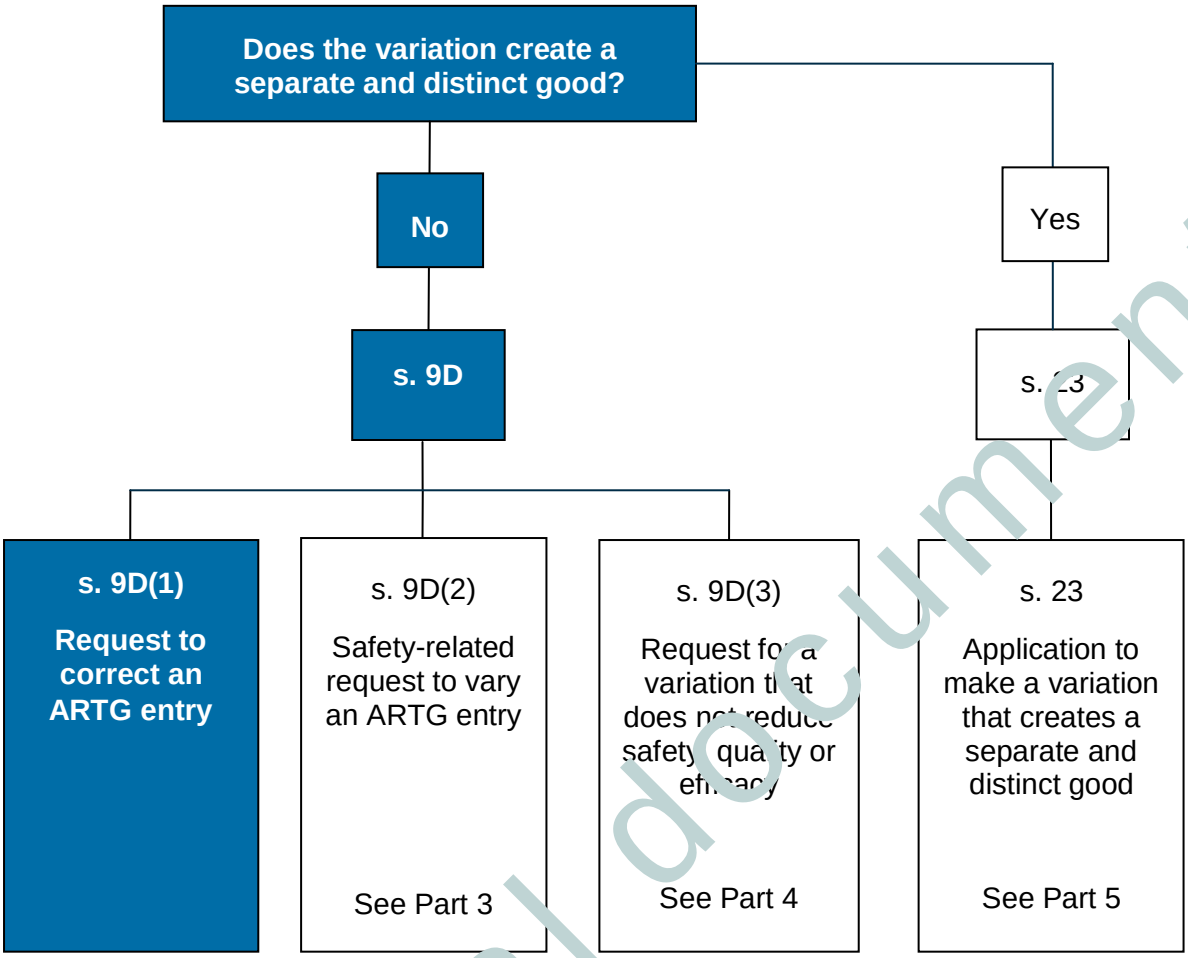
1.6 Mechanism to approve one-off changes to medicines

Occasionally, circumstances arise during the manufacture of a batch of a prescription medicine that result in a slight deviation from the approved process, but the change can be shown to not reduce the quality, safety or efficacy of the product. An example of this is variation to the shelf life for a specific batch of the product. It is possible that this batch can still be released for supply, provided that appropriate data are evaluated and the modification is approved by the TGA. The process for obtaining this approval is to request a Category 3 quality-related change to the entry under s. 9D(3), to add a new condition of registration for the product. This new condition, which is approved under s. 28(3A), will specify that the relevant batches of product are able to have a different shelf life, as approved by the TGA. The data that should be submitted to the TGA will depend on the nature of the change, as described in subsequent sections. If the particular circumstance relates to quality requirements that are specified in a legislated standard (that is, the *British Pharmacopoeia* [BP], *United States Pharmacopeia – National Formulary* [USP], *European Pharmacopoeia* [Ph. Eur.] or a therapeutic goods order [TGO]), sponsors should make a request to obtain consent under s. 14 to supply the specific batches.

Historical document

Part 2
Requesting a correction to an incorrect or incomplete entry in the Australian Register of Therapeutic Goods: s. 9D(1)

Historical document



Variations under s. 9D(1) comprise minor changes to spelling or typography		
Level of assessment	**Application type**	**Timeframe (working days)**
Verification of details provided by the sponsor	Correction to, or completion of, an ARTG entry	No statutory timeframe

ARTG = Australian Register of Therapeutic Goods

Historical document

2.1 What is a correction to an ARTG entry?

A correction to an entry in the Australian Register of Therapeutic Goods[23] (ARTG) is generally a minor change to correct or complete information that was inadvertently recorded incorrectly or omitted in the ARTG entry, including the product information (PI). In some cases, errors in quality-related specifications may need to be corrected.

Sponsors can request corrections to ARTG entries under s. 9D(1) of the *Therapeutic Goods Act 1989*[24] (TG Act). Alternatively, the Secretary can make corrections to ARTG entries under s. 9D(1), at his or her initiative.

Examples of these variations include correcting typographical errors in quantities of excipients, correcting grammatical errors in the records held about a product or adding a manufacturing step for a licensed manufacturer that was inadvertently omitted.

2.2 Changes to the product information for corrections to ARTG entries

Variations under s. 9D(1) can generally include only minimal changes to the PI—for example, correcting a typographical error in the street name of the sponsor's address. Any other requested variation that also requires a change to the PI, such as moving text from one section of the PI to another, does not meet the criteria for correcting or completing an ARTG entry and cannot be made under s. 9D(1). Similarly, updates to the PI to reflect changes made to equivalent documents in other countries cannot be made under s. 9D(1); depending on their nature, these types of changes should be made as safety-related requests (see Part 3 of this document) or under s. 9D(3) (see Part 4 of this document). However, adding previously approved text that was inadvertently omitted from the PI—with suitable evidence— would be an example of an appropriate correction to an ARTG entry If sponsors do not understand which procedure to follow, they should contact the TGA.

See Section 1.4 for general information on changes to the product information.

Historical document

[23] <http://www.tga.gov.au/industry/artg.htm>
[24] <http://www.comlaw.gov.au/Series/C2004A03952>

2.3 How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit a request. The TGA can provide advice on general requirements for the request and relevant parts of the legislation, but cannot provide detailed, specific information about a particular request until it has been lodged.

Further information is also on the TGA website[25].

Sponsors can request corrections to ARTG entries by downloading the form 'Request to Correct an ARTG entry under subsection 9D(1)' from the TGA website. The completed form, together with any required information or documents, and the relevant fee should be sent to:

Application Entry and Support Team
Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

The processes and requirements described in this section also apply to corrections to ARTG entries that are identified by the Secretary.

What do I need to provide?

For each request, the sponsor should provide **all** of the following:

- a completed 'Request to Correct an ARTG entry under subsection 9D(1)' form, with justifications or documentary evidence
- if a change to the approved PI is involved, a clean and marked-up copy of the approved PI (see Section 1.4 of this document)
- if relevant, a table, provided as an attachment to the letter of request, outlining each of the proposed changes to the PI with brief explanatory text, including justifications

  details of when the entry became incorrect or incomplete (if possible), preferably including a relevant file or submission number
- relevant evidence of GMP (clearance letter if an overseas site of manufacture is involved, or Australian manufacturing licence), if this is relevant to the request
- an assurance that the only changes being made to the ARTG entry are those identified in the request

[25] <http://www.tga.gov.au>

Historical document

- the relevant fee (see 'What fees do I pay?', below).

Sponsors must fully disclose all intended changes in a request letter. Any undisclosed, additional changes that are embedded in data or other accompanying documents cannot be approved.

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the Therapeutics Goods Regulations 1990. These fees are subject to change from time to time; current fees[26] are published on the TGA website. The fee for requests under s. 9D(1) is in item 2A(a) of Part 2 of Schedule 9.

If the variation is initiated by the Secretary, no fee is payable.

What are the timeframes?

There is no statutory timeframe for requests under s. 9D(1); however, the TGA tries to process requests as quickly as possible.

What happens to my request?

If all the requirements for a correction to an ARTG entry have been met, including payment of the appropriate fee, the request is referred to the relevant TGA evaluation area for assessment.

The TGA will only review those variations that are described in the cover letter provided with the request at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the request at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the Secretary is satisfied that the ARTG entry is incorrect or incomplete, an appropriate change will be approved. If not, the request will be rejected. The person making the request will be sent a letter outlining the decision. Reasons for the decision will be provided if the request is rejected.

If the variation to the ARTG entry is approved, the entry will be updated and any necessary changes to the PI will also be approved under s. 25AA(4) of the TG Act. Sponsors should lodge copies of the updated PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[27] system within 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

[26] <http://www.tga.gov.au/about/fees.htm>
[27] <https://www.ebs.tga.gov.au/>

Historical document

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 9D(1) and s. 25AA(4) are subject to review under s. 60 of the TG Act.

Sponsors can withdraw their request at any time during the process but fees are not refundable.

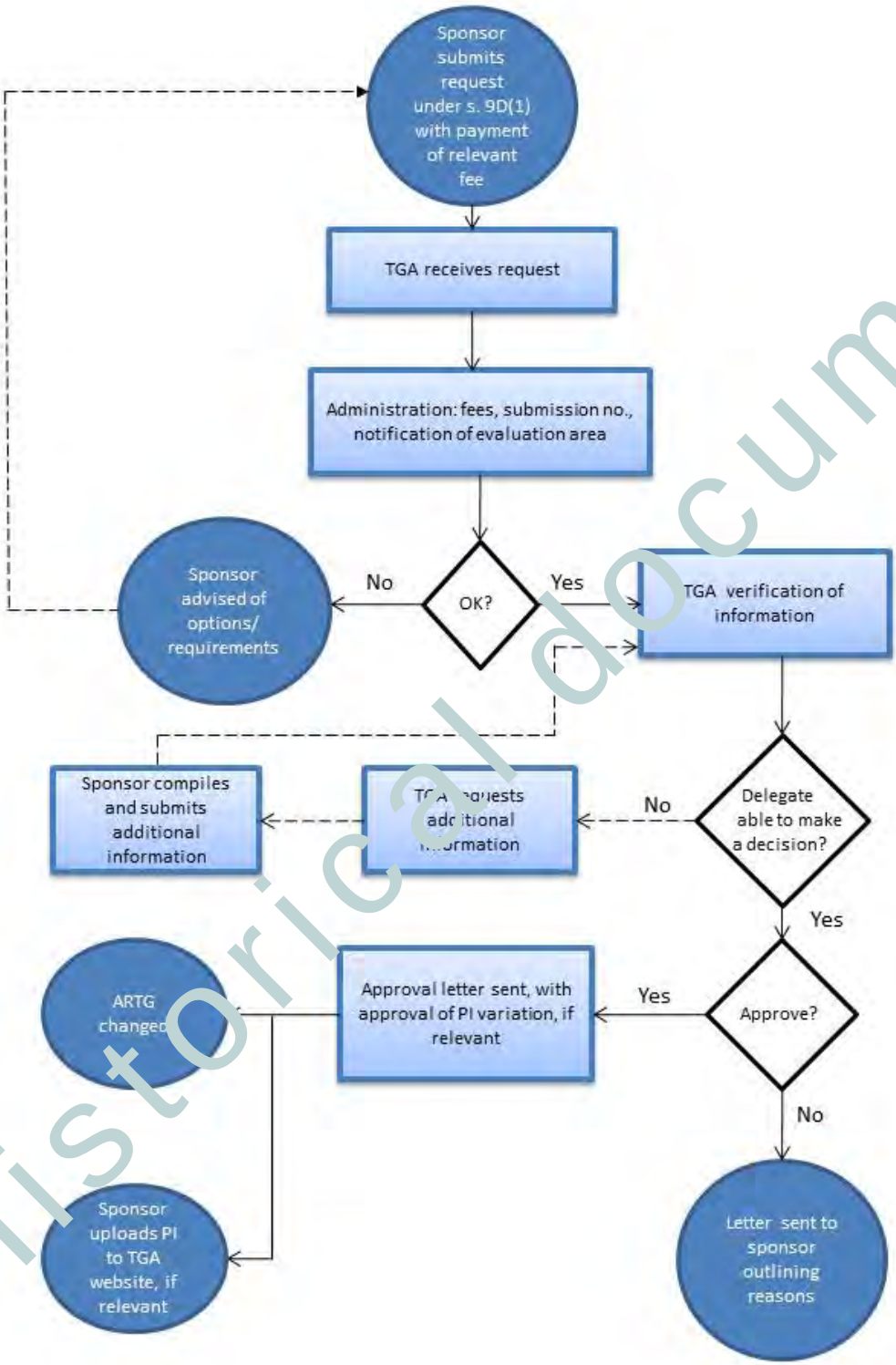
If the Secretary proposes to vary the entry on his or her initiative, a letter will be sent to the sponsor informing them of the decision.

2.4 Summary of variations under s. 9D(1)

Figure 2.1 shows a flowchart of the processes for making a decision under s. 9D(1).

Historical document

Figure 2.1 Process for requesting corrections to ARTG entries under s. 9D(1) of the *Therapeutic Goods Act 1989*

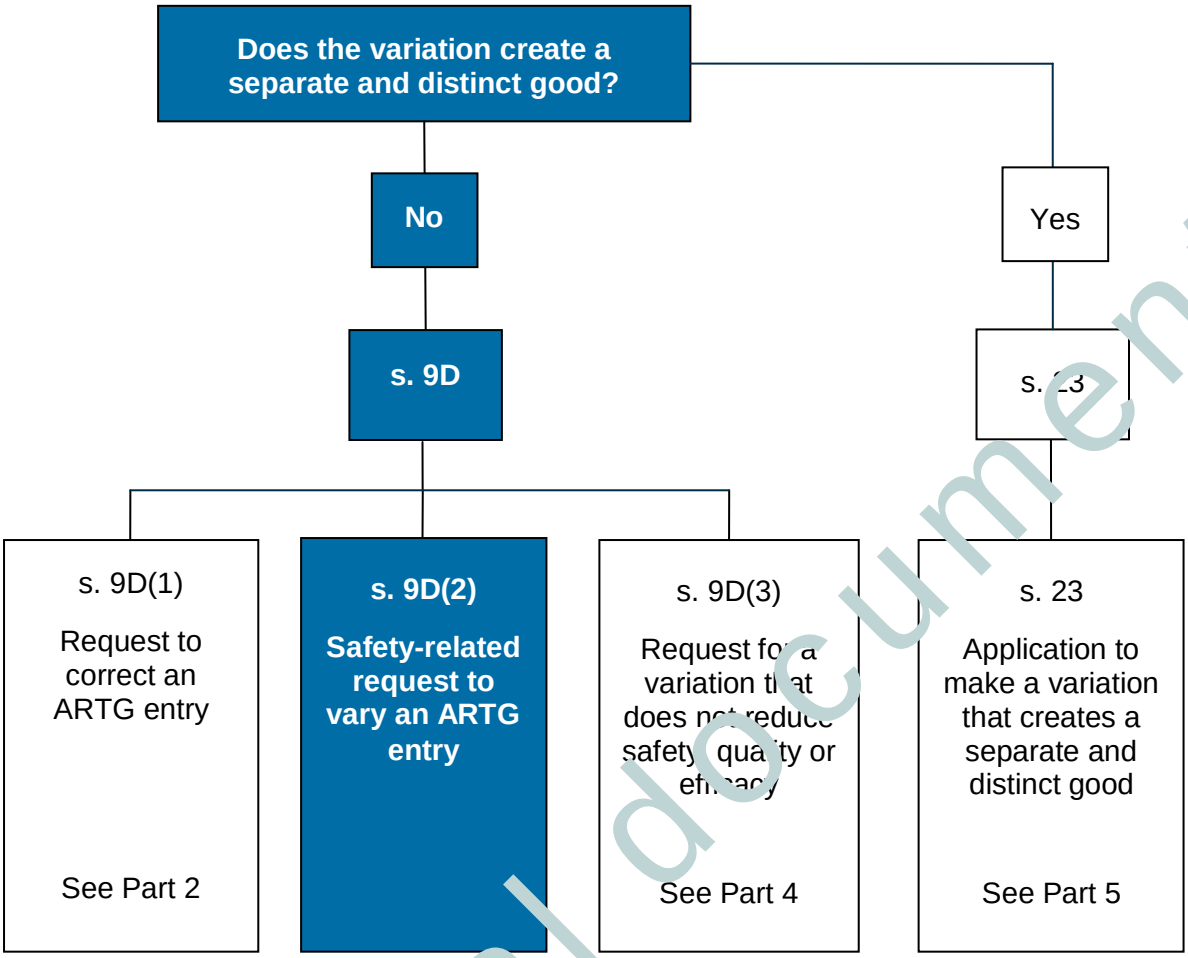


ARTG = Australian Register of Therapeutic Goods; PI = product information; TGA = Therapeutic Goods Administration

Historical document

Part 3
Making a safety-related request to vary an entry in the Australian Register of Therapeutic Goods: s. 9D(2)

Historical document



Some variations under s. 9D(2) require supporting data; others do not. This is assessed on a case-by-case basis		
Level of assessment	**Application type**	**Timeframe (working days)**
Verification of details provided by the sponsor	Safety-related request	No statutory timeframe (TGA processes as soon as possible)
Evaluation of data submitted to the TGA	Safety-related request with data	No statutory timeframe (TGA processes as soon as possible)

ARTG = Australian Register of Therapeutic Goods; TGA = Therapeutic Goods Administration

Historical document

3.1 What is a safety-related request?

A safety-related request to vary an entry in the Australian Register of Therapeutic Goods[28] (ARTG) is one where the variation has one of two possible outcomes:

- to reduce the patient population that can receive the medicine (for example, remove an indication or limit the use of the medicine)
- to add a warning or precaution (for example, an adverse effect or interaction).

These two types of variations are discussed further below. Safety-related requests must be made under s. 9D(2) of the *Therapeutic Goods Act 1989*[29] (TG Act). Requests are assessed on a case-by-case basis and the proposed variation must meet the criteria of being safety-related. Sponsors should be able to justify how a request meets these criteria. Safety-related variations always require changes to the product information (PI).

Variations that reduce the patient population

These types of safety-related variations reduce the number of people who can take the medicine. In most cases, the TGA only needs to verify the details of the request. Examples include:

- removing an indication[30]
- restricting use of the medicine to certain patient groups (for example, patients within a particular age range)
- adding certain contraindications (for example, contraindicated in patients with renal impairment).

Additions approved to the PI that provide further information from clinical trials relating to the patient population (including quantitative information), but not linked to a request to reduce the number of people taking the medicine, cannot be approved as a safety-related request.

Variations that add a warning or precaution

Warnings and precautions

Proposed changes to an ARTG entry (and/or the approved PI for a product) can have the effect of adding a warning or precaution without actually using the words 'warning' or 'precaution'. For example, adding 'oedema' or 'dizziness' to a list of adverse effects in the PI will have the effect of warning prescribers about a risk associated with the product. These types of changes meet the criteria of s. 9D(2) and are considered to be 'safety-related'.

[28] <http://www.tga.gov.au/industry/artg.htm>
[29] <http://www.comlaw.gov.au/Series/C2004A03952>
[30] Note that under s. 9D(2A) of the TG Act, changes to indications made under s. 9D(2) do not create a separate and distinct good and do not require an application to be made under s.23 of the TG Act.

Historical document

Examples of variations that have the effect of adding a warning or precaution are:

- adding a clearly identified warning or precaution
- adding an adverse effect
- adding an interaction
- adding a contraindication
- restricting or reducing use of the medicine to a specified period of time (for example, the medicine must only be taken for 2 weeks)
- changing the 'Use in pregnancy' category to a more restrictive classification
- increasing the frequency of a known adverse effect (for example, changing from 'common' to 'very common') or upgrading its severity (for example, moving it from the 'Adverse effects' to the 'Precautions' sections of the PI)
- specific warnings about handling, storage or disposal of a product.

Variations that don't add a warning or precaution

Not all adverse effects, contraindications and so on will meet the criteria of being safety-related. All proposed variations are assessed on a case-by-case basis to determine whether they are in fact safety-related within the meaning of s. 9D(2).

Examples of variations that do **not** have the effect of adding a warning or precaution are:

- a change that may unintentionally broaden the use of the product (for example, a statement that patients with impaired liver function should not take the medicine for an unapproved indication may imply that people with healthy livers can use the medicine to treat the unapproved indication)
- adding a warning, precaution or claim that compares the medicine with another medicine of the same class (for example, product A is less toxic than product B)[31]
- adding information on appropriate medical treatment of overdose, unless recommended by the TGA or Therapeutic Guidelines[32]
- adding modifying phrases which reduce the impact of a warning (for example, adding a statement such as 'no causal relationship has been established').

If the proposed change is a simple addition of a short, qualitative word or phrase (for example, adding an adverse effect such as 'headache'), verification of the details by the TGA is sufficient for approval. However, sponsors should be able to provide the TGA with data to support the proposed change if the TGA requests it.

[31] Section 9D(2) expressly excludes warnings or precautions that includes a comparison of the goods with any other goods by reference to quality, safety or efficacy—see s. 9D(2)(b)(ii).
[32] <http://www.tg.org.au/>

Historical document

Variations requiring evaluation of data by the TGA

If the proposed change is more than adding a simple word or phrase to the approved PI, or is intended to reflect findings from a clinical trial or other type of study, the TGA may need to evaluate supporting data. This will be determined on a case-by-case basis. However, the request will still be processed as a safety-related request, and not as part of the Streamlined Submission Process, provided it meets the criteria of s. 9D(2). Examples of cases where supporting data may be needed are where the proposed variation:

- includes a clarification, discussion or description of the variation (for example, the clinical significance of the variation). If a finding has potential safety implications, these should be clearly stated as a warning or precaution, without any subsequent explanatory text, statements such as 'the clinical significance of the finding is unknown' are not sufficient as a warning or precaution without evaluation of supporting data
- includes quantitative data (describing values or incidence of certain findings)
- describes a detailed causal relationship, including clinical significance
- adds detailed information on interactions with other medicines.

If a request is not safety-related, as described above, it may be able to be approved through a separate request under s. 9D(3), if the quality, safety and efficacy of the product are not reduced. An example of a change to the PI requiring evaluation of data that is not likely to meet the criteria of s. 9D(2) (and will therefore need to be submitted as a Category 1 application) is adding clinical trial information relating to efficacy rather than safety, such as meta-analysis from from clinical trials without accompanying safety statements.

See Part 4 for more information about changes under s. 9D(3).

3.2 Changes to the product information for safety-related requests

Usually, the only variation being requested under s. 9D(2) is a change to the PI. Proposed changes to the approved PI that meet the criteria of being safety-related must be identified as safety-related requests and submitted using the appropriate form. If proposed changes to the PI that are safety-related are identified during evaluation of a Category 1 application (Streamlined Submission Process[33]), the sponsor may be asked to submit a separate safety-related request under s. 9D(2). Following the incorrect process is likely to cause delays in approval of important safety-related changes to the product.

See Section 1.4 for general information on changes to the product information.

[33] <http://www.tga.gov.au/industry/pm-ssp.htm>

Historical document

3.3 How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit a request. The TGA can provide advice on general requirements for the request and relevant parts of the legislation, but cannot provide detailed, specific information about a particular request until it has been lodged.

Further information is also on the TGA website[34]

Sponsors can lodge safety-related requests by downloading the form 'Safety related request (SRR): Request to vary an ARTG entry under subsection 9D(2)' from the TGA website. The completed form, together with any required information or documents, and the relevant fee, should be sent to:

Application Entry and Support Team
Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Some safety-related requests may be urgent—for example, if the subject of the variation poses a serious risk to public health. Sponsors should identify urgent requests so that the TGA can process them as quickly as possible. An urgent request should be submitted as a stand-alone request under s. 9D(2), and not with other requests such as a self-assessable request under s. 9D(3). Sponsors are also able to notify healthcare professionals about any safety concerns regarding a product; for example, during discussions about the request with the TGA during the approval process.

The TGA may also ask sponsors to submit a safety-related request (see Section 3.4).

What do I need to provide?

For each request, the sponsor should provide **all** of the following:

- a completed 'Safety-related request (SRR): Request to vary an ARTG entry under subsection 9D(2)' form outlining each proposed variation to the ARTG entry, with justification for its request under s. 9D(2)
- clean and marked-up copies of the approved PI (see Section 1.4 of this document)
- a table, provided as an attachment to the form, outlining each of the proposed changes to the PI with brief explanatory text, including justifications
- an assurance that the only changes being made to the ARTG entry and PI are those identified in the request

[34] <http://www.tga.gov.au>

Historical document

- the relevant fee (see 'What fees do I pay?', below).

In addition, the sponsor should provide **either**:

- an assurance that the sponsor has data to support the proposed changes that can be provided to the TGA on request

  or

- relevant data to support the proposed changes in common technical document (CTD) format (see 'Submission of supporting information', below), if applicable.

Submission of supporting information

In some cases, the Secretary needs more information to decide if a request meets the criteria of s. 9D(2), and is therefore considered to be 'safety-related'. For example, a sponsor may want to add a statement to the 'Precautions' section of the PI because a clinical trial showed that some patients are at higher risk of a particular adverse event. The Secretary may want to evaluate the sponsor's supporting data to ensure that the proposed addition to the PI is accurate and appropriate, and may ask the sponsor to provide this information. This type of request will still be processed by the TGA as a safety-related request (with evaluation of data).

Any supporting information provided by the sponsor should meet the requirements of the relevant European Medicines Agency (EMA)/International Conference on Harmonisation (ICH) guidelines[35] that have been adopted by the TGA.

The sponsor can also provide supporting information without being requested to do so by the Secretary. This is appropriate for complex issues such as adding a warning based on data from clinical trials, or adding quantitative information to describe an adverse effect.

If sponsors are not sure which approach to take, they should contact the TGA. A higher fee applies to requests with supporting information that needs to be evaluated. (See 'What fees do I pay?' for more information about applicable fees.)

All data submitted to support a safety-related request should be prepared in the most recent version of the CTD format. Only data that are relevant to the proposed variation should be included, and the sponsor only needs to submit a single copy of the data. Refer to the TGA website for additional guidance on Australia-specific requirements for CTD submissions[36].

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the Therapeutics Goods Regulations 1990. These fees are subject to change from time to time; current fees are published on the TGA website.

Two levels of fees apply to safety-related requests to vary an ARTG entry under s. 9D(2). The fee the sponsor pays depends on the level of assessment required for the Secretary to make a decision. In most cases, the TGA can make a decision based on the sponsor's own assessment of the variation, and no supporting data are required. Item 2A of Part 2 of Schedule 9 applies to these requests.

[35] <http://www.tga.gov.au/industry/pm-euguidelines.htm>
[36] <http://www.tga.gov.au/industry/pm-ctd.htm>

Historical document

Where the TGA needs to evaluate supporting data to make a decision, a higher fee applies. This is in item 2CA of Part 2 of Schedule 9. In some cases, the TGA may determine that it needs to evaluate supporting data during the course of assessing a safety-related request. If there are multiple changes being requested under s. 9D(2) in the same submission, the TGA will approve any of the changes that do not require evaluation of data. Any other changes that require evaluation of supporting data should be lodged in a separate submission. If all proposed changes require evaluation of supporting data, the sponsor will be invoiced for the balance of the higher fee not yet paid. This fee should be paid when the relevant data are submitted. A new request does not need to be made.

What are the timeframes?

There is no statutory timeframe for safety-related requests. However, because approved safety-related requests are expected to improve the safety of a medicine, the TGA tries to process these requests as quickly as possible. This depends on the nature and urgency of the request: variations relating to major public health concerns are given the highest priority. Sponsors are also able to notify healthcare professionals about any safety concerns regarding a product; for example, during discussions about the request with the TGA during the approval process.

The TGA processes stand-alone safety-related requests as a priority over safety-related requests that are submitted with other requests (such as a request for 'minor editorial changes' under s. 9D(3)). Sponsors are therefore encouraged to submit safety-related requests separately from other types of requests.

Safety-related requests should **not** be included in streamlined submission process applications, that is, Category 1 and 2 applications. Following the incorrect process is likely to cause delays in approval of important safety-related changes to the product.

What happens to my request?

If all the requirements for a safety-related request have been met, including payment of the appropriate fee, the request is referred to the relevant TGA evaluation area for assessment. If a requirement has not been met (for example, the sponsor has not included a correctly marked-up copy of the proposed new PI), the sponsor will be asked to submit the required information before the request can be processed. This will not change the fees payable.

If the Secretary is sure that the proposed variation is safety-related (that is, will reduce the patient population that can take the medicine, or have the effect of adding a warning or precaution), it must be approved. In most cases, verification of the information provided in the sponsor's self-assessment will be sufficient for a decision. Verification involves a brief review of the information provided, including any proposed changes to the PI, to confirm the nature of the proposed variation. It also usually includes discussions between the Secretary's delegate and the sponsor to ensure that the most appropriate wording is used in any changes to the PI.

If the Secretary needs supporting data to make a decision (whether the data are submitted at the TGA's request or on the sponsor's own initiative), the evaluation will be conducted according to guidelines and procedures set out in the ARGPM and other relevant guidance (for example, relevant EMA guidelines).

See 'What do I need to provide?' for more information about supporting information.

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the request at the time of submission. Any new

Historical document

information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the variation to the ARTG entry is approved, the entry will be updated and any necessary changes to the PI will also be approved under s. 25AA(4) of the TG Act. Sponsors should lodge copies of the updated PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[37] system within 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 9D(2) and s. 25AA(4) are subject to review under s. 60 of the TG Act.

If the Secretary is not satisfied that the proposed variation is safety-related, the request will be rejected. The person making the request will be sent a letter outlining the decision. Reasons for the decision will be provided if the request is rejected.

Sponsors can withdraw their request at any time during the process but fees are not refundable.

3.4 Safety-related variations identified by the TGA

If the TGA identifies the need for a safety-related variation to a product in a sponsor's range, and a consequential change to the approved PI, it can initiate discussions with the sponsor about safety-related requests. This may be to align the approved PI with other PIs for products that contain the same active ingredient, or if a signal is identified during postmarket monitoring of the medicine. The processes and requirements described in this section, including fees, also apply to safety-related variations identified by the TGA.

Alignment of product information approved for the same active ingredient

To ensure that the information that is available to healthcare professionals and the public is consistent, all approved PIs for registered prescription medicines containing the same active ingredient should be comparable in terms of the safety information provided. If a change to a PI is approved, such as following a safety-related request, the TGA encourages sponsors to ensure that the approved PIs of all other related products are similarly updated by the same process.[38]

Changes to the product information based on postmarket monitoring

Additional safety information about a product often becomes available after the product has entered the marketplace. The TGA may identify a signal during postmarket monitoring and decide that a safety-related variation is appropriate. In this case, the TGA usually contacts the sponsor directly to discuss the requirements, and the specific statements that should be added or removed from the approved PI. In some instances, the TGA may evaluate data provided by

[37] <https://www.ebs.tga.gov.au/>
[38] It is a specific condition of registration that the product information for generic products be updated within one month of safety-related changes made by the innovator.

Historical document

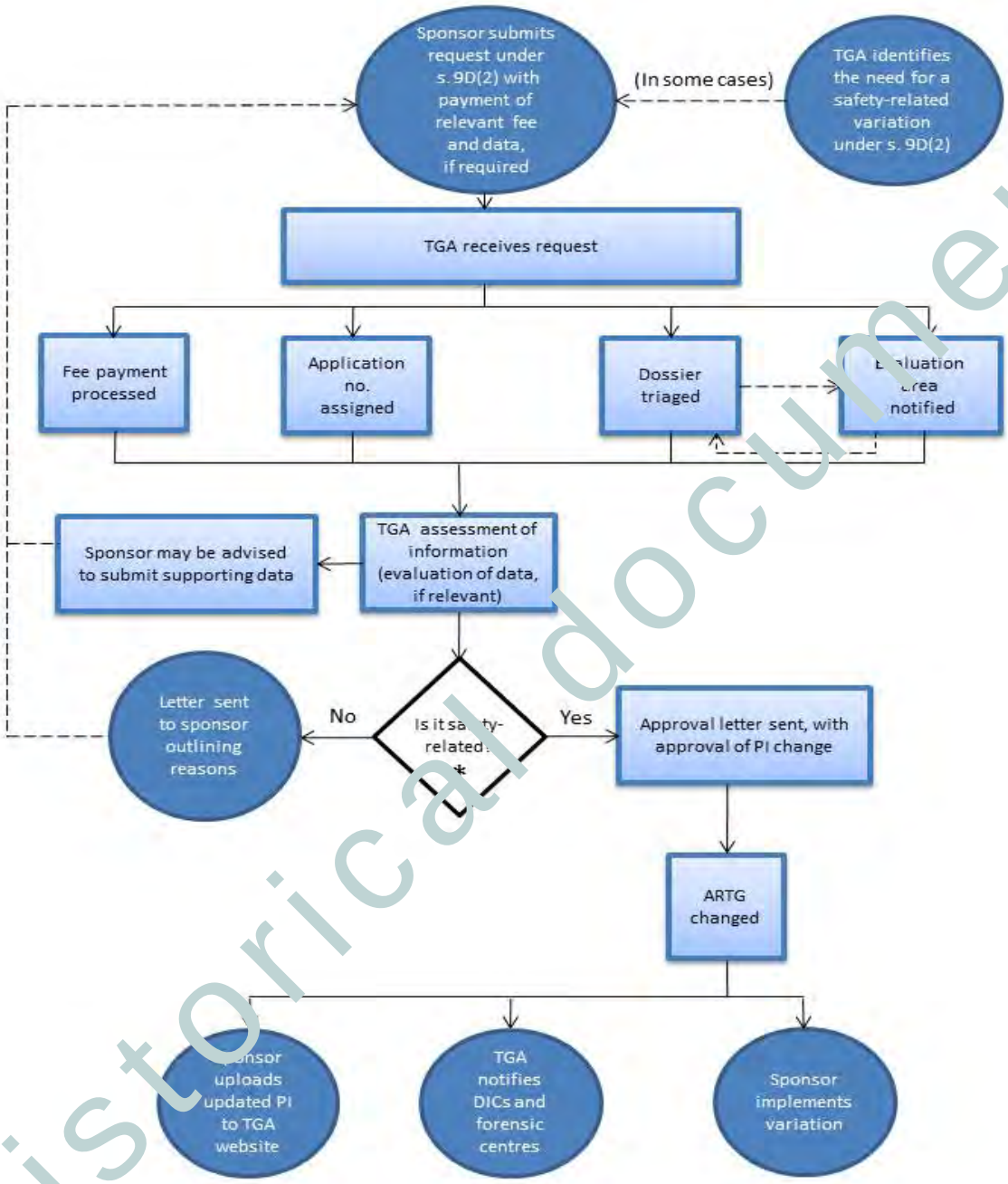
the sponsor to be satisfied that the appropriate warning will be added to the PI. Once this is finalised, the TGA will ask the sponsor to submit a safety-related request, with the appropriate fee, depending on whether or not data were evaluated. The variation to the ARTG entry will then be formally approved, along with the consequential change to the PI.

3.5 Summary of safety-related variations under s. 9D(2)

Figure 3.1 shows a flowchart of the processes for making a decision under s. 9D(2).

Historical document

Figure 3.1 Process for requests under s. 9D(2) of the *Therapeutic Goods Act 1989*



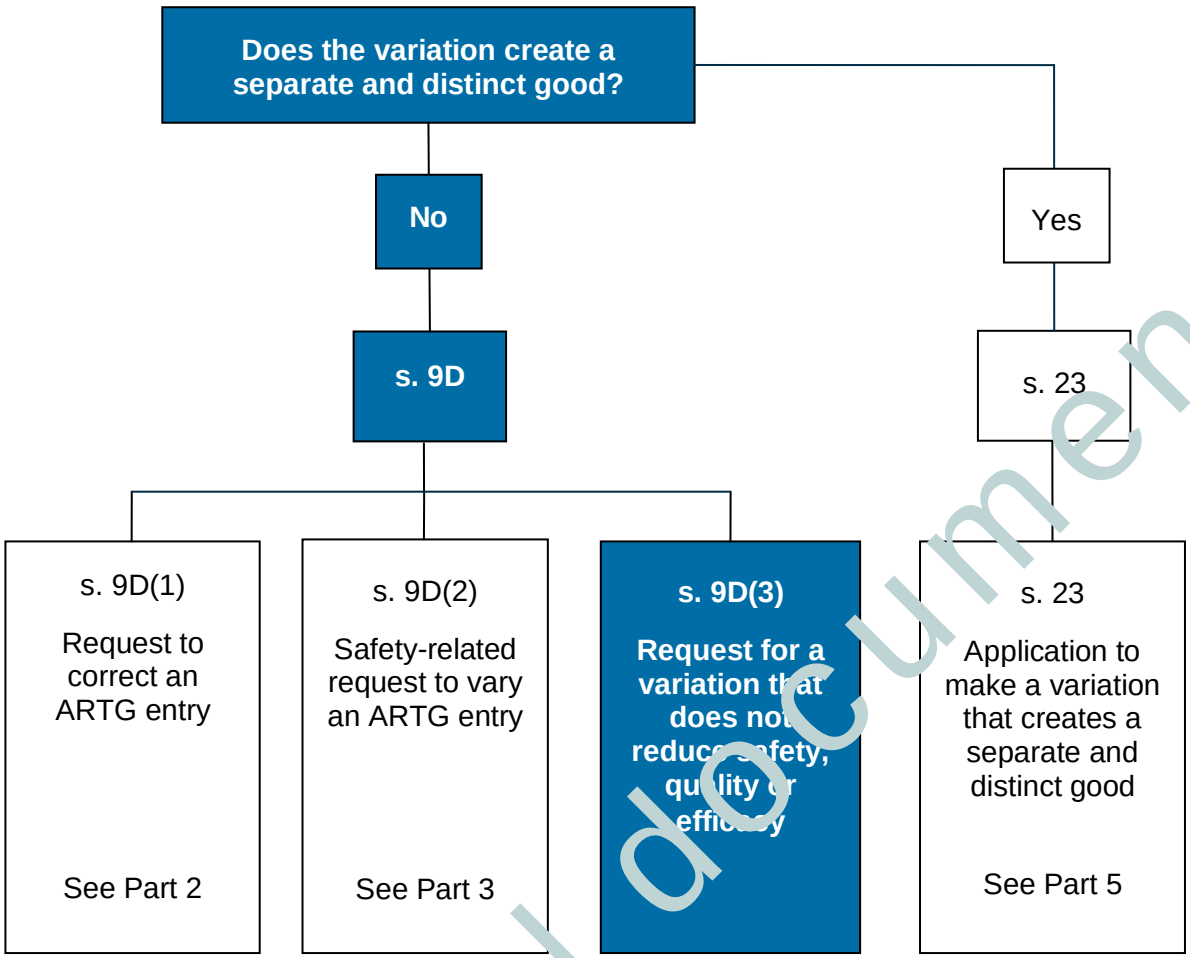
ARTG = Australian Register of Therapeutic Goods; DIC = drug information centre; PI = product information; TGA = Therapeutic Goods Administration

* The delegate will make a decision on as many parts of a single request as possible, and any parts requiring TGA evaluation of data will be lodged in a separate submission.

Historical document

Part 4
Requesting a variation that does not reduce quality, safety or efficacy: s. 9D(3)

Historical document



Some variations under s. 9D(3) are self-assessable; others require data to be submitted to the Therapeutic Goods Administration for evaluation		
Level of assessment	**Application type**	**Timeframe**
Verification of details provided by the sponsor	Self-assessable request to vary an ARTG entry	45 working days
Evaluation of quality data only	Category 3 application: variation to ARTG entry	45 working days
Full evaluation (combination of clinical, nonclinical, bioequivalence and quality data)	Category 1 or Category 2 application: variation to ARTG entry with consequential PI change (streamlined submission process). Refer to the ARGPM for guidance on these application types	255 working days for Category 1; 175 working days for Category 2

ARTG = Australian Register of Therapeutic Goods; PI = product information

Historical document

4.1 What types of variations are covered under s. 9D(3)?

Variations to registered prescription medicines that are not safety-related (that is, do not meet the criteria for a safety-related request under s. 9D(2)) can be made under s. 9D(3) of the *Therapeutic Goods Act 1989*[39] (TG Act), provided that the variation **does not:**

- reduce the quality, safety or efficacy of the product
- create a separate and distinct good.

Most minor variations made under s. 9D(3) relate to the quality of registered prescription medicines. Some requests under s. 9D(3) only involve making consequential changes to the product information (PI). Some PI changes may require evaluation of nonclinical, clinical or bioequivalence data as a Category 1 or 2 application (see below).

For more information about safety-related requests to vary entries in the ARTG, see Part 3.

For more information about variations that create separate and distinct goods, see Part 5.

There are two application routes for requests to change only the quality aspects of registered prescription medicines:

- **Requests that require submission of data**
  Most s. 9D(3) requests are quality related and require a Category 3 application and evaluation of relevant quality data by the Therapeutic Goods Administration (TGA). Requests that require evaluation of nonclinical, clinical or bioequivalence data will require a Category 1 or 2 application under s. 9D(3) under the Streamlined Submission Process[40].
- **Requests that can be assessed by the sponsor (self-assessable request)**
  If requested variations are considered to be minor by the TGA, sponsors can assess the supporting data themselves and then make a request to the TGA based on this self-assessment. Minor changes must be appropriately validated as unlikely to reduce the safety, quality or efficacy of a medicine (in fact, some proposed variations can improve the quality of the product). Requests should meet specific conditions to be considered self-assessable. The sponsor must then make a request for approval of the variation, but must provide the supporting data if requested to do so by the TGA.

Section 4.2 of this document outlines the self-assessable requests that can be made under s. 9D(3) of the TG Act and their specific conditions.

Section 4.3 of this document outlines the variations under s. 9D(3) that require data to be submitted to the TGA for evaluation as Category 3 applications.

See the *Australian Regulatory Guidelines for Prescription Medicines*[41] (ARGPM) for more information about Category 1 and Category 2 applications.

[39] <http://www.comlaw.gov.au/Series/C2004A03952>
[40] <http://www.tga.gov.au/industry/pm-ssp.htm>
[41] <http://www.tga.gov.au/industry/pm-argpm.htm>

Historical document

Approval

The Secretary's approval is required for all variations under s. 9D(3) of the *Therapeutic Goods Act 1989*[42]. This means that, even if the data to support the proposed variation do not have to be evaluated by the TGA (and the approval is based on the sponsors' self-assessment of the proposed change), the variation must be formally approved before it can be implemented.

If a sponsor decides not to implement a quality-related variation after it has been approved, they should notify the TGA as soon as possible.

4.2 Self-assessable requests

Conditions for self-assessable requests

All self-assessable requests should be made using the procedures outlined in this section and receive the Secretary's approval before the variation is implemented.

Sponsors should comply with the general requirements in this section and all the specific conditions listed for each proposed variation.

The TGA reserves the right to request copies of the experimental (validation) data at its discretion, and to follow up the validation during an inspection of the manufacturing site.

This section outlines the general requirements for making self-assessable requests, as well as the specific conditions for different types of variations.

The validation data specified in this document are the minimum requirements, and any additional necessary validation (for example, to comply with the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme [PIC/S] *Guide to Good Manufacturing Practice for Medicinal Products*[43]) must also be conducted. If validation data are needed to support a variation, these data may be generated using either pilot plant–scale or full-production batches of the product,[44] except for variations to batch size, where the data should be generated from full production-scale batches. The use of pilot scale batches should be justified.

If the validation tests show a difference between pre-variation and post-variation batches, an appropriate Category 3 application for evaluation should be made (see Section 4.3) unless otherwise allowed in this document or agreed to by the TGA.

[42] <http://www.comlaw.gov.au/Series/C2004A03952>
[43] <http://www.tga.gov.au/industry/manuf-pics-gmp-medicines.htm>
[44] The role of pilot-scale batches is to provide data that are predictive of the production-scale product. These may be used in the process development phase, to support formal stability studies, and to support nonclinical and clinical evaluation. The choice of pilot batch size should be justified.

Historical document

Depending on the nature of the variation and the significance of the differences in results, additional data—such as information on bioavailability, clinical safety or efficacy—may be needed. The application will then become a Category 1 or 2 application. If this was the case, sponsors would need to submit a new application in the Streamlined Submission Process.

It is not mandatory for sponsors to use the self-assessment procedure. Any proposed variations to registered medicines may be submitted as a formal Category 3 application for evaluation, in which case the normal data requirements and evaluation fee will apply.

General requirements

The following general requirements always apply to self-assessable requests and the sponsor must ensure that they comply.

- The product must be registered in the ARTG.
- No request for a variation that requires TGA evaluation of data should be submitted as a self-assessable request.
- All of the validation data specified for each proposed variation must have been generated.
- Experimental (validation) data must be supplied to the TGA if requested.
- Validation data must be provided upon request during a good manufacturing process (GMP) inspection.
- The person signing the form must be an authorised officer with access to the supporting data.

How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit a request. The TGA can provide advice on general requirements for the request and relevant parts of the legislation, but cannot provide detailed, specific information about a particular request until it has been lodged.

Further information is also on the TGA website[45]

What do I need to provide?

Self-assessable requests should be accompanied by **all** of the following:

- a completed 'Self-assessable request (SAR): Request to vary an ARTG entry under subsection 9D(3)'

[45] <http://www.tga.gov.au>

Historical document

- an assurance that the only variations being made to the ARTG entry are those identified in the request, and that no other aspects of the quality information have been changed, including manufacturing procedures and equipment, and raw material and drug product specifications
- a statement that all of the general requirements and all of the applicable specific conditions have been complied with
- if relevant, clean and marked-up copies of the proposed PI (see Section 1.4 of this document)
- relevant evidence of GMP (clearance letter if an overseas site of manufacture is involved, or Australian manufacturing licence), if this is a condition of self-assessment
- any other information specified as 'Required information' for that type of change (see subsequent sections)
- the relevant fee (see 'What fees do I pay?', below).

The form 'Self-assessable request (SAR): Request to vary an ARTG entry under subsection 9D(3)' is available on the TGA website; all sections of the form should be completed. The completed hard copy of the form should be signed by the person who is taking responsibility for ensuring that all of the general and specific conditions relevant to the proposed variation have been complied with, and any specified validation data have been generated and self-assessed by the sponsor as acceptable.

The form, together with any covering letter, required information or documents, and the relevant fee, should be sent to:

Application Entry and Support Team
Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Note that any validation or experimental data that were generated for self-assessment purposes should not be submitted with the request. However, these data may be requested by the TGA for review at a later date. Depending on the type of variation proposed, different types of self-assessable requests require different types of information. Details of these specific requirements are provided in the relevant subsections of Section 4.2 of this document. The information should relate only to the specific variations requested; no other data should be provided.

It is a condition of registration that variations cannot be implemented without prior approval by the TGA. If a minor variation is implemented without approval (refer to Section 1.5), a category 3 application, including payment of any applicable evaluation fee, will be required to regularise the change, and the full validation data will be required for evaluation. Breaching the conditions of registration of a product can result in penalties and/or cancellation of the registration of the product by the Secretary under s. 30(2) of the TG Act. **Self-assessment is not a means of regularising unauthorised changes made to registered medicines.**

All self-assessable variations that are approved by the TGA will be documented as approved variations to the entry in the ARTG of the product under the provisions of s. 9D(3) of the TG Act.

If the type of change does not meet the criteria of a self-assessable request or not all of the specific conditions have been met, the request cannot be approved because the correct

Historical document

procedures have not been followed. Sponsors will be advised to submit the correct form '[Category 3 application: Request to vary an ARTG entry under subsection 9D(3)]' and the necessary supporting information in a new request, if they still wish to vary the ARTG entry.

For information on requests under s. 9D(3) that require data, see [Section 4.3].

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the [Therapeutic Goods Regulations 1990][46]. These fees are subject to change from time to time; [current fees][47] are published on the TGA website. The fees for self-assessable requests under s. 9D(3) are listed at item 2A(a).

What are the timeframes?

Under regulation 16F of the Therapeutic Goods Regulations 1990, which applies to all requests under s. 9D(3) that do not require TGA evaluation of clinical, nonclinical or bioequivalence data, the Secretary must make a decision about the request and notify the sponsor within 45 working days of receiving the request and payment (whichever is later) or, if necessary, raise an objection concerning the application (refer to [Section 1.2]). An objection usually means that the Secretary will ask the sponsor questions about the product that are necessary for them to make a decision about the request, to which the sponsor must respond.

If an objection is raised by the Secretary, the clock will stop from the time the objection is raised (that is, the matter is raised with the sponsor), and will start again when the TGA receives the response to the objection from the sponsor. The Secretary then has 30 working days from the day on which they receive the response to notify the sponsor of the decision.

If the Secretary does not make a decision within the 45 working day timeframe (or subsequent 30–working day period after a response to an objection), the request is taken to have been approved.

What happens to my request?

If all the requirements for a self-assessable request have been met, including payment of the appropriate fee, the request is referred to the relevant TGA evaluation area for assessment. If a requirement has not been met (for example, the sponsor has not included a correctly marked-up copy of the proposed new PI), the sponsor will be asked to submit the required information before the request can be processed.

When all the necessary information has been received by the TGA (including payment), the clock starts on the application. The TGA verifies the sponsor's self-assessment of the variation and approves the request, if applicable. If the Secretary is not able to make a decision, the clock stops while the TGA asks for information under s. 31 of the TG Act or raises an objection (see above). The clock restarts on receipt of the complete response to the request for information. There is no limit on the number of clock stops under s. 31. The person making the request will be sent a letter outlining the decision about the proposed variation when it is made. Reasons for the decision will be provided if the request is rejected.

[46] <http://www.comlaw.gov.au/Series/F1996B00406>
[47] <http://www.tga.gov.au/about/fees.htm>

Historical document

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the request at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the variation to the ARTG entry is approved, the entry will be updated and any necessary changes to the PI will also be approved under s. 25AA(4) of the TG Act. Sponsors should lodge copies of the updated PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[48] system within 2 weeks 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 9D(3) and s. 25AA(4) are subject to review under s. 60 of the TG Act.

Sponsors can withdraw their request at any time during the process but fees are not refundable.

Historical document

[48] <https://www.ebs.tga.gov.au/>

Types of self-assessable requests

The types of quality-related changes listed on the following pages are considered self-assessable, provided that the relevant specific conditions are met. The specific information that needs to be provided with the request for each type of change is also detailed below.

It includes the following broad categories of quality-related variations under s 9D(3):

A Changes to the drug substance or excipients

B Changes to drug product specifications

C Change to the site of product manufacture

D Replacement of an in-house reference standard

E Establishment of a new working cell bank or seed lot

F Changes to the quality aspects of the product information

G Changes to product labels

H Changes to the pack size

I Changes to fermentation processes

J Changes to purification processes

K Changes to storage of the drug substance

L Changes to filling

M Changes to packaging

N Changes to the shelf life or storage conditions of the drug product

O Changes to plasma fractionation intermediates

P Changes specific to influenza vaccines

Q Other changes

Historical document

The guidance provided below is in addition to the information in 'How to apply to the TGA', above.

Note on certified product details (CPD) documents

An updated CPD document is usually provided when a change is made to aspects of the drug product specifications, such as test requirements, limits of acceptance or non-pharmacopoeial test methods.

If a self-assessable request results in changes to the product specifications or the non-pharmacopoeial test methods, an updated and complete CPD document should be provided in PDF format after approval of the variation. See Appendix 7 of the *Australian Regulatory Guidelines for Prescription Medicines*[49] (ARGPM). Templates for providing CPDs are available on the TGA website.

Updates to pharmacopoeial monographs

Section 3 of the TG Act lists three pharmacopoeias that are defined as 'default standards' used to specify the quality, method of manufacture and other aspects of therapeutic goods. These are the British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia—National Formulary.

Pharmacopoeial monographs may be available for any of the following:

- a particular ingredient or raw material, for example digoxin
- a particular drug product, for example digoxin tablets
- general monographs applying to groups of products, for example tablets.

They may also relate to matters other than tests and limits, for example guidance about viral safety.

These monographs may be updated from time to time. A given product must comply with the applicable official standard at the time the batch of product is supplied by the sponsor. Sponsors therefore need to seek prior TGA approval (by SAR) for the implementation of changes consequent to pharmacopoeial updates, before any relevant product is supplied.

[49] <http://www.tga.gov.au/industry/pm-argpm.htm>

Historical document

A Changes to the drug substance or excipients

The following changes to vary the drug substance, starting materials, intermediates or excipients in the drug product are self-assessable:

A1 More stringent limits for test results

A2 Addition of a new test and limit to the existing specifications

A3 Changes resulting from amendments to pharmacopoeial requirements or the requirements of therapeutic goods orders

A4 Change to equipment used for quality control testing

A5 Change to assay method

A6 Change to the method for determining the content of residual solvents, including water

A7 Change to the method of analysis of non-biological excipients for biological medicine products

A8 Minor changes to physicochemical tests for excipients

A9 Change to source, manufacturing process or site of manufacture of excipients derived from Category C ruminant tissues

A1 More stringent limits for test results

Limits for test results may be made more stringent within the existing specifications provided that this does not change the composition of the substance. An example of a change that might alter the substance is narrowing the test limits for isoelectric point, which could result in omission of a charge isoform of a protein.

Specific conditions

- The proposed limits must be consistent with any applicable official standard or guidelines adopted by the TGA.

Required information

- The revised set of specifications for the substance.
- An updated certified product details (CPD) document, if applicable (see box 'Note on certified product details [CPD] documents', above).

A2 Addition of a new test and limit to the existing specifications

The test should be relevant and appropriately validated.

Historical document

Specific conditions

- Appropriate validation data should have been generated for the test method.
- The limits proposed should be based on batch analytical data and must comply with any applicable official standard or relevant guidelines.

Required information

- Details of the test method.
- The revised set of specifications for the substance.
- An updated CPD document, if applicable (see box 'Note on certified product details [CPD] documents', above).

A3 Changes resulting from amendments to pharmacopoeial requirements or the requirements of therapeutic goods orders

Sponsors must make a request to the TGA under s. 9D(3) before any necessary changes resulting from amendments to official standards are implemented. This can be submitted as a self-assessable request, provided that it meets the specific conditions listed below. If a substance complies with the requirements of an earlier edition of an official pharmacopoeia, such as the BP, it would be appropriate to substitute the requirements of the current edition of that pharmacopoeia. However, any tests that were performed in addition to those of the pharmacopoeial monograph should continue to be applied. Note that changing from the requirements of one pharmacopoeia to those of another, such as from the USP to the BP, is not covered by this section and may require evaluation of data by the TGA.

Specific conditions

- The change should not involve changing from the requirements of one pharmacopoeia to those of another.
- The new pharmacopoeial monograph or amended TGO must be applicable to the substance.

Required information

- The revised set of specifications for the drug substance.
- An updated CPD document, if applicable (see box 'Note on certified product details [CPD] documents', above).

A4 Change to equipment used for quality control testing

Specific conditions

- The change should meet previously approved validity criteria for the test method. Changes that do not meet previously approved validity criteria are not self-assessable, and the TGA will need to evaluate supporting data.
- Appropriate validation data should have been generated for the changed equipment using the previously approved criteria and, where applicable, the same validation protocol as was used for the previously approved equipment.

Historical document

- If the type or brand of consumables used with the equipment is critical (that is, included in the protocol), appropriate validation data should also be generated for the relevant consumables.

Required information

- Description of the new equipment.
- An updated CPD document, if applicable (see box 'Note on certified product details [CPD] documents', above).

A5 Change to assay method

Changes in the assay method are only self-assessable if an in-house assay method is replaced with a pharmacopoeial method. If there are differences in specifications between the two methods, the most stringent specifications should be maintained. Changes to viral safety testing are not self-assessable.

Specific conditions

- The method being changed must not be a viral safety testing method.
- The stringency of the specifications should not decrease as a result of the change.
- Batch analytical data for at least three commercial batches should have been generated to demonstrate compliance with the new test and limit.

Required information

- Details of the new method.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

A6 Change to the method for determining the content of residual solvents, including water

Specific conditions

- Appropriate validation data should have been generated for the proposed method.
- The new method should demonstrably improve precision, accuracy or specificity, without reducing any of these parameters. The one exception is that improved specificity or accuracy may be associated with reduced precision, but only if precision remains within the specified limits.

Required information

- Details of the new method.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

Historical document

A7 Change to the method of analysis of non-biological excipients for biological medicine products

Specific conditions

- The change should only be to a non-pharmacopoeial method of analysis. If tested according to a pharmacopoeial method, a change to the method of analysis of a non-biological excipient should not require prior approval.
- The change should demonstrably improve precision, accuracy or specificity, without reducing any of these parameters. The one exception is that improved specificity or accuracy may be associated with reduced precision, but only if precision remains within the specified limits.
- Appropriate validation data should have been generated for the proposed method.

Required information

- Details of the new test method.

A8 Minor changes to physicochemical tests for excipients

Specific conditions

- The change should be a minor change to methods for parameters such as pH, osmolality, hydration state, water content or spectrometry. Any other changes require evaluation of supporting data by the TGA (that is, a Category 3 request under s. 9D(3)).
- The proposed changes should meet pharmacopoeial requirements.
- The proposed changes should not include changes to specifications of excipients.

Required information

- A summary description of the change, and details of the new method.

A9 Change to source, manufacturing process or site of manufacture of excipients derived from Category C ruminant tissues

Category C ruminant tissues are defined in the current edition of the TGA's *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)*[50]. The variations outlined in this section are only applicable if the product is given by the oral, topical, vaginal, rectal or inhalation routes, and there is no potential for cross-contamination with higher risk (Category A or B) tissues.

Specific conditions

- The change should be from a ruminant-derived source to a plant or other non-animal source.
- The product should not be administered by the parenteral, ophthalmic or intra-tracheal routes.

[50] <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>

Historical document

- Either no changes to the specification of the excipients have been made, or the excipients have been changed as allowed in A1–A9, above.

Required information

- Details of the excipients and the proposed changes. Where relevant, current certificate of suitability (CEP) issued by the European Directorate for the Quality of Medicines and HealthCare (EDQM) to the manufacturer of the excipient. However, not all CEPs from the EDQM will be acceptable—this depends on the source country of the animal and the parts of the animal used to manufacture the excipient.
- A declaration that the Category C material has been self-assessed and complies with the TGA's requirements regarding TSE risks.
- An assurance that records of compliance will be maintained for future inspection by the TGA.
- The revised specification, if changes have been made.

Historical document

B Changes to drug product specifications

The following changes to drug product specifications are self-assessable:

B1 More stringent limits for test results within the existing specifications

B2 Addition of a new test and limit to the existing specifications

B3 Changes resulting from amendments to pharmacopoeial requirements or the requirements of therapeutic goods orders

B4 Change to equipment used for quality control testing

B5 Change to sterility test method

B6 Reduction or removal of overage

B7 Changes to dimensions, shape, inked imprint, or embossing and debossing of solid dosage forms

B8 Minor changes to physicochemical tests

B1 More stringent limits for test results within the existing specifications

Specific conditions

- The proposed limits must be either the same as, or more stringent than, any applicable official standard or relevant accepted guidelines.

Required information

- The revised set of specifications.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

B2 Addition of a new test and limit to the existing specifications

Specific conditions

- Appropriate validation data should have been generated for the new test method.
- The proposed limit (release and expiry) should be based on batch analytical data and should comply with, or be more stringent than, any applicable official standard or relevant accepted guidelines for such a test.

Historical document

- The test method should only be used at a registered quality control testing site that has appropriate GMP clearance.

Required information

- Details of the new test method.
- The revised set of drug product specifications (release and expiry).
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

B3 Changes resulting from amendments to pharmacopoeial requirements or the requirements of therapeutic goods orders

Sponsors must make a request to the TGA under s. 9D(3) before any necessary changes resulting from amendments to official standards are implemented. This can be submitted as a self-assessable request, provided that it meets the specific conditions listed below.

Specific conditions

- The new pharmacopoeial monograph or TGO should be suitable for the product and, if necessary, appropriate validation data should have been generated.
- The change should not involve changing from the requirements of one pharmacopoeia to those of another.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO should continue to be performed.
- The test method should only be used at a registered quality control testing site that has appropriate GMP clearance.

Required information

- The revised set of drug product specifications (release and expiry).
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).
- If the change involves updating microbiological test requirements for non-sterile products to meet TGO No. 77—Microbiological standards for medicines (TGO 77), the product should have undergone a risk assessment for objectionable microorganisms, in addition to those specified in the pharmacopoeias that form the basis of TGO 77. An assurance should be provided that the report of the risk assessment is available for review, if required by the TGA.

B4 Change to equipment used for quality control testing

Specific conditions

- The change should meet previously approved validity criteria for the test method. Changes that do not meet previously approved validity criteria are not self-assessable, and the TGA will need to evaluate supporting data.

Historical document

- Appropriate validation data should have been generated for the changed equipment using the previously approved criteria and, where applicable, the same validation protocol as was used for the previously approved equipment.
- If the type or brand of consumables used with the equipment is critical (that is, included in the protocol), appropriate validation data should also be generated for the relevant consumables.

Required information

- Description of the new equipment.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

B5 Change to sterility test method

Specific conditions

- All aspects of the test are in accordance with the requirements of the internationally harmonised test published in the BP, Ph. Eur. or USP and as specified in TGO 77.
- The test follows the guidelines on particular aspects of the sterility test in Appendix 17 of the ARGPM.
- Comparative batch data should have been generated using validated test methods.

Required information

- Details of the new test method.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

B6 Reduction or removal of overage

Specific conditions

- Stability testing of the product with reduced overage on at least three production batches of the post-variation product should show that all products meet specifications at the expiration date. This should be done according to International Conference on Harmonisation (ICH) requirements, and data should be made available to the TGA on request. Any failure to meet drug product specifications during the stability trials should be notified to the TGA as a priority. The TGA reserves the right to withdraw the product from the market if this requirement is not met.
- Any excipient involved should not be an antioxidant or another ingredient whose function (at least in part) involves being 'consumed' over time.
- Manufacture of the product with reduced overage should have been validated appropriately.

Required information

- The revised manufacturing formula.

Historical document

- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

B7 Changes to dimensions, shape, inked imprint, or embossing and debossing of solid dosage forms

Definitions

An **inked imprint** is a marking or pattern on the product made by printing with an ink during product manufacture.

Embossing/debossing is either the raised (embossed) or depressed (debossed) marking, pattern or engraving on the product that is formed by special tools used during product manufacture.

Specific conditions

- The product should be a solid dosage form (note that capsules are considered to be solid dosage forms, but impregnated sponges are not).
- There should be no concurrent change to the formulation except as allowed in Section 5.2 of this document.
- There should be no change to, or addition or deletion of, scoring.
- Where an inked imprint is changed, there should be no change to the imprinting ink used.

Required information

- The new product description.
- The revised set of drug product specifications at release and expiry.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).
- Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.4 of this document.

B3 Minor changes to physicochemical tests

Specific conditions

- There is no change in test method other than minor changes to existing test methods for physicochemical parameters of the drug product such as pH, density, specific gravity, optical rotation, extractable volume, osmolality, osmolarity or viscosity.

Required information

- A summary description of the change, and details of the new method.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

Historical document

C Change to the site of manufacture

Some minor changes to sites of manufacture do not require prior approval; these are discussed in Section 6 of this document.

The following changes to sites of product manufacture are self-assessable:

C1 Addition of a new site of secondary packaging operations for an already registered product

C2 Deletion of site of manufacture

C3 Change to manufacturer or supplier of excipients or raw materials

C4 Change to site of quality control testing

C5 Addition of a new site of release for supply operations for an already registered product

Definitions

The following definitions apply for the purposes of this document:

- **Change in site of manufacture** means a change in the location of the manufacturing premises. Some changes related to changes in site of manufacture may not be self-assessable.
- **Packaging material** means any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as **primary** or secondary according to whether or not they are intended to be in direct contact with the product. **Secondary packaging** includes any packaging or labelling (including repackaging or labelling, over-labelling or supplementary labelling) where the medicine remains in the primary container and that primary container is not opened, breached or modified in the secondary packaging process.

Note that primary and secondary packaging require different levels of good manufacturing process certification.

- **Release for supply** means that 'medicinal products are not sold or supplied before an authorised person has certified that each production batch has been produced and controlled in accordance with the requirements of the market authorisation and other regulations relevant to the production control and release of medicinal products' (from the *Guide to Good Manufacturing Practice for Medicinal Products*).[51]

[51] There may be more than one site involved in release for supply of a product. However, release for supply should only happen once, to ensure that the complete batch records (and responsibility for release) are held in one place. All sites must demonstrate compliance with good manufacturing practice

Historical document

C1 Addition of a new site of secondary packaging operations for an already registered product

Specific conditions

- If the new site is in Australia, the site must have a current manufacturing licence for this type of manufacture issued by the TGA. If the new site is overseas, the product sponsor must have a current GMP clearance letter (valid at the time of application) issued by the TGA for the new manufacturing site and for that type of manufacture.
- Apart from the change in site of manufacture, there should be no changes to any other aspect of the quality data other than changes to manufacturing equipment. Where a change in manufacturing equipment is made, this should have been validated in accordance with the principles of GMP.

Required information

- Details of the manufacturing step(s) undertaken at the new site of manufacture.
- A copy of the Australian licence and/or GMP clearance.

C2 Deletion of site of manufacture

Specific conditions

- None.

Required information

- The name and site address of the manufacturer and the steps of manufacture to be deleted.
- GMP clearance letter to show that there is at least one validly registered site of manufacture performing the same step(s) of manufacture as the deleted site. This evidence should be in the form of the current printout from the TGA eBusiness Services website[52] for the product or a copy of the TGA approval letter.

C3 Change to manufacturer or supplier of excipients or raw materials

Specific conditions

- The change should not be to excipients or raw materials of animal or human origin.
- The change should not be to excipients or raw materials used in heparin products.
- The change should not be to excipients produced by recombinant DNA technology.

(GMP) through a Therapeutic Goods Administration licence or clearance. Compliance with shipping conditions during importation into Australia is the responsibility of the Australian sponsor for products released for supply overseas. The sponsor does not require a GMP licence to perform this step.

[52] <https://www.ebs.tga.gov.au>

Historical document

Required information

- The name and street address of the new manufacturer.
- An assurance that the excipients or raw materials comply with previously approved acceptance criteria and/or storage conditions.

C4 Change to site of quality control testing

Specific conditions

- There should be no modifications to the testing procedure, and the previously approved validation criteria should be met.
- If the new site is in Australia, the site must have a current manufacturing licence for this type of manufacture issued by the TGA. If the new site is overseas, the product sponsor must have a current GMP clearance letter (valid at the time of the application) issued by the TGA for the new manufacturing site and for that type of manufacture.
- There should be no changes to the test methods used for testing the product, whether or not the test methods have been provided to the TGA previously, except where allowed by other sections within this document.
- There should be no impact on existing method validations and the test methods have been adequately qualified to generate results comparable to that of currently approved quality control sites. The qualification data should be provided to TGA on request.
- The change should not be a change to a viral safety testing site.

Required information

- The name and address of the new site.
- Details of the manufacturing step(s) undertaken at the new site of manufacture.
- A copy of the Australian licence and/or GMP clearance letter.

C5 Addition of a new site of release for supply operations for an already registered product

Specific conditions

- If the new site is in Australia, the site should have a current manufacturing licence for this type of manufacture issued by the TGA. If the new site is overseas, the product sponsor must have a current GMP clearance letter (valid at the time of application) issued by the TGA for the new manufacturing site and for that type of manufacture (see definition of 'release for supply' in box 'Definitions' above).

Required information

- Details of the new site of manufacture.
- A copy of the Australian licence and/or GMP clearance.

Historical document

D Replacement of an in-house reference standard

Specific conditions

- The TGA should have explicitly approved the protocol for establishing a replacement standard. The protocol should have been submitted with the application for registration or a subsequent Category 3 application to change the in-house reference standard. This also includes a change in shelf life of the reference standard.

Required information

- Details of the new reference standard, including assigned values.
- The reference to the TGA approval of the protocol (that is, TGA submission number).
- The proposed date of implementation, allowing time for TGA approval.
- An updated CPD document (see box 'Note on certified product details [CPD] documents', above).

Historical document

E Establishment of a new working cell bank or seed lot

The following changes to establish a new working cell bank or seed lot are self-assessable:

E1 Addition of a new working cell bank or working seed lot

E2 Change to the storage site for the master cell bank or seed lot, or working cell bank or seed lot

E1 Addition of a new working cell bank or working seed lot

Specific conditions

- The new working cell bank (WCB) or working seed lot (WSL) should be derived from the previously approved master cell bank or master seed lot.
- The TGA should have explicitly approved the protocol for this purpose. The protocol should have been submitted with the application for registration or a subsequent Category 3 application to change the WCB or WSL.
- There should be no effects on genetic stability, product yield, adventitious agent safety, or quality and purity, as shown by the validation study.

Required information

- Details of the new WCB or WSL.
- The proposed date of implementation, allowing time for TGA approval.
- A declaration that the WCB or WSL has been validated by an approved protocol (stating the date of approval of the protocol) and found to be acceptable.

E2 Change to the storage site for the master cell bank or seed lot, or working cell bank or seed lot.

Specific conditions

- The change should be to backup/reserve storage site only.

Required information

- The address of the new site.
- Details of the facility that has taken responsibility for GMP compliance for the secondary storage site.

Historical document

F Changes to the quality aspects of the product information

Changes to the product information (PI) under s. 9D(3)

Most quality-related changes to the PI are approved as consequential changes made at the same time as approval of a request under s. 9D(3) (that is, any of the types of changes listed in this section of this document). There is no need to make a separate self-assessable request to change the PI in these cases.

The types of changes in this section are requests for changes to the PI where the only proposed change being requested under s. 9D(3) is a change to the PI.

Specific conditions

- The change should be one or more of the following:
  - adding the names of excipients in the product, whether or not those excipients are referred to in the TGO pertaining to labels
  - adding the Chemical Abstracts Service (CAS) number, chemical structure, molecular formula, molecular weight and/or chemical name/nomenclature of the drug substance
  - changing the name, address or other details of the product's sponsor or distributor
  - putting into effect the guidelines in sections 3.1–3.3 and 3.5 of Appendix 20 of the ARGPM ('Supplementary guidelines for radiopharmaceuticals')
  - changing the PI of radiopharmaceuticals to specifically
    - give instructions and information about the enhancement of radiation protection and safety of the user and the patient. These may include radiation shielding data, decay charts, procedures to minimise radiation doses to staff and unwanted doses to patients, and references to guidelines and codes of practice relating to radiation protection
    - give instructions to users that the patient dose should be measured by a suitable radioactivity calibrator immediately before the dose is administered.
- Any included technical information should be accurate and should be obtained from recognised reference sources.
- All names and terminology used in the PI must be Australian approved names or entered in the TGA eBusiness Services code tables.
- Products should not be supplied with a new PI until the change has come into effect.
- The approved amended PI must be updated on the TGA website when the proposed changes come into effect.

Required information

- Details of changes to the PI as outlined in Section 1.4 of this document. If the amendments are necessary because of other regulatory actions that have already been approved or notified, evidence of such approval or notification.

Historical document

G Changes to product labels

Requirements for labels

Mandatory labelling requirements for prescription medicines are set out in the therapeutic goods order that pertains to labels (currently Therapeutic Goods Order No. 69—General requirements for labels for medicines), as amended from time to time. It is the sponsor's responsibility to ensure that their product labels meet any state and territory government requirements. When making changes to labels, sponsors should consider the recommendations in the TGA document *Best Practice Guideline on Prescription Medicine Labelling*[53]

Self-assessment of proposed changes to product labels is only allowed for the types of changes detailed in this section. Also see Part 6 of this document for other types of changes to labels that do not require prior approval or notification.

Specific conditions

- The change must be one or more of the following:
  - change to warning statements
    - addition of, or changes to, a warning or precaution statement resulting from a safety-related variation to the PI under s. 9D(2) of the TG Act, where the PI change has been approved by the TGA
    - addition of warning or cautionary statements where an incorrect route or method of administration may be hazardous, such as 'Not for injection', 'For external use only' and 'Not for oral use', or addition of mandatory warning or cautionary statements in the current edition of the TGA document *Required Advisory Statements for Medicine Labels*[54], if relevant.
  - change to quality or manufacturing aspects
    - addition of the names of excipients, whether or not the excipients are referred to in the TGO that relates to labels
    - addition of the release rate for transdermal patches
    - amendment of the means of expressing the proportion of drug substance in topical preparations
    - addition or amendment of the terms hypotonic, hypertonic and isotonic in the labels of large-volume injections
  - changes as a result of other TGA requirements
    - amendments that have been approved by the TGA under s. 9D(1) of the TG Act (correction of an incomplete or incorrect entry in the ARTG)
    - addition of a new TGA-approved route of administration for injectable medicines

[53] <http://www.tga.gov.au/industry/labelling-pm-best-practice.htm>
[54] <http://www.tga.gov.au/industry/labelling-rasml.htm>

Historical document

- amendments resulting from the implementation of a self-assessable request that is either submitted simultaneously or has been previously approved by the TGA
- amendments resulting from the implementation of changes allowed in Part 6 of this document that have been notified to the TGA, including changes to the sponsor name, sponsor address and medicines scheduling
- changes to the method of expressing the content of active ingredients or excipients, in accordance with the current TGO pertaining to labels, such as changing '0.5 mg' to '500 micrograms'
- changes as a result of product rescheduling (following from changes to the *Standard for the Uniform Scheduling of Medicines and Poisons*[55])—for example, changes to directions for use and statement of purpose(s) of the product that are in accordance with the approved PI (see Part 6 of this document for more information)
- changes that must be made to labels to comply with current TGOs. Note that updating old labels that have not previously been evaluated and approved by the TGA is not self-assessable
- change to names of active ingredients, excipients or dosage forms as a result of changes in the Australian Approved Name or TGA eBusiness Services code tables.

– changes to presentation, sponsor details, and so on
  - changes to the colour, design or layout of labels with no change to content, provided that there is no loss of differentiation between packs that contain different strengths
    - change to layout should not introduce a day-of-week or time-of-day (or similar) dosing schedule panel, although variations to such panels that were previously approved may be allowed, provided that there is no change to the dosing regimen
    - change to the layout or design of a physician sample pack may include changes in content if this is to ensure compliance with Australian pharmaceutical industry codes of conduct
    - deletion of repeated text (present elsewhere on a label) from selected side panels is acceptable, provided that the information is not mandatory and its removal is in accordance with the best practice guideline on prescription medicine labelling
  - addition or deletion of, or change to, the name or address of the Australian sponsor or supplier of the product
  - addition or deletion of, or change to, the company logo or livery
  - deletion of existing graphics, pictures or diagrams and any associated text
  - addition or deletion of, or change to, simple instructional, informational or anti-tampering statements, such as 'Consumer medicines information enclosed', 'Break security seal before opening', 'Push tablets through blister foil' and 'Do not accept if security seal is broken'
  - addition or deletion of, or change to, the statement of country of origin or manufacture for imported products, as required by other relevant Australian legislation

[55] <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>

Historical document

  - addition or deletion of, or change to, label text of outer protective pouches or overwraps of the container or primary pack where the new text is not confusing, promotional or contradictory to text on the container or primary pack labels
  - addition or deletion of, or change to, the pictogram of a product or its dosage form, provided that it does not contravene the *Best Practice Guideline on Prescription Medicines Labelling*.
- All changes to the label must be identified in the request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels.
- For addition of, or changes to, a company website address, the website should have:
  - an Australian address (that is, ends with '.au' or other justified suffixes that reflect Australian ownership of the address)
  - information about the product (including any direct links from the website) that is consistent with the information approved by the TGA for that product.

Required information

- Copies of the existing labels and final copies or mock-ups of the amended labels, including any logos, designs or graphics. The copy should be actual size and should indicate the colours to be used. If there are multiple strengths or pack sizes, one representative label or copy will be sufficient, provided that the only difference between the labels is the pack size or strength, unless this would contravene the strength differentiation requirement.
- If batch number and expiry date are printed on the labels during packaging, a statement to this effect, stating the prefixes to be used.
- For addition of, or changes to, a company website address, an assurance that the sponsor has full control over the content of the site.
- For changes to labels resulting from other regulatory actions that have been either already notified or approved, appropriate evidence of the notification or approval, for example a TGA submission number.

Historical document

H Changes to the pack size

Reducing the number of units (vials, syringes, ampoules, cartridges) in a pack is self-assessable; increasing the number of units in a pack is not.

Definitions

For the purpose of this document, pack size is defined as follows:

- For products presented as **discrete dosage units** (for example, tablets, capsules, compressed or moulded suppositories, pessaries, or other single-dose medicine inside a unit container), the pack size is the number of units in the container.
- For **non-sterile solid, powder, semi-solid and liquid products**, the pack size is the weight or volume of the container contents.
- For **injections and other sterile preparations**, the pack size is the number of ampoules, vials, prefilled syringes, bags, bottles and so on per primary pack (carton).
- For **transdermal patches**, the pack size is the number of patches per primary pack (carton).
- For **pressurised metered-dose preparations or dry powder inhalers**, the pack size is the nominal number of doses in the container.
- For **non-pressurised metered-dose preparations**, the pack size is the minimum number of doses in the container, or the volume or weight of the container contents.

Volume of fill of a sterile product is defined as the nominal volume of solution in the container, the total content of which represents the strength of the product as listed on the label. It may include an overfill. Note that inclusion of a new volume of fill, or a change in the existing nominal volume of fill of an injection or a peritoneal dialysis solution is considered under the legislation as a change in product strength and requires a Category 1 application.

Specific conditions

- The change should not be a change in the volume of fill of an injection or other sterile preparation.
- The change should be the result of either of the following:
  - Pharmaceutical Benefits Advisory Committee recommendation (including a larger pack size)
  - to introduce a smaller pack size; or
  - deletion of an existing pack size that is no longer to be supplied.
- The change in pack size should not be accompanied by changes to dosage regimen or indications.

Historical document

- The label for the new pack size should be the same as for the current pack size, except for quantity of goods or other changes allowed in other sections of this document.
- The additional or changed pack size should be consistent with the treatment recommendations in the PI.
- The container material, size and shape should be either unchanged, or changed in a manner permitted in this document.

Required information

- Relevant details regarding the change in pack size.
- A copy of the label for the new pack size, as appropriate.
- Where the proposed change would involve approval of an amended PI, details of changes to the PI, as outlined in Section 1.4 of this document.

Historical document

I Changes to fermentation processes

The following changes to fermentation processes are self-assessable:

I1 Reduction in fermentation period

I2 Change in manufacturer of the filter

I3 More stringent internal process controls

I1 Reduction in fermentation period

Specific conditions

- The reduction in fermentation period should not change the batch size.
- There should be no change to internal process controls.

Required information

- Reasons for the change.
- Details of the change.

I2 Change in manufacturer of the filter

Specific conditions

- There should be no change to internal process controls.
- The filter should not be used for steps that require viral safety validation.

Required information

- Reasons for the change.
- Details of the new manufacturer.
- An assurance that the new filter meets the same acceptance criteria as the previous filter.
- An assurance that the internal process controls for the filtrate have not been changed.

Historical document

I3 More stringent internal process controls

Specific conditions

- There should be no change to the quality characteristics of the product.

Required information

- Details of the new internal process controls.
- Reasons for the change.

Historical document

J Changes to purification processes

The following changes to purification processes are self-assessable:

J1 Reduction in holding times

J2 Reduction in column life

J1 Reduction in holding times

Specific conditions

- The change should not be a change to a plasma-derived product.

Required information

- Scientific justification for the reduction in holding times.

J2 Reduction in column life

Specific conditions

- None.

Required information

- Scientific justification for the reduction in column life.

Historical document

K Changes to storage of the drug substance

The following changes to storage of the drug substance are self-assessable:

K1 Reduction in shelf life

K2 Change in dimensions or manufacturer of storage container

K1 Reduction in shelf life

Specific conditions

- None.

Required information

- Details of the new shelf life.
- A reason for the planned reduction in shelf life.

K2 Change in dimensions or manufacturer of storage container

Specific conditions

- The surface area in contact with the product should not change.
- The dimensions of the storage container should only increase by 50% or less.
- There should be no change to the container material.

Required information

- Details of the change.
- Justification for the change.
- An assurance that stability studies have been conducted.

Historical document

L Changes to filling

L1 Introduction of a similar filling line

Specific conditions

- The new filling line should be similar to the existing filling line.
- There should be no modifications to the procedure, and the previously approved validation criteria (including validated aseptic holding and filling times) and/or release specifications should be met.
- This can include upgrades to an existing filling line.

Required information

- General details of the new/upgraded filling line.

Historical document

M Introduction of anti-tamper packaging for the drug product

Specific conditions

- The packaging materials should not contact the product.

Required information

- Details of the change.

Historical document

N Changes to the shelf life or storage conditions of the drug product

The following changes to shelf life and storage conditions for the drug product are self-assessable:

N1 Reduction in shelf life

N2 Changes to excursion temperature during manufacture

N3 Addition of a restrictive shelf life or storage condition

N1 Reduction in shelf life

Specific conditions

- None.

Required information

- Details of the new shelf life.
- A reason for the reduction in shelf life.

N2 Changes to excursion temperature during manufacture

Specific conditions

- The change is one of the following:
  - a removal of an excursion temperature
  - a reduction in the time spent out of refrigeration, including time out of the freezer.

All other changes to the excursion temperature require the TGA to evaluate the data (see Section 4.3 F for further information).

Required information

- Details of the change.

Historical document

N3 Addition of a restrictive shelf life or storage condition

Specific conditions

- The change should be to a more restrictive shelf life or storage conditions.

Required information

- Details of the change.
- The reason for the change.

Historical document

O Changes to plasma fractionation intermediates

The following changes to plasma fractionation intermediates are self-assessable:

O1 More stringent internal process controls

O2 Reduction in column life

O1 More stringent internal process controls

Specific conditions

- There should be no change to the quality characteristics of the product.

Required information

- Details of the change.
- The reason for the change.

O2 Reduction in column life

Specific conditions

- None.

Required information

- Details of the change.
- A justification for the proposed reduction.

Historical document

P Changes specific to influenza vaccines

Some of the processes for regulating quality-related changes to influenza vaccines are slightly different from the processes for other vaccines, because of the changing nature of the vaccine virus strains. This section may also be applicable to new vaccines that have similar requirements to influenza vaccines.

The following changes that are specific to influenza vaccines are self-assessable:

P1 Change in the passage or lot number of the approved reassorted virus or approved virus isolate

P2 Change in the working seed lot

P3 Replacement of reference reagent

P4 Strain-specific variations to manufacturing processes

P1 Change in the passage or lot number of the approved reassorted virus or approved virus isolate

Specific conditions

- The new lot should be derived from an approved reassorted virus or virus isolate, using an approved process.

Required information

- The lot number and passage history.

P2 Change in the working seed lot

Specific conditions

- The working seed lot should be derived from an approved reassorted virus or virus isolate, using an approved process.
- Neuraminadase identity should be performed on the first three monovalent pooled harvests from the changed working seed lot, and data should be supplied to the TGA before any lots will be released.

Required information

- The lot number and passage history.

Historical document

P3 Replacement of reference reagent

Specific conditions

- Changes can only be made to the reference antigen or antiserum.

Required information

- The lot number and source of the reference antigen or antiserum.

P4 Strain-specific variations to manufacturing processes

Specific conditions

- Changes can only be made within previously approved parameters.

Required information

- Details of the changes.

Historical document

Q Other changes

The following further changes are self-assessable:

Q1 Change in details of albumin manufacturer or supplier

Q2 Change in manufacturer or supplier of crude heparin

Q3 Changes to medicines and poisons scheduling

Q1 Change in details of albumin manufacturer or supplier

Specific conditions

- The change may apply to the name or contact details of albumin suppliers or manufacturers, but not to the site or process of manufacture. (Changes to site or process of manufacture of albumin products require TGA evaluation of supporting data.)

Required information

- Details of the new manufacturer or supplier.
- Evidence of GMP clearance, showing the changed name.

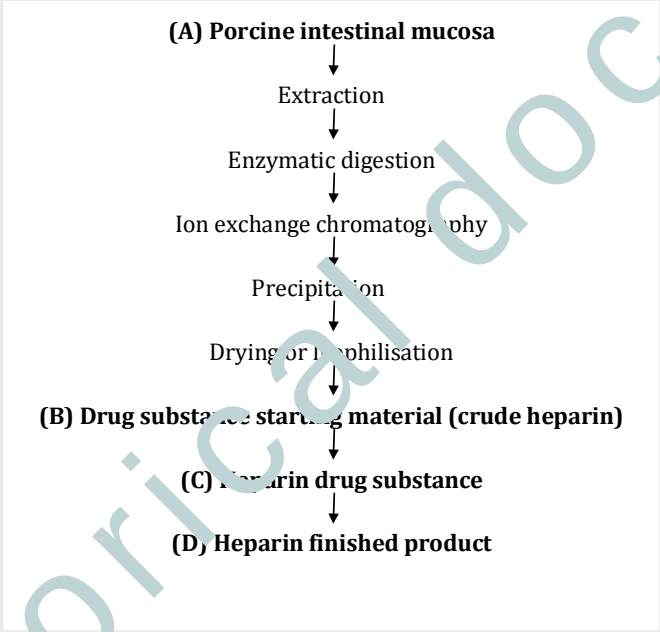
Historical document

Q2 Change in manufacturer or supplier of crude heparin

Note on heparin products

The stage of manufacture at which starting material for a heparin product is considered to be the drug substance (also known as the active pharmaceutical ingredient, or API) is earlier than for other biological medicines. This is described in current monographs and good manufacturing practice (GMP) requirements for heparin products. It means that GMP clearance is required earlier in the process for heparin products than for products that do not contain heparin.

The point at which the drug substance starting material is introduced into the process, as interpreted by the Therapeutic Goods Administration (TGA) for manufacture of a heparin drug substance, is defined in the flowchart below. It is important to note that steps A to B in the flowchart are the only steps in manufacture that do not have to be covered by TGA-issued GMP clearance.



Flowchart of the manufacturing process for heparin drug product from porcine intestinal mucosa

Manufacturing steps A to B result in the drug substance starting material (crude heparin). Any step of manufacture beyond this point is regarded as drug substance manufacture and must be covered by TGA-issued GMP clearance.

Specific conditions

- There should be no change to the country of origin of the crude heparin.

Required information

- Details of the change, including the following:

Historical document

- names and addresses of the supplier(s) of the crude heparin
- names and addresses of the suppliers of the raw starting material (the porcine intestinal mucosa)
- names and addresses of the suppliers any of the intermediates up to the crude heparin.

Q3 Changes to medicines and poisons scheduling

Note that any changes to the *Standard for the Uniform Scheduling of Medicines and Poisons*[56] signal heading and cautionary statements are matters for the states and territories, and therefore should be handled through state and territory authorities. If a medicine has been rescheduled from Schedule 4 or 8 to Schedule 2 or 3, any necessary changes to the product should be handled according to the *Australian Regulatory Guidelines for Over-the-Counter Medicines*[57], where appropriate.

Specific conditions

- The change in scheduling is from a Schedule 2 or 3 medicine to a Schedule 4 or 8, or from a Schedule 4 to a Schedule 8 medicine, or
- The medicine has been rescheduled from Schedule 4 or 8 to Schedule 2 or 3, but continues to be regulated as a prescription medicine (see Part 1 of Schedule 10 of the Regulations).

Required information

- Relevant evidence of the change, such as a copy of the final Advisory Committee on Medicines Scheduling decision
- A copy of the revised label
- A clean and marked-up copy of the proposed amended PI, as outlined in Section 1.4 of this document.

Historical document

[56] <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>
[57] <http://www.tga.gov.au/industry/otc-argom.htm>

4.3 Requests that require submission of data

This section outlines the procedures for submitting a Category 3 application to request a variation to an ARTG entry under s. 9D(3). Category 3 applications relate to requests to vary the quality information held in the ARTG entry for prescription medicines.

The data required to support a Category 3 application are detailed in this section. The types of changes listed in this section are representative and not intended to be an exhaustive list of all quality-related changes requiring evaluation of data by the TGA. The requirements are essentially the same as for the corresponding section of an application to register a new prescription medicine. The requirements of the relevant EMA/ICH guidelines adopted by the TGA should be met, as appropriate.

Requests for variations that require evaluation of clinical, nonclinical or bioequivalence data will require a Category 1 or Category 2 application in the Streamlined Submission Process[58]. If a Category 3 application is submitted, but the TGA determines that evaluation of clinical, nonclinical or bioequivalence data is required, sponsors will be informed that the request should be made as a Category 1 or Category 2 application with relevant supporting data. Sponsors should be aware that r. 16F of the Therapeutic Goods Regulations 1990[59] will not apply to the request if the delegate forms the opinion that TGA evaluation of clinical, nonclinical or bioequivalence data is required. In this case, r. 16E or r. 16D will consequently apply, and sponsors will be required to submit a new Category 1 or Category 2 application for the variation to be approved.

How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit a request. The TGA can provide advice on general requirements for the request and relevant parts of the legislation, but cannot provide detailed, specific information about a particular request until it has been lodged.

Further information is also on the TGA website[60]

What do I need to provide?

For a Category 3 application, sponsors should provide the following:

- a cover letter (see below)
- a completed 'Category 3 application: Request to vary an ARTG entry under subsection 9D(3)' form

[58] <http://www.tga.gov.au/industry/pm-ssp.htm>
[59] <http://www.comlaw.gov.au/Series/F1996B00406>
[60] <http://www.tga.gov.au>

Historical document

- the relevant data in the common technical document (CTD) format. Only a single copy of the supporting data needs to be submitted. The data should relate only to the specific variations requested; no other data should be provided. Depending on the nature of the change, Module 2 data may be required in addition to Module 3 data.

For each proposed change, the sponsor should provide **all** of the following with the cover letter of the application:

- a clear description of the currently approved information that is relevant to the proposed variation
- details of the proposed change, including a brief description of the data provided, with references
- justification for the change(s)
- a summary of technical data to support the proposed change(s) (see 'Data requirements', below)
- a declaration that: 'No aspects of the quality information have been changed, including manufacturing procedures and equipment, and raw material and drug product specifications, other than the changes nominated in this application'.

If the proposed change involves an amendment to the approved PI, the sponsor should provide clean and marked-up copies of the PI, as outlined in Section 1.4 of this document.

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the Therapeutic Goods Regulations 1990[61]. These fees are subject to change from time to time; current fees[62] are published on the TGA website. The fees for requests under s. 9D(3) that require supporting data are listed at item 2B.

What are the timeframes?

Under regulation 16F of the Therapeutic Goods Regulations 1990, which applies to all requests under s. 9D(3) that do not require TGA evaluation of clinical, nonclinical or bioequivalence data, the Secretary must make a decision about the request and notify the sponsor within 45 working days of receiving the request and payment (whichever is later) or, if necessary, raise an objection concerning the application (refer to Section 1.2). An objection usually means that the Secretary will ask the sponsor questions about the product that are necessary for them to make a decision about the request, to which the sponsor must respond.

When an objection is raised by the Secretary, the clock will stop from the time the objection is raised (that is, the matter is raised with the sponsor) and will start again when the TGA receives the response to the objection from the sponsor. The Secretary then has 30 working days from the day on which the response is received to notify the sponsor of the decision.

If the Secretary does not make a decision within the 45–working day timeframe (or subsequent 30–working day period after a response to an objection), the request is taken to have been approved.

[61] <http://www.comlaw.gov.au/Series/F1996B00406>
[62] <http://www.tga.gov.au/about/fees.htm>

Historical document

What happens to my request?

If all the requirements for a s. 9D(3) request have been met, including payment of the appropriate fee, the request is referred to the relevant TGA evaluation area for assessment. If a requirement has not been met (for example, the sponsor has not included a correctly marked-up copy of the proposed new PI), the sponsor will be asked to submit the required information before the request can be processed.

When all the necessary information has been received by the TGA (including payment), the clock starts on the application. The TGA evaluates the data, and approves the request, if applicable. If the Secretary is not able to make a decision, the clock stops while the TGA asks for information under s. 31 of the TG Act or raises an objection (see above). The clock restarts on receipt of the complete response to the request for information. There is no limit on the number of clock stops under s. 31. The person making the request will be sent a letter outlining the decision when it is made. Reasons for the decision will be provided if the request is rejected.

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the request at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the variation to the ARTG entry is approved, the entry will be updated and any necessary changes to the PI will also be approved under s. 25AA(4) of the TG Act. Sponsors should lodge copies of the updated PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[63] system within 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 9D(3) and s. 25AA(4) are subject to review under s. 60 of the TG Act.

Sponsors can withdraw their request at any time during the process but fees are not refundable.

Historical document

[63] <https://www.ebs.tga.gov.au/>

Data requirements

The following requests to vary an ARTG entry require submission of supporting data to the TGA for evaluation as a Category 3 application.

A Changes to an entry that involve consequential changes to quality aspects of the product information

B Changes to specifications of the drug substance, drug product or excipients

C Changes to the method of manufacture of the drug product

D Changes to the site of manufacture of the drug product

E Changes to the source or manufacturing process of excipients of animal origin

F Changes to the packaging

G Change to, or addition of, pack size

H Changes to the shelf life or storage conditions of the drug substance or drug product

I Changes to labelling

J Changes to gene technology aspects

K Changes to cell banks or seed lots

L Changes to filling of the drug product

M Changes to in-house reference standards

N Changes to diluents, kits or product components

O Changes to plasma master files

P Changes to plasma fractionation intermediates

Q Changes specific to influenza vaccines

R Changes to other types of quality-related variations where the change does not create a separate and distinct good

Historical document

Depending on the nature of the proposed change(s), the following supporting technical data should be provided. If not provided, the TGA may request the data. Sponsors should be aware that the types of changes listed in this section are not exhaustive, and the technical data required represent the minimum data necessary for assessment. The TGA reserves the right to request data or information in addition to those specified below, if appropriate.

The guidance provided below is in addition to the information in 'How to apply to the TGA', above.

Comparability studies

Any major change to the manufacturing process, addition of a new manufacturing site or moving of the process from one site to another requires data to demonstrate that the drug substance or product made by the two processes or sites is comparable. The requirements for this type of comparability study are outlined in the International Conference on Harmonisation (ICH) guideline *ICH Topic Q5E: Comparability of Biotechnological/ Biological Products—Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process*.

Where the changes are significant, or variation in product quality parameters is found, stability data may be needed to support retention of the existing shelf life. A minimum of three batches of material at commercial should be provided to validate a major change in manufacturing process. Once validated and approved by the TGA, these batches may be released for supply.

If comparability cannot be demonstrated, supporting nonclinical and clinical data are required as a Category 1 application.

A Changes to an entry that involve consequential changes to quality aspects of the product information

Changes to the product information under s. 9D(3)

Most quality-related changes to the product information (PI) are approved as consequential changes made at the same time as approval of a request under s. 9D(3) (that is, any of the types of changes listed in this part of the document). There is no need to make a separate self-assessable request to change the PI in these cases.

The types of changes in this section are requests for quality-related changes to the PI where the only proposed change being requested under s. 9D(3) is a change to the PI.

Historical document

This section covers all quality-related changes to the ARTG entry resulting in changes to the PI that are not described in Section 4.2.

Required information

- A description of the proposed change to the ARTG entry.
- Details of changes to the PI, as outlined in Section 1.4 of this document.
- Relevant technical data to support the proposed change(s).

B Changes to specifications or test methods of the drug substance or drug product.

This includes changes to, or removal of, a test method, or changes to specifications, where these are not self-assessable changes (refer to Section 4.2).

Required information

- A copy of the revised specifications; where relevant, this should be consolidated to apply to all sites of drug substance manufacture.
- Justification for the proposed changes, including any changes to test procedures. Data demonstrating the equivalence of the alternative and/or pharmacopoeial methods may also be required, if relevant.
- Validation of any changed test procedures (including microbiological tests, if applicable).
- Certificates of analysis for three representative batches (preferably sequential batches) of the bulk drug substance or drug product, demonstrating the manufacturer's ability to meet the revised specifications. Where the expiry specifications change, stability data may be necessary.
- If the change is approved, an updated CPD (see box 'Note on certified product details [CPD] documents', above).

C Changes to the method of manufacture of the drug substance and drug product

Required information

- A detailed description of the changed manufacturing process, including flow diagram.

  Process validation data for the changed process (including validation of sterile manufacture and sterilisation processes, if applicable).
- If the drug substance is made entirely by fermentation, details of any material of animal origin used during the process that is classified as Category C in the TGA's *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible*

Historical document

Spongiform Encephalopathies (TSEs)[64]. If appropriate, provide the necessary assurance regarding self-assessment of TSE risks of such materials.

- Where a manufacturer produces multiple products at the same site, details of the manufacturing process(es) and the measures taken to ensure that there is no cross-contamination of different drug substances.
- Batch analytical data generated for three full production-scale batches of drug substance or drug product manufactured using the proposed process, unless otherwise justified. These data should be compared with data from at least three batches of recently manufactured pre-variation product and the mean, standard deviation and range of historical data. All data should be generated using approved routine quality control methods, unless otherwise justified and details are provided of the non-routine methods used.
- Real-time stability data generated for batches produced using the new process (refer to Appendix 14 of the ARGPM). For biological medicine products requiring refrigeration or freezing, stability testing should be in real time at the specified storage temperature, for at least the requested shelf life. The time out of refrigeration (which also includes time out of the freezer) during normal manufacturing processes, up to the point of return to the fridge or freezer following labelling and packaging, should have been defined and justified. From that point onward, all storage and shipping conditions should be justified by the real-time stability data; the data for justifying any temperature excursions should include real-time studies of the proposed excursion followed by return to the normal storage conditions for the remainder of the shelf life.
- If the changes proposed are to the drug product and may affect bioavailability of the product, comparative bioavailability data. (Note that, if bioavailability data are required and are submitted to support the change, the application becomes a Category 1 application.)
- If the change is likely to affect critical quality parameters, data from comparability studies on pre-variation and post-variation drug substance or drug product.
- If the change is approved, an updated CPD (see box 'Note on certified product details [CPD] documents', above).
- Appropriate validation data (including revised viral load reduction claims), where a change is to a process involved in viral reduction.

D Changes to the site of manufacture of the drug substance and drug product.

Required information

- GMP evidence for the new site (that is, the Australian licence for an Australian site, or a current GMP clearance letter for an overseas site or reference to the clearance submission number). The Australian licence or GMP clearance letter should cover the relevant manufacturing steps and must be valid at the time of the request.

[64] <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>

Historical document

- A declaration that the manufacturing process, including batch size, is the same as that used at the currently approved manufacturing site, or a description of any differences between the processes at the new and currently approved sites.
- For plasma products, comparative impurity profiles from representative batches from the current and new sites of manufacture using validated test methods.
- Appropriate validation of the process at the new site (including validation of sterile manufacture and sterilisation processes, if applicable) to demonstrate that the product manufactured at the new site meets the currently registered requirements for in-process controls and the drug product specifications.
- Description and validation of quality control test methods where there is a change in test procedures or where the laboratory testing the product (site of quality control testing) has changed.
- Certificates of analysis for three sequential, preferably full-scale batches of drug product that were manufactured at both the currently approved site and the new site.
- Relevant comparative data on the product (see 'C: Changes to the method of manufacture of the drug product', above).
- Relevant stability data for batches produced at the new site (refer to Appendix 14 of the ARGPM). For biological medicine products requiring refrigeration or freezing, stability testing should be in real time at the specified storage temperature, for at least the requested shelf life. The time out of refrigeration (which also includes time out of the freezer) during normal manufacturing processes, up to the point of return to the fridge or freezer following labelling and packaging, should have been defined and justified. From that point onward, all storage and shipping conditions should be justified by the real-time stability data; the data for justifying any temperature excursions should include real-time studies of the proposed excursion followed by return to the normal storage conditions for the remainder of the shelf life.
- If the change is likely to affect critical quality parameters, data from comparability studies on pre-variation and post-variation product.
- Appropriate validation data (including revised viral load reduction claims), where a change is to a process involved in viral reduction.

E Changes to the source or manufacturing process of ingredients of human and animal origin

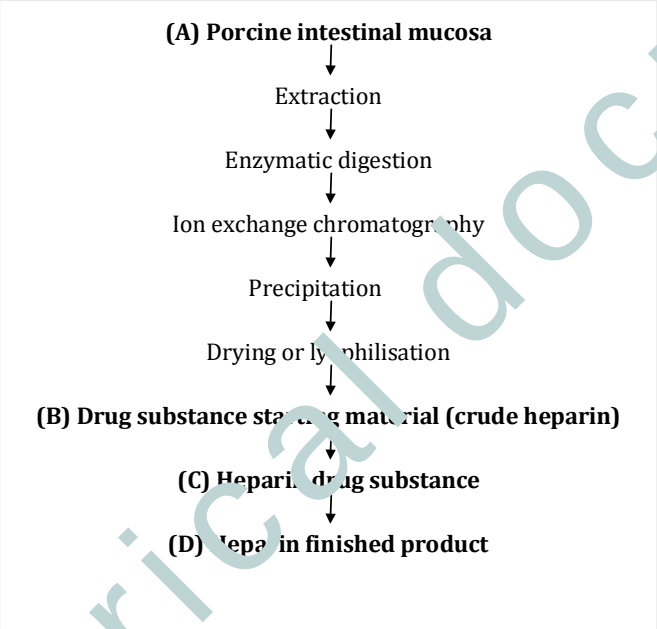
This includes changes to the source or manufacturing process of raw materials of human or animal origin, for example, albumin or heparin.

Historical document

Note on heparin products

The stage of manufacture at which starting material for a heparin product is considered to be the drug substance (also known as the active pharmaceutical ingredient, or API) is earlier than for other biological medicines. This is described in current monographs and good manufacturing practice (GMP) requirements for heparin products. It means that GMP clearance is required earlier in the process for heparin products than for products that do not contain heparin.

The point at which the drug substance starting material is introduced into the process, as interpreted by the Therapeutic Goods Administration (TGA) for manufacture of a heparin drug substance, is defined in the flowchart below. It is important to note that steps A to B in the flowchart are the only steps in manufacture that do not have to be covered by TGA-issued GMP clearance.



Flowchart of the manufacturing process for heparin drug product from porcine intestinal mucosa

Manufacturing steps A to B result in the drug substance starting material (crude heparin). Any step of manufacture beyond this point is regarded as drug substance manufacture and must be covered by TGA-issued GMP clearance.

Required information

- For excipients derived from Category C tissues from TSE-relevant ruminant species that are used in products that are implants or injectable products given by the parenteral, ophthalmic or intra-tracheal routes, or for excipients derived from Category A or B tissues from TSE-relevant ruminant species (see TGA's *Supplementary Requirements for Therapeutic*

Historical document

Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies [TSEs][65]) used in products given by the oral, topical, vaginal, rectal or inhalation routes:

- details of the excipients and the proposed changes
- measures taken by the manufacturer to minimise TSE risks.

Refer to Appendices 9 and 10 of the ARGPM for additional details on requirements for ingredients of human or animal origin. See also Sections 4.3 O and 4.3 P for information about changes to plasma-derived products. Refer to the information box above for special requirements for heparin products.

F Changes to the packaging

This includes container shape, size and material, as well as any measuring or delivery device included in the pack, but excludes container type. It also refers to relevant aspects of packaging of diluents, kits and other product components.

Any change in the material contacting the product will require evidence of biomaterial safety testing and stability data. Changes to the container/closure system will require container/closure integrity testing.

Required information

- Specifications of the packaging and packaging materials.
- If relevant, biomaterial safety evidence that any new polymeric or rubber packaging materials used that are in contact with the product are free from any leachable toxic impurities and comply with BP/Ph.Eur./USP and Australian requirements for polymeric materials used in packaging of medicines.
- Relevant stability data if the packaging may be expected to be less protective than the currently approved packaging or if the change may affect the stability of the product; otherwise, a commitment to generate such data according to relevant stability guidelines and in accord with GMP requirements. Comparative moisture permeability data of the current and proposed container/closure system may be required.
- If the container/closure system is a child-resistant package or is implied by its presentation to be a child-resistant package, a declaration that the re-closable package meets all of the requirements of the current TGO on child-resistant packaging. State in the declaration which of the recognised international standards on child-resistant packaging the closure complies with, and include evidence of adequate directions for opening and reclosing the package.
- Validation data on the changed measuring/delivery system in the pack.
- For sterile products, sterile manufacture information and sterility testing data, as appropriate, including (for example) validation of aseptic media fills and preservative efficacy test data.
- Revised labelling, instructions for use and any other appropriate information or data that relate to the change, if applicable.

[65] <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>

Historical document

- Where the proposed change would require an update to the PI, details of the amended PI, as outlined in Section 1.4 of this document.

G Change to, or addition of, pack size

Definitions

For the purpose of this document, pack size is defined as follows.

- For products presented as **discrete dosage units** (for example, tablets, capsules, compressed or moulded suppositories, pessaries or other single-dose medicine inside a unit container), the pack size is the number of units in the container.
- For **non-sterile solid, powder, semi-solid and liquid products**, the pack size is the weight or volume of the container contents.
- For **injections and other sterile preparations**, the pack size is the number of ampoules, vials, prefilled syringes, bags, bottles and son per primary pack (carton).
- For **transdermal patches**, the pack size is the number of patches per primary pack (carton).
- For **pressurised metered-dose preparations or dry powder inhalers**, the pack size is the number of doses in the container.
- For **non-pressurised metered-dose preparations**, the pack size is the minimum number of doses in the container, or the weight or volume of the container contents.

Volume of fill of a sterile product is defined as the nominal volume of solution in the container, the total content of which represents the strength of the product as listed on the label. It may include an overfill. Note that inclusion of a new volume of fill, or a change in the existing nominal volume of fill of an injection or a peritoneal dialysis solution is considered under the legislation as a change in product strength and requires a Category 1 application.

Required information

- Details of the new or additional pack size and the rationale for its introduction.
- Revised labelling, if applicable.
- Where the proposed change would involve approval of an amended PI, details of the amended PI, as outlined in Section 1.4 of this document.

Historical document

H Changes to the shelf life or storage conditions of the drug substance or drug product

Note on stability testing

For biological medicine products requiring refrigeration or freezing, stability testing should be in real time at the specified storage temperature, for at least the requested shelf life. The time out of refrigeration (which also includes time out of the freezer) during normal manufacturing processes, up to the point of return to the fridge or freezer following labelling and packaging, should have been defined and justified. This should be based on worst-case storage scenarios and include storage conditions inherent in the manufacturing process and transport. From that point onward, all storage and shipping conditions should be justified by the real-time stability data; the data for justifying any temperature excursions should include real-time studies of the proposed excursion followed by return to the normal storage conditions for the remainder of the shelf life.

Refer to Appendix 14 of the ARGPM for additional details on requirements for stability testing of biological medicines.

Required information

- Real-time stability data on at least three production-scale batches to support the change. Data from fewer batches or pilot-scale batches may be acceptable, if justified. Shelf life will not be assigned based on accelerated testing.
- For multi-dose products (drug product only):
  - results of antimicrobial preservative efficacy testing, in accordance with the requirements of TGO 77, to support changes to the closed shelf life
  - results of simulated in-use testing to support changes to the open in-use shelf life. Details on this testing are provided in Appendix 16 of the ARGPM.
- For drug products that are to be reconstituted or diluted before use, data to support changes in the storage periods and conditions if the conditions are specified to be longer than 24 hours at 2–8 °C or 6 hours at room temperature. Appropriate microbiological data consists of microbiological challenge experiments similar to preservative efficacy testing. Ideally, the results should show evidence of microbial death, but demonstration of stasis (that is, not more than 0.5 $\log_{10}$ units higher than the initial value of the inoculum) over the proposed storage period is the minimum requirement. Chemical and physical data showing the stability of the reconstituted product are also required.
- Revised labelling for drug products, if the storage conditions are to be changed.
- Where the proposed change to a drug product would involve approval of an amended PI, details of the amended PI, as outlined in Section 1.4 of this document.
- If the change is approved, an updated CPD (see box 'Note on certified product details [CPD] documents', above).

Historical document

I Changes to labelling

Note on labelling

Any proposed changes to labels must comply with Therapeutic Goods Order No. 69[66]—General requirements for labels for medicines.

Required information

- Description of the proposed changes.
- Copies of both the currently approved labels and the changed labels. The proposed labels should meet the format requirements of Module 1.3.4 of the CTD format[67], and be actual size and in colour.

J Changes to gene technology aspects

Any changes to production cell lines are considered to be major manufacturing changes and will require thorough genetic characterisation, validation, comparability and stability studies. If variation in product quality attributes is found, clinical data will probably need to be provided to support the changes. This would require lodgement of a Category 1 application under the streamlined submission process. If there is any doubt about what type of application is required, contact the TGA.

K Changes to cell banks or seed lots

Types of changes to cell banks and seed lots for which evaluation of data is required include:

- creation of a new master cell bank or seed lot may be permitted as a Category 3 application (rather than a Category 1 or 2 application) only if adequate justification for not providing clinical data is provided
- creation of a new working cell bank or seed lot—this type of change can be self-assessable in some circumstances (see Section 4.2)
- change in storage conditions
- change in the primary storage site(s)[68] of the cell bank or seed lot; the new site will require GMP clearance.

[66] <http://www.comlaw.gov.au/Details/F2009C00264>
[67] <http://www.tga.gov.au/industry/pm-ctd.htm>
[68] A primary storage site for the master or working cell bank or master or working seed lot is the principal storage site or location from which the MCB and WCB cell bank/seed lot is retrieved for use in manufacturing. The site(s) which are used for back-up storage of the master or working cell bank/seed lot are considered secondary storage sites(s).

Historical document

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.

L Changes to filling of the drug product

Types of changes to filling processes for which evaluation of data is required include:

- change to in-process controls
- change in filling equipment that involves use of equipment significantly different from that used previously and that does not involve upgrade of an existing filling line
- increase in filling time.

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.
- If the drug substance is sterile and undergoes no further sterilisation, supporting data for changes to filling time or storage of sterile bulk drug substance. Appropriate validation data to support an increase in filling time should be provided.

M Changes to in-house reference standards

This applies to the introduction of a new reference standard (that is, a reference standard that has not been previously approved by the TGA) or an additional reference standard.

A request (containing the relevant data) can be made to have the process for qualification of an in-house reference standard approved by the TGA to allow subsequent changes in reference standards to be self-assessable (see Section 4.2 D).

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.
- If the change is approved, an updated CPD, if relevant (see box 'Note on certified product details [CPD] documents', above).

Historical document

N Changes to diluents or product components

Any changes to product components require the TGA to evaluate the data. This includes any changes to diluents and any change to, or addition of, a component of a biological medicine.

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.

O Changes to plasma master files

This section also applies to albumin when it is used as an excipient. The format of the plasma master file should comply with the EMA guidance document EMEA/CPMP/BWP/3794/03 *Guideline on the Scientific Data Requirements for a Plasma Master File (PMF)*, which has been adopted by the TGA.

The following types of changes are examples of those that require evaluation of data by the TGA:

- change to country of origin of plasma
- change to include a new organisation acting as a supplier of plasma (addition of a new collection site within an organisation can be provided in the PMF annual update)
- change to tests and site of viral testing of manufacturing plasma pool
- change to manufacturing pool size or number of donations per pool
- change to hold times for plasma
- change to donor selection/exclusion criteria
- change to donation quarantine period.

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.

P Changes to plasma fractionation intermediates

The following types of changes are examples of those that require evaluation of data by the TGA:

- change in manufacturer (for example, alternative supplier of an intermediate, with no change in the method of fractionation); a change in the method of fractionation may require supporting clinical data, and would thus be a Category 1 application

Historical document

- change in filter manufacturer
- change in batch size
- increase in hold times
- change in equipment
- addition or deletion of, or change to, a step
- increase in column life
- change in shelf life for storage of intermediate.

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.

Q Changes specific to influenza vaccines

Some of the processes for regulating quality-related changes to influenza vaccines are slightly different from the processes for other vaccines, because of the changing nature of the vaccine virus strains. This section may also be applicable to new vaccines that have similar requirements to influenza vaccines.

The following types of changes that are specific to influenza vaccines require evaluation of data by the TGA:

- change in strain for seasonal influenza vaccines—details of the reassorted virus or virus isolate should be provided in the application
- change in the approved reassorted virus or virus isolate for influenza vaccines—this refers to a change in the approved reassorted virus or virus isolate of the same strain used to produce the working seed lot. Details of the approved reassorted virus or virus isolate should be provided in the application
- any other changes requiring evaluation, such as strain-specific variations to production processes that exceed approved parameters.

Required information

- Description of the proposed change.
- Justification for the proposed change, including changes to test procedures.
- Appropriate validation data.

Historical document

R Changes to other types of quality-related variations where the change does not create a separate and distinct good

The types of quality-related changes listed in Section 4.3 are not intended to be exhaustive. If there is any doubt about the type of application required for a particular type of change, please contact the TGA.

An example of other types of change is a new supplier or manufacturer of albumin for a blood product.

Required information

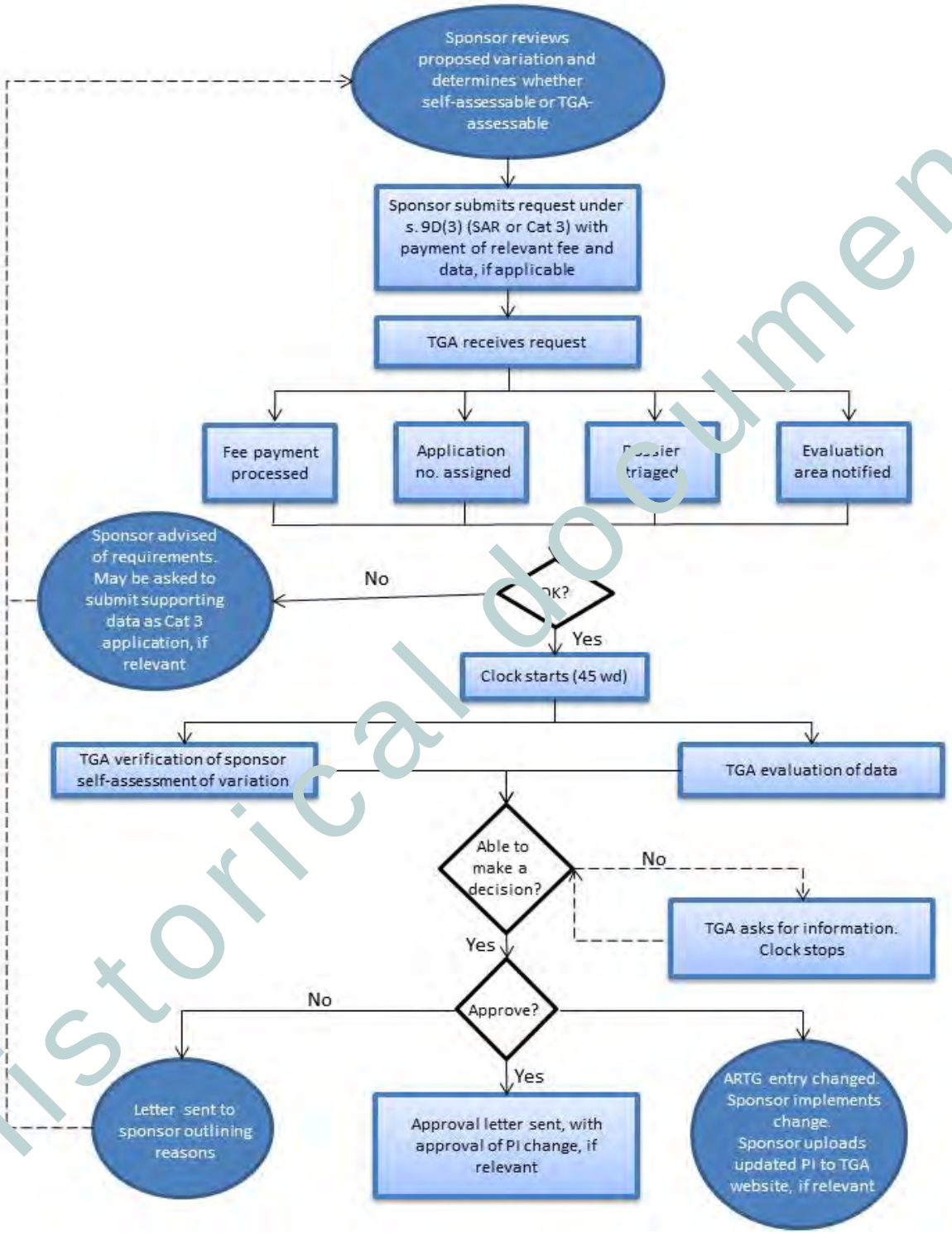
- Appropriate supporting data for the change(s).
- Where the proposed change would involve approval of an amended PI, details of the amended PI as outlined in Section 1.4 of this document.
- If applicable, and if the change is approved, an updated CPD (see box 'Note on certified product details [CPD] documents', above).

4.4 Summary of variations under s. 9D(3)

Figure 4.1 shows a flowchart of the processes for making a decision under s. 9D(3).

Historical document

Figure 4.1 Process for requests under s. 9D(3) of the *Therapeutic Goods Act 1989*

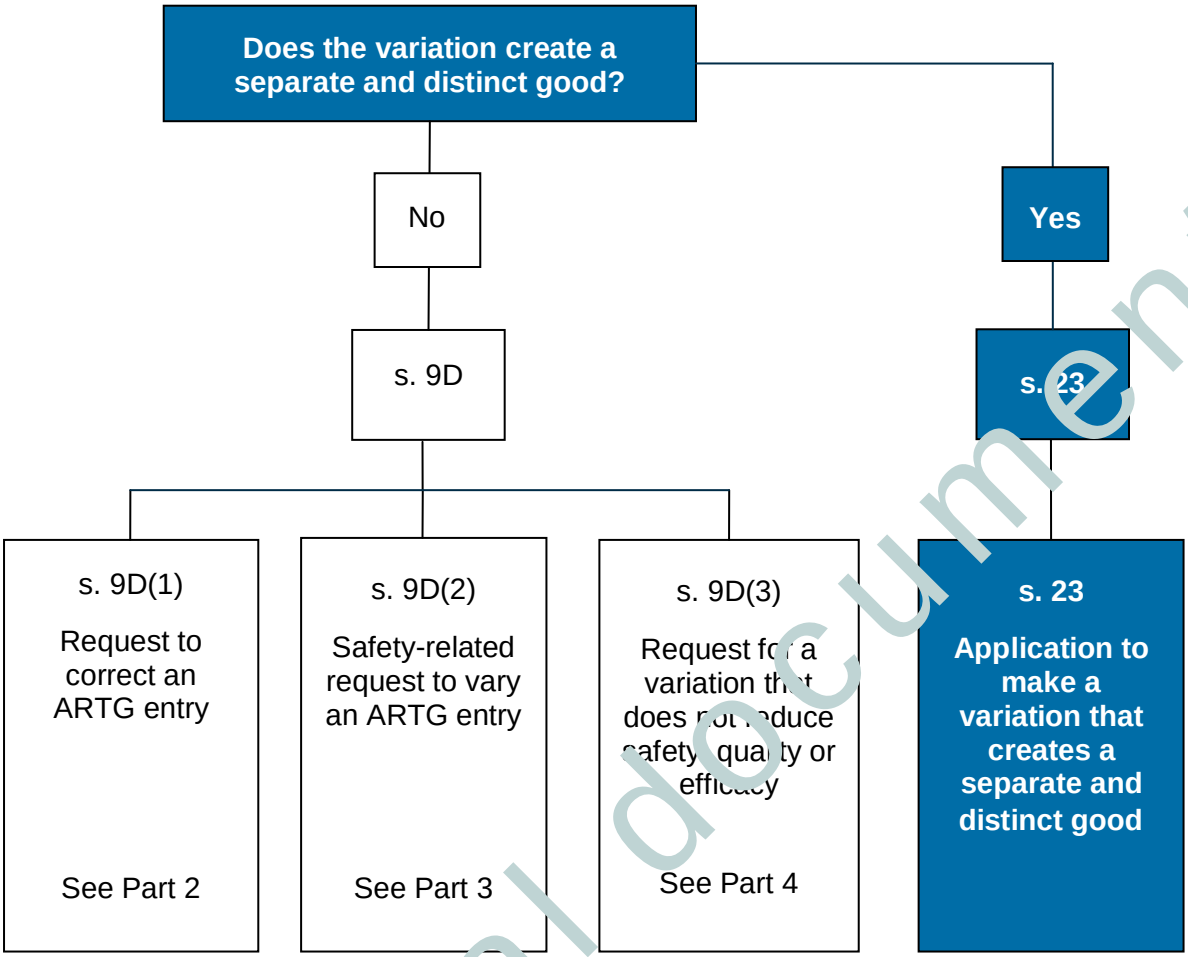


ARTG = Australian Register of Therapeutic Goods; Cat 3 = Category 3 application; PI = product information; SAR = self-assessable request; TGA = Therapeutic Goods Administration; wd = working days

Historical document

Part 5
Applying to make a variation that creates a separate and distinct good: s. 23

Historical document



Some variations under s. 23/s. 25 are self-assessable; others require data to be submitted to the TGA for evaluation		
Level of assessment	**Application type**	**Timeframe**
Verification of details provided by the sponsor	Quality-related variation: self-assessable request	45 working days
Evaluation of quality data only	Category 3 application: quality-related variation	45 working days
Full evaluation (combination of clinical, nonclinical, bioequivalence and quality data)	Category 1 or Category 2 application: major variation (streamlined submission process). Refer to the ARGPM for guidance on these application types	255 working days for Category 1; 175 working days for Category 2

ARTG = Australian Register of Therapeutic Goods

Historical document

5.1 What is a separate and distinct good?

Separate and distinct goods

Under s. 16(1) of the *Therapeutic Goods Act 1989*[69], a medicine is a separate and distinct good from the registered medicine if it has:

- a different formulation, composition or design specification; or
- a different strength or size (disregarding pack size); or
- a different dosage form or model; or
- a different name; or
- different indications;[70] or
- different directions for use; or
- a different type of container (disregarding container size).

Applications for variations to prescription medicines that create a separate and distinct good are made under s. 23 of the *Therapeutic Goods Act 1989* (TG Act) and approved under s. 25 and s. 25AA of the TG Act.

There are two routes for applications to change the quality aspects of medicines where a separate and distinct good is created.

- **Applications that require submission of data**
  Quality-related variations usually require evaluation of relevant data by the Therapeutic Goods Administration (TGA) as a Category 3 application under s.23. Variations that require evaluation of nonclinical, clinical or bioequivalence data will require a Category 1 or 2 application under s. 23 in the Streamlined Submission Process[71].

- **Applications that can be assessed by the sponsor (self-assessable request)**
  If quality-related variations are considered to be minor by the TGA, sponsors can assess the supporting data themselves and then make an application to the TGA based on this self-assessment. Minor changes must be appropriately validated as unlikely to reduce the safety, quality or efficacy of a medicine (in fact, some proposed variations can improve the quality of the product). Proposed variations should meet specific conditions to be considered self-assessable. The sponsor must then apply for approval of the variation, and must provide the supporting data if the TGA requests it.

Section 5.2 of this document outlines the self-assessable variations that can be made under s. 23, s. 25 and s. 25AA and their specific conditions.

[69] <http://www.comlaw.gov.au/Series/C2004A03952>
[70] Except for variations to indications under s. 9D(2) of the *Therapeutic Goods Act 1989*, as described in s. 9D(2A)
[71] <http://www.tga.gov.au/industry/pm-ssp.htm>

Historical document

Approval

The Secretary's approval under s. 25 is required for applications made under s. 23 of the *Therapeutic Goods Act 1989*[72]. This means that, even if the data to support the proposed variation do not have to be evaluated by the TGA, the variation must be formally approved before it can be implemented.

Section 5.3 of this document outlines the applications for quality-related variations made under s. 23 that require data to be submitted to the TGA for evaluation (Category 3 applications).

Because the variations covered in this part of the document will create a separate and distinct good, the 'new' good must be separately entered in the Australian Register of Therapeutic Goods[73] (ARTG). However, depending on the nature of the variation, the provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001[74] may mean that the old AUST R number can be retained for the new product. Where the provisions do not apply a new AUST R number will be provided upon approval.

If the new product keeps the old AUST R number because the Groups Order applies, the sponsor should advise the TGA when supply of the new product commences, by writing to:

Application Entry and Support Team
Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

For variations for which the provisions of the Groups Order **do not** apply, the sponsor should cancel the registration of the old product if they no longer intend to supply it. Sponsors should clearly indicate if they propose to supply both the old product and the new product concurrently.

If the sponsor decides not to supply the new product, they should notify the TGA in writing.

Historical document

[72] <http://www.comlaw.gov.au/Series/C2004A03952>
[73] <http://www.tga.gov.au/industry/artg.htm>
[74] <http://www.tga.gov.au/industry/legislation-groups.htm>

5.2 Self-assessable requests

Conditions for self-assessable requests

All self-assessable requests should be made using the procedures outlined in this section, **and receive the Secretary's approval** before the variation is implemented.

Sponsors should comply with the general requirements in this section and all the specific conditions listed for each proposed variation.

The TGA reserves the right to request copies of the experimental (validation) data at its discretion, and to follow up the validation during an inspection of the manufacturing site.

This section outlines the general requirements for making self-assessable requests, as well as the specific conditions for different types of self-assessable variations.

The validation data specified in this document are the minimum requirements and any additional necessary validation (for example, to comply with the *Guide to Good Manufacturing Practice for Medicinal Products*[75]) should also be conducted. If validation data are needed to support a variation, these data may be generated using either pilot plant–scale or full production batches of the product,[76] except for variations to batch size, where the data should be generated from full production-scale batches.

If the validation tests show a difference between pre-variation and post-variation batches, an appropriate Category 3 application for evaluation should be made (see Section 5.3) unless otherwise allowed in this document or agreed to by the TGA.

Depending on the nature of the variation and the significance of the differences in results, additional data, such as studies of bioavailability, clinical safety or efficacy, may be needed—the application will then become a Category 1 or 2 application. If this was the case, sponsors would need to submit a new application in the Streamlined Submission Process.

It is not mandatory for sponsors to use the self-assessment procedure. Any proposed variations to registered medicines may be submitted as a formal Category 3 application for evaluation, in which case the normal data requirements evaluation fee will apply.

General requirements

The following general requirements always apply to self-assessable requests, and the sponsor should ensure that they comply:

- The product must be registered in the ARTG.

[75] <http://www.tga.gov.au/industry/manuf-pics-gmp-medicines.htm>
[76] The role of pilot-scale batches is to provide data that are predictive of the production-scale product. Pilot-scale studies may be used in the process development phase to support formal stability studies, and to support nonclinical and clinical evaluation. The choice of pilot batch size should be justified.

Historical document

- No application for a variation that requires TGA evaluation of data should be submitted at the same time as the self-assessable request, unless the two applications are clearly identified and appropriate procedures are followed. Note that separate fees may apply if the different applications do not fall under the same type of submission, as defined in Part 1 of Schedule 9 of the Therapeutic Goods Regulations 1990[77].
- All of the validation data specified for each proposed variation should be generated.
- Experimental (validation) data must be supplied to the TGA, if requested.
- Validation data should be provided upon request during a good manufacturing practice (GMP) inspection.

How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit an application. The TGA can provide advice on general requirements for the application and relevant parts of the legislation, but cannot provide detailed, specific information about a particular application until it has been lodged.

Further information is also on the TGA website[78]

What do I need to provide?

Self-assessable requests should be accompanied by **all** of the following:

- a completed 'Self-assessable request (SAR): Quality-related variation under section 23' form (see below)
- an assurance that the only variations being made to the ARTG entry are those identified in the application, and that no other aspects of the quality information have been changed, including manufacturing procedures and equipment, and raw material and drug product specifications
- a statement that all of the general conditions and all of the applicable specific conditions have been complied with
- clean and marked-up copies of the product information (PI) (see Section 1.4 of this document)
- relevant evidence of GMP (clearance letter if an overseas site of manufacture is involved, or Australian manufacturing licence), if this is a condition of self-assessment

[77] <http://www.comlaw.gov.au/Series/F1996B00406>
[78] <http://www.tga.gov.au>

Historical document

- any other information specified as 'Required information' for that type of change (see subsequent sections)
- the relevant fee (see 'What fees do I pay?', below).

The form 'Self-assessable request (SAR): Quality-related variation under section 23' is available on the TGA website; all sections of the form should be completed. The completed hard copy of the form should be signed by the person who is taking responsibility for ensuring that all of the general and specific conditions relevant to the proposed change have been complied with, and any specified validation data have been generated and self-assessed by the sponsor as acceptable.

The form, together with any covering letter, required information or documents, and the relevant fee, should be sent to:

Application Entry and Support Team
Office of Medicines Authorisation
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Note that any validation or experimental data that were generated for self-assessment purposes should not be submitted with the application. However, these data may be requested by the TGA for review at a later date. Depending on the type of variation proposed, different types of self-assessable requests require different types of information. Details of these specific requirements are provided in the relevant subsections of Section 5.2 of this document. The information should relate only to the specific variations applied for; no other data should be provided.

Variations resulting in separate and distinct prescription medicines cannot be implemented without prior approval by the TGA. Doing this means that an unregistered product is being supplied. If such a variation is implemented without approval by the TGA (refer to Section 1.5), a Category 3 application, including payment of any applicable evaluation fee, will be required to regularise the change, and the full validation data will be required for evaluation. It is an offence under the Act to supply unregistered prescription medicines. **Self-assessment is not a means of regularising unauthorised changes made to registered medicines which create separate and distinct goods.**

All s. 23/s. 25 self-assessable variations that are approved by the TGA will be documented as new ARTG entries under the provisions of s. 25 of the TG Act. If a proposed variation does not meet the criteria of a self-assessable request or not all of the specific conditions have been met, the application cannot be approved because the correct procedure has not been followed. Sponsors will be advised to submit the correct form 'Category 3 application: Quality-related variation under section 23' and the necessary supporting information in a new application, if they still wish to vary the entry.

For information on applications under s. 23 that require data, see Section 5.3.

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the Therapeutic Goods Regulations 1990[79]. These fees are subject to change from time to time; current fees[80] are

[79] <http://www.comlaw.gov.au/Series/F1996B00406>

Historical document

published on the TGA website. The fees for self-assessable requests under s. 23 are listed at item 2(a).

What are the timeframes?

Under regulations 16G and 16F of the Therapeutic Goods Regulations 1990, which apply to all quality-related applications under s. 23, the Secretary must make a decision about the application and notify the sponsor within 45 working days of receiving the application and payment (whichever is later) or, if necessary, raise an objection concerning the application (refer to Section 1.2). An objection usually means that the Secretary will ask the sponsor questions about the product that are necessary for them to make a decision about the application, to which the sponsor must respond.

If an objection is raised by the Secretary, the clock will stop from the time the objection is raised (that is, the matter is raised with the sponsor) and will start again when the TGA receives the response to the objection from the sponsor. The Secretary then has 30 working days from the day on which the response is received to notify the sponsor of the decision.

If the Secretary does not make a decision within the 45–working day timeframe (or subsequent 30–working day period after a response to an objection), the application is taken to have been approved.

What happens to my application?

If all the requirements for a self-assessable variation have been met, including payment of the appropriate fee, the application is referred to the relevant TGA evaluation area for assessment. If a requirement has not been met (for example, the sponsor has not included a correctly marked-up copy of the proposed new PI), the sponsor will be asked to submit the required information before the application can be processed.

When all the necessary information has been received by the TGA (including payment), the clock starts on the application. The TGA verifies the sponsor's self-assessment of the variation, and approves the application if applicable. If the Secretary is not able to make a decision, the clock stops while the TGA asks for information under s. 31 of the TG Act or raises an objection (see above). The clock restarts on receipt of the complete response to the request for information. There is no limit on the number of clock stops under s. 31. The person making the application will be sent a letter outlining the decision when it is made. Reasons for the decision will be provided if the application is rejected.

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the application at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the application is approved under s. 25, a new entry will be created and a new PI will also be approved under s. 25(4) and s. 25AA(1) of the TG Act. Sponsors should lodge copies of the new PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[81] system within 2 weeks of the date of approval. For injectable prescription medicines, the current

[80] <http://www.tga.gov.au/about/fees.htm>
[81] <https://www.ebs.tga.gov.au/>

Historical document

approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 25 and s. 25AA(1) are subject to review under s. 60 of the TG Act.

Sponsors may withdraw their application at any time during the process. If they do so after the application has been accepted, they will forfeit the fees paid.

Types of self-assessable requests

The following changes are self-assessable under s. 23 of the TG Act.

A Formulation change relating to colouring agent, flavour or fragrance

B Addition or deletion of, or variation to, an inked imprint

A Formulation change relating to colouring agent, flavour or fragrance

The AUST R number can be retained

Certain changes to, or addition or deletion of, colouring agents, flavour or fragrance of a product may be made through self-assessment. Under s. 16(1) of the *Therapeutic Goods Act 1989*[82], a change in formulation means that the reformulated product is a separate and distinct good from the existing product, and this requires a new ARTG entry.

However, the provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001 allow the AUST R number of the existing product to be retained for the new product if the new product replaces the existing product.

Specific conditions

- The colouring agent, fragrance or flavour is present in the formulation at not more than 2% w/w or w/v, and contains only substances that are already entered in the ARTG.
- Any new colour is listed in the current TGA list of colours permitted in medicines for oral use, and complies with the specifications in the same list (see the TGA guideline '*Colourings permitted in medicines for oral use*[83]').
- Any new proprietary excipient[84] to be used should be already entered in the ARTG.

[82] <http://www.comlaw.gov.au/Series/C2004A03952>
[83] <http://www.tga.gov.au/industry/cm-colourings-oral-use.htm#colourings>

Historical document

- Relevant comparative data of the type listed below should have been generated for the dosage form manufactured using the new and old formulations. At least three recently manufactured batches of the pre-variation product and one production batch of the post-variation product should be tested, preferably at the same time and using the same method. The second and third batches manufactured under the new conditions, if not available at the time of application, should be tested, and the results should be reviewed by the sponsor as soon as they become available. The TGA should be notified of any differences as a priority.
  - For all **solid dosage forms** (for example, tablets, capsules, compressed suppositories and pessaries), the comparative dissolution profiles should be similar (that is, the similarity factor, f_2, should be between 50 and 100). These data are not required if the drug is in solution at any stage during manufacture of the drug product, or if it is in solution in the drug product or present as liquid globules.
  - For **semi-solid and liquid products** (for example, ointments, creams, lotions, oral liquids, moulded suppositories and pessaries), comparative batch data using appropriate methodology should demonstrate that there has been no change to the particle size distribution and polymorphic form of the drug substance in suspension. These data are not required if the drug substance is in solution at any stage during manufacture of the drug product, or if it is in solution in the drug product or present as liquid globules.
- A stability test on the reformulated product should have begun on at least one production-scale batch, and should begin on the second and third batches as they become available. If the results of the stability test do not meet the specifications, the TGA should be notified immediately, and the reformulated product may be withdrawn from the market at the TGA's discretion.
- If relevant, the drug product specifications (release and expiry) should be revised to incorporate any new product description or other organoleptic properties of the product.

Required information

- The code number for the new proprietary excipient, together with its ARTG number, if relevant.
- A comparative list of the current and new product formulations.
- Information on use or non-use of human embryos or human embryonic stem cells, or other material sourced from human embryos or human embryonic stem cells, in the manufacture of the product (this is a requirement under regulation 9B).
- An updated certified product details (CPD) document for the product that incorporates the changes if applicable (see box 'Note on certified product details [CPD] documents', in Section 4.2).
- A clean copy of the PI must be provided. Where the proposed change would involve approval of a new PI, a marked-up copy should also be provided, as outlined in Section 1.4 of this document.

[84] As defined in the Therapeutic Goods (Groups) Order No. 1 of 2001

Historical document

B Addition or deletion of, or variation to, an inked imprint

The AUST R number can be retained

An inked imprint is a mark made by printing with an ink during product manufacture, where the ink itself is part of the product formulation. Inked imprints on a solid oral dosage form may be added, deleted or varied through self-assessment.

Addition, deletion or change in formulation of an ink is a change in product formulation. Under s. 16(1) of the *Therapeutic Goods Act 1989*[85], this means that the reformulated product is a separate and distinct good from the existing product and requires a new entry on the ARTG.

However, the provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001 allow the AUST R number of the existing product to be retained for the new product if the new product replaces the existing product.

Note that, if the proposed change is to the inking pattern, but the same ink is used, this represents a change to an existing ARTG entry. Refer to Section 4.2 B for requirements.

Specific conditions

- Any new colour or dye of an ink should be listed in the current TGA list of colours permitted for use in medicines for ingestion (see the TGA guideline '*Colourings permitted in medicines for oral use*[86]'), and should comply with the specifications in that list.
- Any new proprietary excipient to be used should be already entered in the ARTG.
- If relevant, the drug product specification should be revised to incorporate any change in product description.

Required information

- A comparative list of the current and new product formulations, if relevant.
- Information on use or non-use of human embryos or human embryonic stem cells, or other material sourced from human embryos or human embryonic stem cells, in the manufacture of the product (this is a requirement under regulation 9B).
- The revised product description (if this has changed), incorporated into the revised set of drug product specifications (release and expiry).
- The code number for the proprietary excipient, if relevant, together with its ARTG number.

[85] <http://www.comlaw.gov.au/Series/C2004A03952>
[86] <http://www.tga.gov.au/industry/cm-colourings-oral-use.htm#colourings>

Historical document

- An updated CPD document for the product that incorporates the changes, if applicable (see box 'Note on certified product details [CPD] documents', in Section 4.2).
- A clean copy of the PI must be provided. Where the proposed change would involve approval of a new PI, a marked-up copy should also be provided, as outlined in Section 1.4 of this document.

Historical document

5.3 Applications that require submission of data

This section outlines the procedures for submitting a Category 3 application for a quality-related change under s. 23.

The data required to support a Category 3 application for a variation to the quality information that result in a separate and distinct good are detailed in this section. The types of changes listed in this section are representative, and are not intended to be an exhaustive list of all quality-related changes requiring evaluation of data by the TGA. The requirements are essentially the same as for the corresponding section of an application to register a new medicine. The relevant European Medicines Agency (EMA)/International Conference on Harmonisation (ICH)[87] guidelines adopted by the TGA should be followed, as appropriate.

Applications for variations that require evaluation of clinical, nonclinical or bioequivalence data will require a Category 1 or Category 2 application in the Streamlined Submission Process[88]. If a Category 3 application is submitted, but the TGA determines that evaluation of clinical, nonclinical or bioequivalence data is required, sponsors will be informed that the relevant guidance advises that the application should be made as a Category 1 or Category 2 application with relevant supporting data. Sponsors should be aware that r. 16G and r. 16F of the Therapeutic Goods Regulations 1990[89] will not apply to the application if the delegate forms the opinion that TGA evaluation of clinical, nonclinical or bioequivalence data is required. In this case, r. 16C or r. 16D will consequently apply and sponsors will be required to submit a new Category 1 or Category 2 application for the variation to be approved.

How to apply to the TGA

Advice for sponsors

If you want clarification about which procedure to follow, contact the TGA.

You can also contact the TGA for general information before you submit an application. The TGA can provide advice on general requirements for the application and relevant parts of the legislation, but cannot provide detailed, specific information about a particular application t until it has been lodged.

Further information is also on the TGA website[90]

What do I need to provide?

For a Category 3 application, sponsors should provide the following:

- a cover letter (see below)

[87] <http://www.tga.gov.au/industry/pm-euguidelines.htm>
[88] <http://www.tga.gov.au/industry/pm-ssp.htm>
[89] <http://www.comlaw.gov.au/Series/F1996B00406>
[90] <http://www.tga.gov.au/>

Historical document

- a completed 'Category 3 application: Quality-related variation under section 23' form
- the relevant data in the common technical document[91] (CTD) format. Only a single copy of the supporting data needs to be submitted. The data should relate only to the specific variations proposed; no other data should be provided.

For each proposed change, the sponsor should provide **all** of the following in the cover letter of the application:

- a clear description of the currently approved information that is relevant to the proposed variation
- details of the proposed change
- justification for the change(s)
- technical data to support the proposed change(s) (see 'Specific conditions', below)
- a declaration that 'No aspects of the quality information have been changed, including manufacturing procedures and equipment, and raw material and drug product specifications, other than the changes nominated in this application.'

The sponsor should provide clean and marked-up copies of the PI, as outlined in Section 1.4 of this document.

What fees do I pay?

The fees payable for services provided by the TGA are listed in Schedule 9 of the Therapeutic Goods Regulations 1990[92]. These fees are subject to change from time to time; current fees[93] are published on the TGA website. The fees for applications under s. 23 that require supporting data are listed at items 2(bj) and 4(h).

What are the timeframes?

Under regulations 16G and 16I of the Therapeutic Goods Regulations 1990, which apply to all quality-related applications under s. 23, the Secretary must make a decision about the application and notify the sponsor within 45 working days of receipt of the application and payment (whichever is later) or, if necessary, raise an objection concerning the application (refer to Section 1.3). An objection usually means that the Secretary will ask the sponsor questions about the product that are necessary for them to make a decision about the application, to which the sponsor must respond.

If an objection is raised, the clock will stop from the time the Secretary raises the objection (that is, asks for the necessary information) and will start again when the TGA receives the response to the objection from the sponsor. The Secretary then has 30 working days from the day on which they receive the response to notify the sponsor of the decision.

If the Secretary does not make a decision within the 45–working day timeframe (or subsequent 30–working day period after a response to an objection), the application is taken to have been approved.

[91] <http://www.tga.gov.au/industry/pm-ctd.htm>
[92] <http://www.comlaw.gov.au/Series/F1996B00406>
[93] <http://www.tga.gov.au/about/fees.htm>

Historical document

What happens to my application?

If all the requirements for a s. 23 application have been met, including payment of the appropriate fee, the application is referred to the relevant TGA evaluation area for assessment. If a requirement has not been met (for example, the sponsor has not included a correctly marked-up copy of the proposed new PI), the sponsor will be asked to submit the required information before the application can be processed.

When all the necessary information has been received by the TGA (including payment), the clock starts on the application. The TGA evaluates the data, and approves the application, if applicable. If the Secretary is not able to make a decision, the clock stops while the TGA asks questions under s. 31 of the TG Act or raises an objection (see above). The clock restarts on receipt of the complete response to the questions asked. There is no legal limit to the number of clock stops under s. 31. The person making the application will be sent a letter outlining the decision when it is made. Reasons for the decision will be provided if the application is rejected.

The TGA will only review those variations requested under the relevant part of the Act that are described in the application form provided with the application at the time of submission. Any new information will only be accepted if the TGA requests them as part of the review process, except under justifiable extenuating circumstances. Any other ongoing regulatory activity, such as a change in sponsorship, is usually considered independently of minor variations.

If the application is approved under s. 25, a new entry will be created and a new PI will also be approved under s. 25(4) and s. 25AA(1) of the TG Act. Sponsors should lodge copies of the new PI and Consumer Medicine Information with the TGA via the TGA eBusiness Services[94] system within 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI must also be supplied in hard copy with the medicine (this is a condition of registration for injectable medicines only).

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. All decisions made under s. 25 and s. 25AA(1) are subject to review under s. 60 of the TG Act.

Sponsors can withdraw their application at any time during the process but fees are not refundable.

[94] <https://www.ebs.tga.gov.au/>

Historical document

Data requirements

The following applications to vary an ARTG entry to create a separate and distinct good require submission of supporting data to the TGA for evaluation:

A Formulation changes

B Change to container type

C Gene technology aspects

D Replacement of trade name

Depending on the nature of the proposed change(s), the supporting technical data described below should be provided. If not provided, the data may be requested by the TGA. Sponsors should be aware that the types of changes listed in this section are not exhaustive, and that the technical data required represent the minimum data necessary for assessment. The TGA reserves the right to request data or information in addition to those specified below, if appropriate.

The guidance provided below:

- is in addition to the information in 'How to apply to the TGA', above
- applies only to biological medicines.

A Formulation changes

Changes to the formulation of a biological medicine require evaluation of clinical and nonclinical data. These types of variations should be submitted as Category 1 or Category 2 applications under the streamlined submission process. Some minor formulation changes with no clinical impact may be submitted as a Category 3 application. Please contact the TGA to discuss proposed changes that may meet these criteria.

Historical document

B Changes to container type (drug product)

The AUST R number cannot be retained

Under s. 16(1) of the *Therapeutic Goods Act 1989*[95], a change in container type means that the repackaged product is a separate and distinct good from the existing product, and this requires a new ARTG entry. The provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001 **do not apply so it is not possible for the current AUST R number to be used for the new product**.

Applications to change the container type can be submitted as Category 3 applications under s. 23 only if no other changes requiring evaluation of clinical and nonclinical data are proposed. An example of a change where this is applicable is changing from a vial to a prefilled syringe or cartridge.

If other types of changes (such as changing the indications or route of administration) are also proposed, these should be submitted as Category 1 or Category 2 applications under the streamlined submission process.

Required information

- Container description and relevant specifications.
- The proposed shelf life and storage conditions in the new container type.
- Stability data (including physical, chemical and microbiological aspects, as applicable) as per TGO 77[96] from at least three production-scale batches, to confirm the stability of the product in the new type of container.
- Information on use or non-use of human embryos or human embryonic stem cells, or other material sourced from human embryos or human embryonic stem cells, in the manufacture of the product (this is a requirement under regulation 9B of the Therapeutic Goods Regulations 1990).
- For sterile products, information on sterile manufacture, validation of sterilisation processes, validation of container closure integrity, preservative efficacy data and sterility testing data, as appropriate.
- For non-sterile products, details of the revised manufacturing process in the new container, together with process validation data, if appropriate.
- Revised labelling, if applicable.

  A clean copy of the PI must be provided. Where the proposed change would involve approval of a new PI, a marked-up copy should also be provided, as outlined in Section 1.4 of this document.

[95] <http://www.comlaw.gov.au/Series/C2004A03952>
[96] <http://www.tga.gov.au/industry/legislation-tgo.htm>

Historical document

C Gene technology aspects

Any change to production cell lines is considered to be a major manufacturing change and will require thorough genetic characterisation, validation, and comparability and stability studies. If the product quality varies as a result of the change, clinical data are likely to be needed. This requires lodgement of a Category 1 application under the streamlined submission process. If sponsors have any doubt about the type of application required, they should contact the TGA.

Sponsors should revalidate the manufacturing process if there is any change in batch size or batch definition (for example, pooling of multiple batches from fermentation), or a change to the in-process controls. Analytical validation will need to be redone if there are any changes to analytical methods or specifications. If the sponsor chooses not to provide validation they should include a statement of assurance that there have been no changes to the process, in-process controls, analyses and specifications.

D Replacement of trade name

The AUST R number can be retained

Under s. 16(1) of the *Therapeutic Goods Act 1989*[97], a change in trade name means that the renamed product is a separate and distinct good from the existing product, and this requires a new ARTG entry. However, the provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001 allow the AUST R number of the existing product to be retained for the new product, if the new product replaces the existing product.

Only the trade name—not the nonproprietary name of the drug substance—can be changed under this application type. The details of the product, including indications and sponsor, should remain the same.

Required information

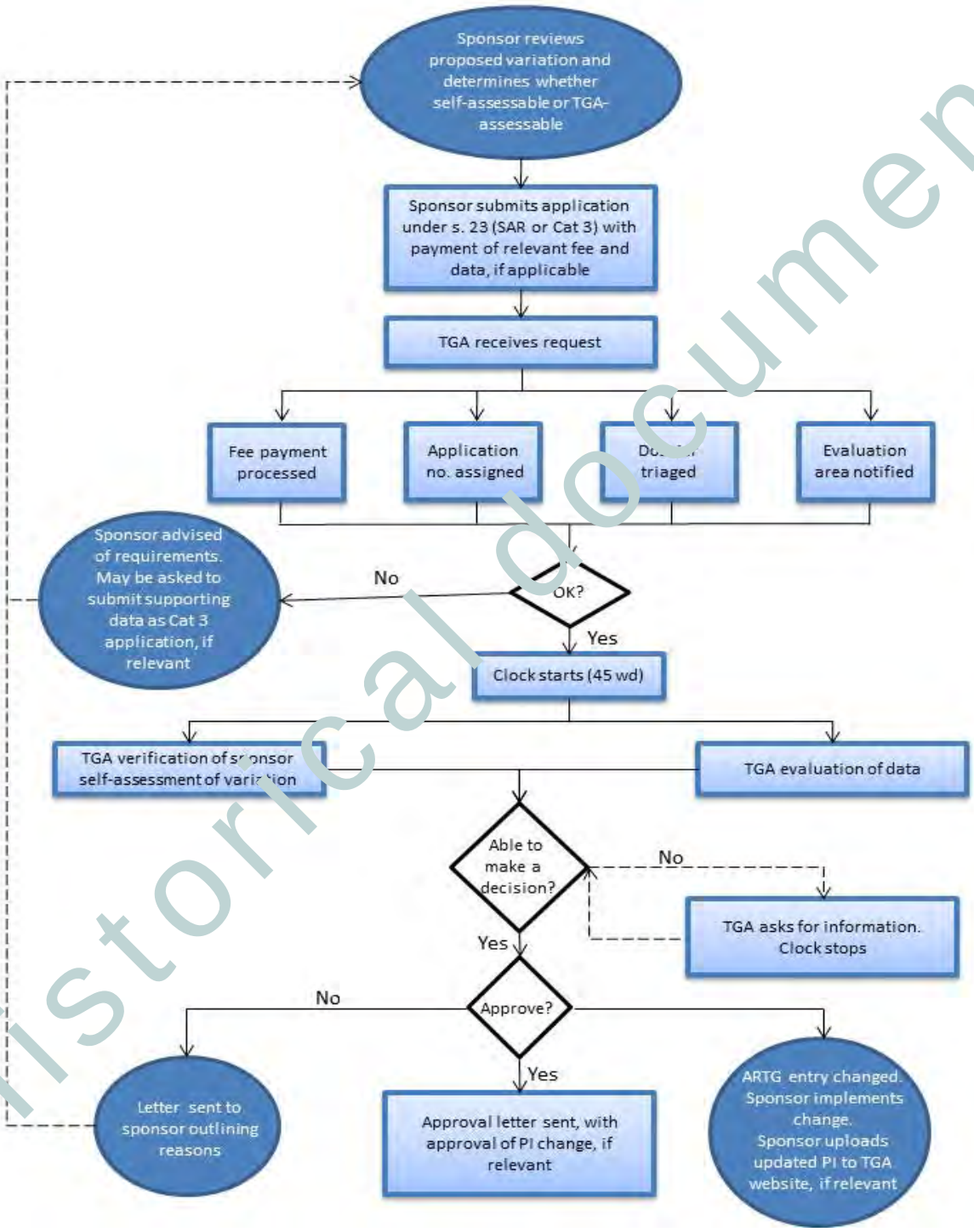
- Proposed replacement trade name.
- The revised label.
- Information on use or non-use of human embryos or human embryonic stem cells, or other material sourced from human embryos or human embryonic stem cells, in the manufacture of the product (this is a requirement under regulation 9B of the Therapeutic Goods Regulations 1990[98]).
- A clean copy of the PI must be provided. Where the proposed change would involve approval of a new PI, a marked-up copy should also be provided, as outlined in Section 1.4 of this document.

[97] <http://www.comlaw.gov.au/Series/C2004A03952>
[98] <http://www.comlaw.gov.au/Series/F1996B00406>

Historical document

5.4 Summary of variations under s. 23

Figure 5.1 Process for applications under s. 23 of the *Therapeutic Goods Act 1989*



ARTG = Australian Register of Therapeutic Goods; Cat 3 = Category 3 application; PI = product information; SAR = self-assessable request; TGA = Therapeutic Goods Administration; wd = working days

Historical document

Part 6
Changes that do not require prior approval

Historical document

IMPORTANT

The processes described in Part 6 cannot be used if the proposed changes require a consequential change to the approved product information of the registered medicine.

6.1 Changes that do not require notification to the TGA

The TGA does not need to be notified about the following changes:

- changes to the local distributor of the drug substance and excipient, including material of biological origin (same site and method of manufacture, specification and, where applicable, biological source, including geographical origin and supplier)
- the following changes to product labels **with strictly no other changes** and where minimum letter height requirements of the therapeutic goods order pertaining to labels are observed:
  - changes to colours of artwork, provided that it does not impair legibility of labels (and unless colour-coding is used to indicate product strength)
  - change of typeface and increase in font size of print only
  - inclusion or removal of foreign national registration number
  - inclusion or removal of, or changes to, name and address of supplier in New Zealand
  - inclusion or removal of state of manufacture of product
  - inclusion or removal of, or changes to, sponsor or supplier telephone/facsimile number, barcodes, Australian Business Number or Australian Company Number, product code number, recycle logo and associated text, trademark and other such symbols (for example, ®, © and ™)
  - change to AUST R number following an approved change that requires a new AUST R number (for example, new formulation). (For other aspects of changes to product labels, see sections 4.2 G and 4.3 I in this document)
  - change in web address, without a change in the content of the website

any other change that the TGA has advised does not require notification to the TGA.

6.2 Changes that require notification to, but not prior approval by, the TGA

The TGA should be notified of the following changes, but prior approval is not required:

- change to manufacturer's name (provided that they are not the product sponsors) or the manufacturing address, provided the actual site location does not change

Historical document

- certain changes to plasma master files.

Notification, together with any relevant documentary evidence required in support, should be made in writing and the date of implementation advised. No specific form is required. The self-assessable request form (see sections 4.2 and 5.2) should not be used for this purpose. Further details for each type of change are given below.

Change to manufacturer's name only (provided that they are not the product sponsors), but not the manufacturing site address

The notification, together with valid good manufacturing practice (GMP) evidence of the company with the new name, should be sent to:

Office of Manufacturing Quality
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

A new GMP clearance letter or an Australian manufacturing licence will be issued, as appropriate. GMP clearance may also be required when an overseas manufacturer changes company name.

The information about the name change, together with a covering letter from the sponsor, should then be forwarded to the Information Technology Section of the TGA, with a request to update the client database in the TGA eBusiness Services. This will ensure that ARTG entries for the products concerned include the new company name.

A copy of the notification, together with the new GMP clearance letter, should be sent to the Application Entry and Support Team in the Office of Medicines Authorisation at the same address. This procedure should be followed by every sponsor whose products are manufactured by the affected manufacturer.

Changes to plasma master files

The following changes are included in annual updates to plasma master files and therefore do not require separate notification to the TGA:

- addition or removal of collection centres for a currently approved collection organisation (see Appendix 9 of the *Australian Regulatory Guidelines for Prescription Medicines*[99])
- change of sites for testing of individual donations
- change of tests for testing individual donations.

Editorial changes to documentation for the manufacturing process

Typographical and editorial changes to documentation for the manufacturing process do not require prior approval by the TGA, provided that they do not change the performance of the procedure.

[99] <http://www.tga.gov.au/industry/pm-argpm.htm>

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Notification, together with any relevant documentary evidence required in support, should be made in writing and the date of implementation advised. No specific form is required. Sponsors should provide clean and marked-up copies of the description of the manufacturing process.

Changes to method of manufacture of drug substance or drug product

Changes to acceptance criteria for raw materials do not require prior approval by the TGA, provided that the changes meet the specifications of the relevant official standard, and there is no reduction in the quality of the product.

Notification, together with any relevant documentary evidence required in support, should be made in writing and the date of implementation advised. No specific form is required. Sponsors should provide a summary of the new acceptance criteria, preferably in tabular format.

Historical document

Glossary

Note: terms that are highlighted in bold type in this glossary are specifically defined in s. 3(1) of the *Therapeutic Goods Act 1989*[100] (TG Act).

adjuvant	A component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses.
antibiotic	A selective antimicrobial agent (other than disinfectants, antiseptics and substances solely used as anti-neoplastics) that, on application to living tissue or by systemic administration, kills or prevents growth of susceptible microorganisms.
application (under s. 23 of the TG Act)	Variations to Australian Register of Therapeutic Goods (ARTG) entries that create separate and distinct goods under s.16(1) of the *Therapeutic Goods Act 1998* (TG Act) are made by submitting an 'application' to the TGA under s. 23 of the TG Act, which is approved under s. 25. The word 'application' is used in the legislation. Other types of variations to ARTG entries that are discussed in this document are made by submitting a 'request' to the TGA under s. 9D of the TG Act.
Australian Register of Therapeutic Goods[101] (ARTG)	The register maintained under s. 9A of the TG Act for the purpose of compiling information in relation to, and providing for evaluation of, therapeutic goods for use in humans.
ARTG entry	A separate and distinct product included in the ARTG, as described by the criteria in s. 16(1) of the TG Act. *See also* Australian Register of Therapeutic Goods (ARTG)

[100] <http://www.comlaw.gov.au/Series/C2004A03952>
[101] <http://www.tga.gov.au/industry/artg.htm>

Historical document

batch	As defined in s. 3(1) of the TG Act, a quantity of the product that is: • uniform in composition, method of manufacture and probability of chemical or microbial contamination; and • made in one cycle of manufacture and, in the case of a product that is sterilised or freeze dried, sterilised or freeze dried in one cycle. A **production-scale batch** is a batch of the size that will be produced during routine marketing of the product. Data from production-scale batches may not always be available before registration of the product. The role of a **pilot-scale batch** is to provide data that are predictive of the production-scale product. Pilot-scale studies may be used in the process development phase to support formal stability studies, and nonclinical and clinical evaluations.
Category 1, 2 or 3 application	The type of administrative application made to the TGA to register new products or vary existing products.
certified product details (CPD)	A statement of product details, specifications and test methods generated by the sponsor at the request of the TGA.
clock	Recording of working days by the TGA, by which statutory timeframes for requests and applications are measured.
common technical document[102] (CTD) format	An internationally agreed set of specifications for a submission dossier. The CTD format includes five modules that set out the requirements for a consistent, unambiguous and transparent dossier that can be easily navigated by TGA staff and evaluators .
composite pack	A medicinal product in which the primary pack or container contains two or more therapeutic goods, but does not contain therapeutic devices or medical devices. They are used for a single treatment or a single course of treatment, and the components are either combined before treatment or administered in a particular sequence. The composite pack itself is regulated as a separate and distinct good and must have its own unique AUST R number. Individual components within the pack may or may not have separate registrations or listings. Examples of composite packs are a blister pack that contains several different oral contraceptives, and a vial of medicine that is a lyophilised powder that is packaged with an ampoule or vial containing a diluent.

[102] <http://www.tga.gov.au/industry/pm-ctd.htm>

Historical document

consequential change (to the approved product information)	A required change to the approved product information for a medicine as a result of a variation to the ARTG entry for that medicine.
container	The immediate covering of the goods. This could be a bottle, tube, ampoule, syringe, vial, sachet, strip pack, blister pack, wrapper, cover or other similar article that immediately covers the goods. It does not include an article intended to be ingested. *See also* packaging
container type	The terms used to describe containers that hold medicines. Descriptions of the various types of containers are listed in the 'Container code' table on the TGA eBusiness Services website[103]. Container types are independent of the material used to make the container, the size of the container and type of closure (if any).
default standard	Sections 3 and 10 of the TG Act list three pharmacopoeias, defined as 'default standards', that are used to specify the quality, method of manufacture and other aspects of therapeutic goods. These are the *British Pharmacopoeia*, *European Pharmacopoeia* and *United States Pharmacopeia- National Formulary*. Wherever possible, a relevant monograph in one of the default pharmacopoeias (including their supplements) serves as the standard for substances used in medicines. Some exclusions from this requirement are described in specific therapeutic goods orders.
diluent	A sterile liquid, supplied as a component of some medicines or as a separate product, and intended for use in reconstitution/dilution of the drug product in preparation for administration (for example, water for injections).
dosage form	The pharmaceutical form in which a product is presented for therapeutic administration (for example, tablet, cream). Descriptions of the various kinds of dosage forms, and their definitions, are listed in the 'Dosage forms' table on the TGA eBusiness Services website.
drug product	The finished or final dosage form of the therapeutic good, after all stages of manufacture (other than release for sale) have been completed. Also known as finished product.
drug substance	The therapeutically active component in the final formulation of therapeutic goods that are biological medicines. Also known as active ingredient.

[103] <https://www.ebs.tga.gov.au/>

Historical document

excipient	Any component of a drug product other than an active ingredient. In some cases, the distinction between an active ingredient and an excipient may not be clear—for example, sodium chloride used to adjust tonicity of an injection is an excipient.
fee	A sum payable to the TGA by a person making a request or application in relation to that request or application, as set out in Part 2 of Schedule 9 of the Therapeutic Goods Regulations 1990[104] (for example, an evaluation fee).
fill volume	Agreed specification of the target volume of a drug product in the final container.
good manufacturing practice (GMP)	A set of principles and procedures that, when followed by manufacturers of therapeutic goods, helps ensure that the products manufactured will have the required quality. A basic tenet of GMP is that quality should be built into each batch of product during all stages of the manufacturing process. *See also* Guide to Good Manufacturing Practice for Medicinal Products
GMP clearance letter/licence	Official approval from a regulatory agency that a manufacturer meets the requirements of the *Guide to Good Manufacturing Practice for Medicinal Products*.
Guide to Good Manufacturing Practice for Medicinal Products[105]	A publication that outlines good principles and practices to be followed in the manufacture of therapeutic goods to provide assurance of product quality and compliance with products entered in the ARTG.
indications	The specific therapeutic uses of the goods.
initial decision	Decisions of the Secretary (or a delegate) under various sections of the TG Act for which an internal review under s. 60 of the TG Act or under r. 48 of the Therapeutic Goods Regulations 1990 can be requested.

[104] <http://www.comlaw.gov.au/Series/F1996B00406>
[105] <http://www.tga.gov.au/industry/manuf-pics-gmp-medicines.htm>

Historical document

kit	A therapeutic good that contains multiple components to be used as a unit. A kit may consist of registered medicines, listed medicines, exempt medicines, biologicals or exempt biologicals but cannot be a composite pack or system or procedure pack (see s.7B(1) of the TG Act). Kits may include other items or 'articles' that are normally regarded as medical devices when supplied on their own but, because of their nature and intended use, are regulated as part of a prescription medicine product. The legislative basis for this is the Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2010. In this order, the medicine and the other item form a single integral product that is intended exclusively for use in the given combination and is not reusable (although it may be multi-dose). An example of a kit is a cream or ointment supplied with a purpose-built applicator.
label	A display of printed information that is on or attached to, the goods, or on or attached to a container or primary pack in which the goods are supplied, or supplied with such a container or pack.
manufacture	To produce the goods, or to engage in any part of the process of bringing the goods to their final state, including processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.
manufacturer	The corporation or person carrying out one or more of the manufacturing steps. *See also* manufacture
manufacturing site	Premises that are for use in the manufacture of a particular kind of therapeutic good, and at which the same persons have control of management of production of the goods and procedures for quality control.
medicine	Therapeutic goods that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human or animal. Medicines do not include products that are defined as biologicals in s.32A of the TG Act; these are regulated under the Biologicals Regulatory Framework[106] (Part 3-2A of the TG Act).
overage	Increased content of drug substance, usually due to loss of potency on storage.

[106] <http://www.tga.gov.au/industry/biologicals.htm>

Historical document

overfill	Increased volume of drug product to account for loss during delivery.
packaging	**Secondary packaging** means any packaging or labelling process (including repackaging and labelling, over-labelling and supplementary labelling) where the medicine is already in the primary container, and that primary container is not opened, breached or modified in the secondary packaging process. **Primary packaging** means any other type of packaging operation. Note that primary and secondary packaging require different levels of good manufacturing practice certification.
pack size	Size of the goods in terms of the quantity contained in the container (for example, volume in a multi-use container) and/or the number of items in the primary unit or pack (for example, number of tablets in a bottle). *See also* packaging
Parliamentary Secretary	The Parliamentary Secretary for Health and Ageing, who assists the Minister for Health in relation to the regulation of therapeutic goods.
plasma master file	A compilation of all the required scientific data on the quality and safety of human plasma relevant to medicines, medical devices and investigational products that use human plasma in their manufacture. These data cover all aspects of the use of plasma, from collection to plasma pool.
primary pack	The complete pack in which the goods, or the goods and their container, are to be supplied to consumers.
product	The commercial presentation or marketed entity of therapeutic goods, excluding pack size.
product information (PI)	Information relating to the safe and effective use of the goods, including information regarding the usefulness and limitations of the goods. A PI is approved by the Secretary under s.25AA of the Act as part of the approval of the registration of a prescription medicine. All PIs must comply with the specified form for providing product information[107] for a restricted medicine.

[107] <http://www.tga.gov.au/industry/legislation-pi-form.htm>

Historical document

quality	The composition, strength, potency, stability, sterility, purity, bioburden, design, construction and performance characteristics of goods.
raw material	A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or drug substances.
Release for supply	**Release for supply** means that 'medicinal products are not sold or supplied before an authorised person has certified that each production batch has been produced and controlled in accordance with the requirements of the market authorisation and other regulations relevant to the production control and release of medicinal products' (from the *Guide to Good Manufacturing Practice for Medicinal Products*).[108]
request	Variations to the ARTG entries that do not create separate and distinct goods are made by submitting a 'request' to the TGA under s. 9D of the TG Act. Variations to ARTG entries that create a separate and distinct good are made by submitting an 'application' to the TGA under s. 23 of the TG Act. The word 'application' is used in the legislation.
route of administration	Route by which a therapeutic good is applied on, or introduced to, the body.
safety-related	A safety-related request to vary an entry in the ARTG is one where the variation has one of two possible outcomes: • to reduce the patient population (for example, remove an indication or limit the use of the medicine) • to have the effect of adding a warning or precaution (for example, an adverse effect or interaction). Safety-related requests must be made under s. 9D(2) of the TG Act.

[108] There may be more than one site involved in release for supply of a product. However, release for supply should only happen once, to ensure that the complete batch records (and responsibility for release) are held in one place. All sites must demonstrate compliance with good manufacturing practice (GMP) through a Therapeutic Goods Administration licence or clearance. Compliance with shipping conditions during importation into Australia is the responsibility of the Australian sponsor for products released for supply overseas. The sponsor does not require a GMP licence to perform this step.

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Secretary	The Secretary of the Department of Health and Ageing. The Secretary can delegate powers under various provisions of the TG Act to officers of the Department of Health and Ageing (officers of the TGA). When exercising these powers, the officers are known as delegates. Throughout this document, 'the Secretary' means the Secretary or a delegate of the Secretary.
self-assessable	If requested s. 9D variations or s.23 applications are considered to be minor or low risk by the TGA (as specified in this document), sponsors can assess the supporting data themselves and then make a request or application to the TGA based on this self-assessment. Minor changes should be appropriately validated as unlikely to reduce the safety, quality or efficacy of a medicine. Requests and applications should meet specific conditions to be considered self-assessable. The sponsor must then make a request or application for approval of the variation, and must provide the supporting data if the TGA requests it.
separate and distinct goods	Under s. 16(1) of the TG Act, a medicine is a separate and distinct good from other registered medicines if it has: • a different formulation, composition or design specification; or • a different strength or size (disregarding pack size); or • a different dosage form or model; or • a different name; or • different indications;[109] or • different directions for use; or • a different type of container (disregarding container size).

[109] Except for variations to indications under s. 9D(2) of the TG Act, as described in s. 9D(2A).

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sponsor	Where this expression is used in the TG Act in relation to therapeutic goods, a sponsor means: • a person who exports, or arranges the exportation of, the goods from Australia; or • a person who imports, or arranges the importation of, the goods into Australia; or • a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere); but does not include a person who: • exports, imports or manufactures the goods; or • arranges the exportation, importation or manufacture of the goods; on behalf of another person who at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia. Where the expression is used in this document in relation to a request under s.9D, or application under s.23 of the TG Act, it means the person in relation to whom the medicine is registered.
standard	The published criteria that a product must meet. For registered prescription medicines, the standard must be specified in a therapeutic goods order, or the *British Pharmacopoeia*, *European Pharmacopoeia* or *United States Pharmacopeia* to be considered an official standard.
starting material	An API starting material is a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.
step in manufacture	Any part of the process of bringing goods to their final state that may be completed separately from other parts of the process.
streamlined submission process	The TGA's administrative process for assessing applications under s.23 of the TG Act or requests under s.9D(3) in relation to prescription medicines that require evaluation of nonclinical, clinical or bioequivalence information, usually in addition to quality information (Category 1 and Category 2 applications only). Category 3 applications are not made through the streamlined submission process.
strength	The quantity of a drug substance in a medicine.

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supplier	A person or organisation that is involved in the supply and distribution of the product, but not involved in product manufacture.
therapeutic goods order (TGO)	An Australian standard made under s.10 of the TG Act that relates to a particular type of therapeutic good or specifies particular requirements for labelling, packaging or other aspects. Links to current TGOs, and guidance for some TGOs, are available on the TGA website.
validation data	Experimental data generated to support a request or application to vary an ARTG entry.
variation	A change to an ARTG entry.
warning or precaution	One or more statements in the product information (PI) that draw attention to potential adverse effects resulting from product use. Proposed changes to an ARTG entry (and/or the PI for a product) can have the effect of adding a warning or precaution without actually using the words 'warning' or 'precaution'. For example, adding 'oedema' or 'dizziness' to a list of adverse effects in the PI will have the effect of warning prescribers about a risk associated with the product. These types of changes are considered to be safety-related and must be requested under s. 9D(2) of the TG Act.
working day	For the purposes of determining the time period within which an application under s.23, or request under s.9D, of the TG Act must be processed, it means a day that is not a Saturday, Sunday or holiday day for Commonwealth offices in the Australian Capital Territory (see also r. 16A of the Therapeutic Goods Regulations 1990).

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Therapeutic Goods Administration

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