Minor variations to registered prescription medicines
Chemical entities

Version 1.2, May 2013
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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Abbreviations and acronyms

API  active pharmaceutical ingredient
ARGPM  *Australian Regulatory Guidelines for Prescription Medicines*
ARTG  Australian Register of Therapeutic Goods
BP  *British Pharmacopoeia*
CEP  Certificate of Suitability of a Monograph of the *European Pharmacopoeia*
CPD  certified product details
CPMP  Committee for Proprietary Medicinal Products
CTD  common technical document
DMF  Drug Master File
EDQM  European Directorate for the Quality of Medicines and HealthCare
EMA  European Medicines Agency
GMP  good manufacturing practice
HPLC  high-performance liquid chromatography
ICH  International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
PE  polyethylene
Ph. Eur.  *European Pharmacopoeia*
PI  product information
PVC  polyvinyl chloride
TG Act  *Therapeutic Goods Act 1989*
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<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>TGO</td>
<td>therapeutic goods order</td>
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<tr>
<td>TSE</td>
<td>transmissible spongiform encephalopathy</td>
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<tr>
<td>USP</td>
<td><em>United States Pharmacopeia – National Formulary</em></td>
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Part 1
General information
1.1 About this document

All prescription medicines available for general marketing in Australia are registered in the Australian Register of Therapeutic Goods (ARTG). Section 2.5 of the Australian Regulatory Guidelines for Prescription Medicines (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.

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. Most prescription medicines are contained in Schedules 4 and 8 of the Standard for the Uniform Scheduling of Medicines and Poisons.

This document provides guidance for minor variations to the ARTG entry for registered prescription medicines for which the active substances are synthetic chemical entities. This document also applies to active substances that are antibiotics, short-chain synthetic polypeptides and some hormones (steroid hormones and synthetic polypeptides of usually less than 32 amino acids—some exceptions may apply).

All other registered prescription medicines are defined as biological medicines. Biological medicines include vaccines, natural peptides, monoclonal antibodies and other recombinant products.

Guidance for minor variations to biological medicines is provided in Minor Variations to Registered Prescription Medicines: Biological Medicines.

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

This document applies only to minor variations to registered prescription medicines (chemical entities). 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

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2 <http://www.tga.gov.au/industry/pm-argpm.htm>
5 <http://www.tga.gov.au/industry/pm-ssp.htm>
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, 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 new 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.

### 1.2 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.6

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.

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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.

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

- 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*, 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; 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.

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8 Except for variations to indications under s. 9D(2) of the *Therapeutic Goods Act 1989*, as described in s. 9D(2A).
Figure 1.1 Pathways for requesting variations to, or making applications for, registered prescription medicines

Does the variation create a separate and distinct good?

No

s. 9D

Yes

s. 23

s. 9D(1)
Request to correct an ARTG entry

See Part 2

s. 9D(2)
Safety-related request to vary an ARTG entry

See Part 3

s. 9D(3)
Request for a variation that does not reduce safety, quality or efficacy

See Part 4

s. 23
Application to make a variation that creates a separate and distinct good

See Part 5

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,9 including suspension or cancellation of registration.10 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.

9 See s. 21A of the Therapeutic Goods Act 1989
10 See s. 30(2)(c) of the Therapeutic Goods Act 1989
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\(^\text{11}\)). 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 the known 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\(^\text{12}\) 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 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. 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 before a decision is made. 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

\(^{11}\) <http://www.tga.gov.au/industry/pm-ssp.htm>
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.
Table 1.1 Relevant submission types for minor variations

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<td>s. 9D(2)</td>
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\(^1\)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.
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[^13]. 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.

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—but 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*. System or procedure packs are defined in s. 41BF—these are regulated as medical devices (see the Australian Regulatory Guidelines For Medical Devices 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 that 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 is administered in a particular sequence. The composite pack itself is regulated as a separate and distinct good and must have its own unique AUSTR 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 packs 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*. 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.

1.3 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
medicine’ (for example, a registered prescription medicine) in the ARTG. The form for providing product information 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

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 can 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**

<table>
<thead>
<tr>
<th>Change to product information</th>
<th>Mark-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Text to be deleted</td>
<td>Use strikethrough font. Text that is proposed to be deleted should be shown in its current position, not in comment boxes in the margin. However, explanatory comments added in the margin may be useful.</td>
</tr>
<tr>
<td>Text to be inserted</td>
<td>Use underlined font.</td>
</tr>
<tr>
<td>Text to be moved</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 can 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.
Figure 1.2  Example of marked-up product information

**Pharmacokinetics**

Each transdermal patch provides a steady delivery of the medicine for up to seven days. The transdermal patches (50 micrograms/h per hour, 100 micrograms/h per hour and 200 micrograms/h per hour) provide dose-proportional increases in total exposure (AUC (area under the curve)) over the 7 day application period. Accumulation of plasma medicine levels did not occur during the 30 days. There was no accumulation of plasma levels of the medicine over a period of 30 days.

**Metabolism**

Metabolism of the medicine in the skin following transdermal patch application is negligible. The medicine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. Ingredient A is the only known active metabolite of the medicine. In a study in post-operative patients, the total clearance of medicine was 75 L per hour.

The interaction between the medicine and CYP3A4 enzyme inducers has not been studied; however, co-administration of medicine and enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin) could lead to increased clearance which might result in reduced efficacy. The medicine has also been shown to be a CYP2D6 inhibitor in vitro.

**Presentation and storage conditions**

*Transdermal patch 50.* Transdermal patch, 50 mg (releases 50 micrograms medicine per hour) (square, white patch, marked with trade name and strength in black ink), *Pack (carton).*

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: 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 Process18. These types of changes to the PI are not discussed in this document.

See the *Australian Regulatory Guidelines for Prescription Medicines*19 (ARGPM) for more information about Category 1 and Category 2 applications.

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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 cannot 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 changes must comply with the specified form for providing product information 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.

1.4 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.

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.

1.5 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 a 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.
Part 2
Requesting a correction to an incorrect or incomplete entry in the Australian Register of Therapeutic Goods: s. 9D(1)
Does the variation create a separate and distinct good?

- **No**
  - s. 9D
    - s. 9D(1) Request to correct an ARTG entry
      - 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

- **Yes**
  - s. 23 Application to make a variation that creates a separate and distinct good
    - See Part 5
  - s. 9D(2) Safety-related request to vary an ARTG entry
    - See Part 3
  - s. 9D(3) Request for a variation that does not reduce safety, quality or efficacy
    - See Part 4

ARTG = Australian Register of Therapeutic Goods
2.1 What is a correction to an ARTG entry?

A correction to an entry in the Australian Register of Therapeutic Goods (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 (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: 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 1.3 for general information on changes to the product information.

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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.\(^{23}\)

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 1.3 of this document)
- if relevant, available, 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

\(^{23}\) <http://www.tga.gov.au>
• 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 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 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 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 the 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.

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25 <https://www.ebs.tga.gov.au>
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).
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
Part 3
Making a safety-related request to vary an entry in the Australian Register of Therapeutic Goods: s. 9D(e)
Does the variation create a separate and distinct good?

No

s. 9D

s. 9D(1)
Request to correct an ARTG entry
See Part 2

s. 9D(2)
Safety-related request to vary an ARTG entry

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

Yes

s. 23
Application to make a variation that creates a separate and distinct good
See Part 5

Some variations under s. 9D(2) require supporting data; others do not. This is assessed on a case-by-case basis.

<table>
<thead>
<tr>
<th>Level of assessment</th>
<th>Application type</th>
<th>Timeframe (working days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification of details provided by the sponsor</td>
<td>Safety-related request</td>
<td>No statutory timeframe (TGA processes as soon as possible)</td>
</tr>
<tr>
<td>Evaluation of data submitted to the TGA</td>
<td>Safety-related request with data</td>
<td>No statutory timeframe (TGA processes as soon as possible)</td>
</tr>
</tbody>
</table>

ARTG = Australian Register of Therapeutic Goods; TGA = Therapeutic Goods Administration
3.1 What is a safety-related request?

A safety-related request to vary an entry in the Australian Register of Therapeutic Goods (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 (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
- 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

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’.

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28 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.
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 can 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)\(^\text{29}\)
- adding information on appropriate medical treatment of overdose, unless recommended by the TGA or Therapeutic Guidelines\(^\text{30}\)
- 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 must be able to provide the TGA with data to support the proposed change if the TGA requests it.

\(^{29}\) 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).

\(^{30}\) [http://www.tg.org.au]
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 Process31), 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 1.3 for general information on changes to the product information.

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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.

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 1.3 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

32 <http://www.tga.gov.au>
• 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 33 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 34.

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.

33 <http://www.tga.gov.au/industry/pm-euguidelines.htm>
34 <http://www.tga.gov.au/industry/pm-ctd.htm>
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 will 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 ARGFM 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 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 eBusiness Services 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.\(^36\)

**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 sponsors.

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\(^35\) [https://www.ebs.tga.gov.au/]

\(^36\) 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.
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).
Figure 3.1  Process for requests under s. 9D(2) of the *Therapeutic Goods Act 1989*

RTG = 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.
Part 4
Requesting a variation that does not reduce quality, safety or efficacy: s. 9D(3)
Does the variation create a separate and distinct good?

No

s. 9D

s. 9D(1)
Request to correct an ARTG entry

See Part 2

s. 9D(2)
Safety-related request to vary an ARTG entry

See Part 3

s. 9D(3)
Request for a variation that does not reduce safety, quality or efficacy

Yes

s. 23

Application to make a variation that creates a separate and distinct good

See Part 5

Some variations under s. 9D(2) are self-assessable; others require data to be submitted to the Therapeutic Goods Administration for evaluation

<table>
<thead>
<tr>
<th>Level of assessment</th>
<th>Application type</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification of details provided by the sponsor</td>
<td>Self-assessable request to vary an ARTG entry</td>
<td>45 working days</td>
</tr>
<tr>
<td>Evaluation of quality data only</td>
<td>Category 3 application: variation to ARTG entry</td>
<td>45 working days</td>
</tr>
<tr>
<td>Full evaluation (combination of clinical, nonclinical, bioequivalence and quality data)</td>
<td>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</td>
<td>255 working days for Category 1; 175 working days for Category 2</td>
</tr>
</tbody>
</table>

ARTG = Australian Register of Therapeutic Goods; PI = product information
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\(^{37}\) (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\(^{38}\).

- **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 should 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\(^{39}\) (ARGPM) for more information about Category 1 and Category 2 applications.

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\(^{38}\) [http://www.tga.gov.au/industry/pm-ssp.htm>  
\(^{39}\) [http://www.tga.gov.au/industry/pm-argpm.htm>
Approval

The Secretary’s approval is required for all variations under s. 9D(3) of the Therapeutic Goods Act 1989. 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 must 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 conditions 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 conditions 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) 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, 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 must be made (see Section 4.3) unless otherwise allowed in this document or agreed to by the TGA.

41 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. Pilot-scale batch size should be at least 10% of the production-scale batch size. For oral solid dosage forms, the minimum scale is generally taken to be one-tenth that of full production, or 100,000 dose units, whichever is greater.
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 conditions**

The following general conditions always apply to self-assessable requests and the sponsors should 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 practice (GMP) inspection.
- The person signing the form should 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[^42].

**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)’ form (see below)

• 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 conditions and all of the applicable specific conditions
have been complied with
• if relevant, clean and marked-up copies of the proposed PI (see Section 1.3 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 may have 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 1.4), 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
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. These fees are subject to change from time to time; current fees 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 stops 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.

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The TGA will only review those variations 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 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.

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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 active pharmaceutical ingredient (API)
B  Changes to the manufacturing method, manufacturing batch size or manufacturing equipment for drug products
C  Change to, or addition of, alternative site of manufacture of drug products
D  Changes to drug product specifications
E  Changes to excipients
F  Changes to the material of a container/closure system
G  Changes to the size, shape or components of the container/closure system
H  Change to, or addition of, pack size
I  Changes to dimensions, shape, inked imprint, or embossing and debossing of solid dosage forms
J  Changes to product shelf life or storage conditions
K  Changes to product labels
L  Changes to pharmaceutical aspects of the product information, including sponsor and/or supplier details
M  Other changes
The guidance provided below is in addition to the information in 'How to apply to the TGA', above.

**Comparative batch data**

Comparative batch data means a comparison of data between the pre-variation product and the proposed post-variation API or drug product.

Unless otherwise specified in these conditions, these data should compare at least the last three batches that were manufactured under existing conditions (using retention samples, if necessary) and the first batch made under the proposed new conditions, before the first batch is released. The second and third batches manufactured under the new conditions should be reviewed as soon as they become available, and the TGA should be promptly informed of any differences.

For manufacturing changes where multiple strength (three or more) products are involved and the various strengths are either direct scales (that is, the quantity of all excipients increases proportionally with the quantity of active ingredient) or have closely similar formulations, comparative data may be generated for the lowest and highest strengths only.

**Updates to pharmacopoeial monographs**

Section 3 of the TG Act lists three pharmacopoeias that are defined as ‘default standards’ used to specify quality, method of manufacture and other aspects of therapeutic goods. These are the British Pharmacopoeia, European Pharmacopoeia, and United States Pharmacopoeia—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.
A Changes to the active pharmaceutical ingredient

The following requests to vary the API are self-assessable:

A1 Changes to a non-biological method (assay) for determining the content of the active substance and/or residual solvents (including water) in the API, starting materials or intermediates used in the API synthesis

A2 Narrowing of the limits for test results within the existing specifications for the API, starting materials or intermediates

A3 Adding a new test and limit to the existing specifications for the API, starting materials or intermediates

A4 Changes as a result of amendments to pharmacopoeial requirements or requirements of a TGO

A5 Changes to identification tests for starting materials, intermediates or the API

A6 Change to, or addition of an alternative, site of manufacture of APIs prepared by chemical synthesis or isolated from a natural source as pure chemical entities

A7 Ceasing an existing site of API manufacture

A8 Change to, or addition of, an alternative site of manufacture of intermediates in APIs that are manufactured by multi-step synthesis, including intermediates prepared wholly or partially by fermentation

A9 Decrease in manufacturing batch size of the API or intermediates at an existing site of manufacture

A10 Minor changes to the manufacture of the API or intermediates at an existing site

A11 Change (addition, revision or deletion) to in-process control tests and limits during manufacture of the API and intermediates

A12 Changes to container/closure system

A13 Revision of Certificate of Suitability to the European Pharmacopoeia monograph (CEP) for the API
A1 Changes to a non-biological method (assay) for determining the content of the active substance and/or residual solvents (including water) in the API, starting materials or intermediates used in the API synthesis

Note: Any changes to biological methods of assay (such as those used for antibiotics) or test method for determining impurities, related substances and degradation products require TGA evaluation of supporting data through a Category 3 application.

Specific conditions

• The assay method being changed should not be a biological method of assay.
• Appropriate validation data should have been generated for the proposed method.
• The new method should demonstrably improve at least one of precision, accuracy or specificity, without a reduction in the other 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.
• Sponsors should generate data for three batches of the API using the current and proposed assay method to demonstrate equivalence of the methods.

Required information

• Details of the new method.

A2 More stringent limits for test results within the existing specifications for the API, starting materials or intermediates

Specific conditions

• The proposed limits should be consistent with any applicable official standard or guidelines adopted by the TGA.
• Increasing stringency of the limits should not result in a different grade of material being produced—for example, changing from unmicronised to micronised material (see also A3, below).
• Sponsors should generate data for at least three production-scale batches to demonstrate compliance with the proposed limits.

Required information

• The revised set of specifications for the starting materials, intermediates or API.

A3 Adding a new test and limit to the existing specifications for the API, starting materials or intermediates

Specific conditions

• The change should not be the result of an altered method of manufacture that changes the material's quality characteristics (such as micronisation).
• Appropriate validation data should have been generated for the test method.

• The limits applied should be based on batch analytical data, and comply with any applicable official standard or relevant guidelines adopted by the TGA.

• The change should not concern a genotoxic impurity.

• Sponsors should generate comparative batch data for at least three commercial batches to demonstrate compliance with the proposed test and limit.

**Required information**

• Details of the test method.

• The revised set of specifications for the starting materials, intermediates or API.

A4 **Changes as a result of amendments to pharmacopoeial requirements or requirements of a therapeutic goods order (TGO)**

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 an API complies with the requirements of a particular edition of a given standard, such as the BP, it would be appropriate to substitute the requirements of a later edition of that standard. 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 API should currently be tested to the existing pharmacopoeial or TGO requirements.

• The change should not involve changing from the requirements of one pharmacopoeia to another.

• The new pharmacopoeial monograph or amended TGO should be applicable to the API.

**Required information**

• The revised set of specifications for the API.

A5 **Changes to identification tests for starting materials, intermediates or the API**

**Specific conditions**

• The changes to identification tests:
  – are from a less specific to a more specific identification test—for example, from an ultraviolet/visible spectrophotometric or chromatographic method, such as thin layer chromatography, gas chromatography or high-performance liquid chromatography (HPLC), to a conventional infrared spectroscopic method; and/or

  – include a new identification test in addition to an existing identification test; and/or
– vary the existing identification test (for example, an HPLC test that demonstrably improves or at least maintains the specificity of the method); and/or
– replace an existing identification test with a near infrared spectroscopic identification test.

• The method should have been validated for specificity.

• Any additional identification test should not serve as an alternative identification test.

• If near infrared spectroscopy is used, the method development and other data requirements (including data collection, establishment of the spectral reference library, calibration and validation of the method) should comply with the current European Medicines Agency (EMA) guideline on the use of near-infrared spectroscopy that has been adopted by the TGA.

**Required information**

• The revised set of specifications.

• Details of the identification test method.

### A6 Change to an existing, or addition of an alternative site of manufacture of APIs prepared by chemical synthesis or isolated from a natural source as pure chemical entities

**Specific conditions**

• The API should not be prepared wholly or partially by fermentation, and should not be sterile.

• There should be no change to the method of synthesis, including to any intermediates and any solvents used in the purification of the final drug substance (the API), or any other aspect of manufacture and specifications.

Note: This means that changes to the site of manufacture of an API may not be made through self-assessment unless either the sponsor of the drug product or the new API manufacturer know the route of synthesis and other details of manufacture of the API at both sites.

• The manufacturing batch size remains the same or smaller.

• The new site should have a current manufacturing licence for this type of manufacture issued by the TGA or, if an overseas manufacturer is proposed, the drug product sponsor should 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.

• Comparative batch data for three batches of the API from the proposed site should have been generated, and all results (including impurity profiles, particle size distribution and polymorphic forms) should be either within the same range as three batches manufactured at the current site (that is, no new impurities or polymorphic forms are present) or remain unchanged.

**Required information**

• The name and address of the new manufacturer.
• A copy of the Australian licence and/or GMP clearance letter.
• The flowchart of the route of synthesis from the existing site and the new site of manufacture.
• The manufacturing batch size at the new site.

A7  Ceasing an existing site of API manufacture

Note: Sites of manufacture that carry out only testing, milling or micronisation of an API are not entered in the ARTG.

Specific conditions
• There should be at least one registered site of manufacture of the API.

Required information
• The name and address of the manufacturer to be ceased.
• Evidence (that is, current TGA eBusiness Services printout for the product or a copy of the TGA approval letter) showing that at least one registered site of manufacture of the API remains to perform the relevant steps of manufacture.

A8  Change to, or addition of, an alternative site of manufacture of intermediates in APIs that are manufactured by multi-step synthesis, including intermediates prepared wholly or partially by fermentation

Specific conditions
• The intermediates should be isolated chemical species and should be at least three steps back in the synthetic scheme from the API. (Purification procedures do not count as steps of synthesis.)
• There should be no change to the overall synthetic route of the API or intermediates.
• There should be no change to the specifications of intermediates, or an improvement in the specifications of the intermediates.
• Comparative batch data (including impurity levels) should have been generated using validated test methods from intermediates manufactured at the current and proposed sites, and from the API synthesised using intermediates from the current and the proposed sites, and the results should show no significant difference in purity profiles.

For intermediates prepared wholly or partially by fermentation:
  – there should be either no change in the strain of the producer organism used or, where there is a change, details of the new producer organism should be provided and the component profiles of the final fermentation broth at harvest made from the new and old strain should be the same
  – there should be no changes to the scale of operation of the fermentation tank and fermentation processes
there should be no changes to the nature of the media ingredients, particularly precursors, activators or components of biological or animal origin (although changes to the quantities used are acceptable, provided that they are not a result of a change in scale of operation).

**Required information**

- The name and site address of the new manufacturer(s) of the intermediates. Note that GMP evidence is not required, as the new site is not entered in the ARTG; the product sponsor or purchaser of the intermediates is responsible for supplier qualification.
- The route of synthesis of the API.
- The name or code number of the intermediates for which the alternative site of manufacture is sought.

**A9 Decrease in manufacturing batch size of the API or intermediates at an existing site of manufacture**

**Specific conditions**

- There should be no change in route of synthesis (including solvents used in the final purification of the API), other than any necessary adjustment to processing conditions or use of different equipment.
- The change should not be due to unexpected events arising during manufacture or to stability concerns.
- The API should not be a sterile substance.
- Comparative batch data should have been generated and the results should show no significant difference in the tested parameters, particularly particle size distribution (for an insoluble API) and impurity profiles.

**Required information**

- Details of the new batch size of manufacture.

**A10 Minor changes to the manufacture of the API or intermediates at an existing site**

**Specific conditions**

- The synthetic route should remain the same, and no new reagents, solvents or catalysts should be used in the amended process.
- The change should not involve the sterilising steps, if there are any.
- The specifications of the API and intermediates should remain unchanged, or be changed in a way that is permitted in other parts of this document.
- Comparative batch data should have been generated, and the results should show no significant difference in the purity profiles or physicochemical properties.
Required information

- Details of the amended manufacturing process, including the synthesis flowchart.

A11 Change (addition, revision or deletion) to in-process control tests and limits during manufacture of the API and intermediates

Specific conditions

- The change should be consistent with any applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products.\(^{46}\)
- The change should not be due to adverse events during manufacture.
- The change should result in equivalent or improved quality of the final isolated material.
- The specifications of the API and intermediates should remain unchanged, or be changed in a way that is permitted in other parts of this document.
- Any new test method used should be appropriately validated and should not be a biological test method.
- Data should have been generated for three batches and the results should be within the same ranges.

Required information

- Details of the new in-process control tests and limits.

A12 Changes to container/closure system

Specific conditions

- The API should not be sterile.
- The material of the container/closure should be either unchanged or changed to a more protective material.
- The thickness of the material should be either unchanged or increased.
- Relevant comparative moisture permeability data for the current and proposed material should have been generated to demonstrate either equivalent or better moisture protection.
- There should be either no change in retest period/storage conditions, or a decrease in retest period and/or more stringent storage conditions in the new container/closure system.
- Stability testing of the API in the new container/closure system should have started in accordance with relevant stability testing guidelines (for example, International Conference on Harmonisation [ICH] guidelines).

Required information

- Details of the new container/closure system.

• Details of the new retest period or storage conditions, if changed.

A13 Revision of Certificate of Suitability to the European Pharmacopoeia monograph (CEP) for the API

Note: This includes changes made to the data package of the API reviewed by the European Directorate for the Quality of Medicines and HealthCare (EDQM) that did not result in the issue of a revised CEP. A request to register a CEP for an API for the first time with the TGA is not acceptable as a self-assessable request.

Specific conditions

• The current CEP should have been approved previously by the TGA.
• The API should not be manufactured wholly or substantially by fermentation.
• The API should not be a synthetic polypeptide.
• The API should not be manufactured as a sterile drug substance.

Relevant comparative data should have been generated for pre-change and post-change batches of the API if the revision to the CEP is due to changes to the method of synthesis that involve using different crystallisation solvents, a different purification process, or milling or micronisation of the final drug substance. Comparative data should be generated using validated test methods to show that there is no change in the crystalline (polymorphic) form of the final substance (if relevant), and the particle size distribution profiles (tested by a laser diffraction or other equivalent method) remain comparable and within the same range as the pre-change API.

Comparative batch data should have been generated from at least one production-scale batches of the final drug substance manufactured or tested according to the changed process, and should demonstrate compliance with any revised API specification. If there is a justifiable reason for not using production-scale batches, three pilot-scale batches may be used.

Where changes to the API specification (including test parameters, limits and test methods) are involved, the same changes should have been adopted by the product sponsor and/or drug product manufacturer, and any new test methods should have been validated as suitable for use.

Where a change to the site of API manufacture is involved, the site should have either a licence to manufacture the API (if the site is in Australia) or a sponsor-specific GMP clearance letter (if the site is overseas). The GMP clearance letter should be valid at the time of the application.

Required information

Documentary evidence that the current CEP has been previously approved by the TGA.
• The updated CEP, including any annexes, or a declaration from the EDQM that, due to the nature of the changes, an updated CEP was not issued.
• A summary of the changes made to the API that resulted in the revision of the CEP.
• The GMP clearance letter (overseas site) or Australian manufacturing licence if the site of manufacture has changed or a new site is included. Note that a GMP clearance letter or
manufacturing licence is not required for the manufacturing site of intermediates or the site of milling/micronisation of the final drug substance. If a manufacturing site for an intermediate is included in the CEP, please make this clear to avoid confusion about the actual site of manufacture of the API.

- The revised API specification adopted by the API manufacturer and the drug product manufacturer/product sponsor, if relevant.

- A declaration that any test requirements in addition to those in the CEP that were previously approved by the TGA will continue to apply.

- A declaration that no significant changes to the API have been made since the revised CEP was issued.

- If relevant, a flow diagram or outline of the revised route of synthesis of the API.
B  Changes to the manufacturing method, manufacturing batch size or manufacturing equipment for drug products

These changes may be made to any products containing chemical entities (including sterile products) covered by this document except those that are specifically excluded under each change.

The following requests to vary the manufacturing method, manufacturing batch size or manufacturing equipment for drug products are self-assessable:

B1  Change to manufacturing method and/or equipment

B2  Reduction in, or removal of, previously approved overages of APIs and excipients, including preservatives

B3  Change to manufacturing batch size

B4  Change (addition, deletion or revision) to in-process control tests and limits (including test methods) during product manufacture

B1  Change to manufacturing method and/or equipment

Specific conditions

- The product should not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.
- The new manufacturing method and equipment should have been validated according to the Guide to Good Manufacturing Practice for Medicinal Products and/or relevant guidelines adopted by the TGA at least one production-scale batch of the product.
- Comparative batch data should have been generated, and should show that all results are comparable and within the same range as those obtained previously, as well as meet currently approved drug product release specifications. Note that, for this type of change, the use of retention samples to compare the last three batches manufactured under previous conditions is only allowed in exceptional circumstances, which should be justified by the sponsor.

Following specific conditions also apply to different types of products:

All solid dosage forms (for example, tablets, capsules, compressed suppositories and pessaries) should have similar comparative dissolution profiles (that is, the similarity factor, f₂, should be between 50 and 100). These data are not required if the API 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.

Note: ‘Comparative dissolution profiles’ mean that data should be generated on three recent pre-variation batches and at least one batch of post-variation product, as follows:
– At least 12 dosage units (for example, tablets, capsules) of each batch should be tested individually, and mean and individual results reported. The percentage of nominal content released should be measured at a minimum of three suitably spaced time points (excluding zero time point) to provide a profile for each batch (for example, at 5, 15, 30 and 45 minutes, or as appropriate to achieve virtually complete dissolution). The batches should be tested using the same apparatus and, if possible, on the same day.

Test conditions should be those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.

– To demonstrate the similarity of two dissolution profiles, the similarity factor, $f_2$, should be calculated using the equation and conditions stated in Appendix I of the European Medicines Agency (EMA) ‘Note for guidance on the investigation of bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The $f_2$ value should be between 50 and 100. In cases where more than 85% of the active substance is dissolved within 15 minutes in all tested batches, dissolution profiles are considered to be similar without the need to calculate the similarity factor.

– Insufficient quantities of recently manufactured batches may be available to meet this requirement. In these cases, it is acceptable to test retention batches, and to explain in the test report why this was done, stating the age and storage history of the samples.

• 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 API in suspension. These data are not required if the API 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 metered-dose pressurised inhalations, metered-dose nasal spray solutions, and dry powders for oral or nasal inhalations, the comparative batch data for the drug mass aerodynamic particle size distribution of the aerosol emitted by the drug product should be in the same range as previously, as measured by either a multi-stage liquid impinger or a multi-stage cascade impactor (Anderson type). These data are not required if the API 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 sterile products, the new method of manufacture (including sterilisation of containers or container components, and use of a second filter in a filling line) or new manufacturing equipment (such as introduction of a similar filling line) should not affect the final sterility of the product. For sterile dosage forms, all of the above specific conditions should be certified as having been met, as appropriate. Other changes to ensure sterility are permitted, provided that:
  
  – the technology to be used already exists at the manufacturing site and is in use for other TGA-approved products
  
  – there are no changes to (or there are improvements in) microbiological environmental standards, bioburden specifications, the sterilisation cycle or its parameters, and sterility assurance levels.

Required information

• Details of the revised method of manufacture and/or equipment, and any relevant flow diagram of the new process.

• Validated process times (for sterile products).
B2 Reduction in, or removal of, previously approved overages of APIs and excipients, including preservatives

Note: Since overages do not change the nominal quantity of API recorded in the ARTG, this type of change is not regarded as a change in product formulation.

Specific conditions

- 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.
- Comparative batch data should have been generated to demonstrate that the results are comparable to those obtained previously (allowing for the reduction in overage). Note that, for this type of change, the use of retention samples to compare the last three batches manufactured under previous conditions is only allowed in exceptional circumstances, which should be justified by the sponsor.
- Stability testing on at least one production batch of the post-variation product should have begun, and at least two more production batches should be similarly tested. 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.

Required information

- The revised manufacturing formula.

B3 Change to manufacturing batch size

Specific conditions

- The change should not be an increase in batch size for sterile products or products manufactured under sterile conditions.
- The product should not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.
- The new manufacturing batch size should have been validated in accordance with the Guide to Good Manufacturing Practice for Medicinal Products and any relevant guidelines adopted by the TGA for the specific dosage form involved.

The following specific conditions also apply to different types of products:

- Depending on the dosage form of the product (as detailed in B1, above), relevant validation data should have been generated.
- For sterile products, a decrease in manufacturing batch size should be either not accompanied by any change in sterile manufacturing process or, where there has been a change, the specific conditions in B1, above, have also been met.

Required information

- Details of the new manufacturing batch size, with the revised batch manufacturing formula, and any revised manufacturing process and flow diagram, if relevant.
B4 Change (addition, deletion or revision) to in-process control tests and limits (including test methods) during product manufacture

Specific conditions

- The change should not relate to the parametric release of sterile products.
- The change should be consistent with any applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products.
- Any change to in-process control test methods should have been validated appropriately.
- The change should result in either improved quality or no change in the quality of the drug product.
- Comparative batch data should have been generated and the results should be within the same range as previously. Note that, for this type of change, the use of retention samples to compare the last three batches manufactured under previous conditions is only allowed in exceptional circumstances, which should be justified by the sponsor.

Required information

- Details of the changes proposed, and the revised set of in-process control tests and limits. Test method details are not required.
C  Change to, or addition of alternative, site of manufacture of drug products

The following requests to change a site, or add an alternative site of manufacture of drug products are self-assessable:

C1  Change to site of manufacture of dosage form

C2  Change to site of packaging and labelling operations

C3  Change to site of quality-control testing, including sterility, microbiological, physical and bacterial endotoxin/pyrogen testing, and release for supply

C4  Cessation of site of manufacture and/or deletion of a step of manufacture at an existing site

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 relating 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.

- **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*).

47 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 GMP through a TGA licence or clearance. Compliance with shipping conditions during importation into Australia is the responsibility of...
C1  Change to site of manufacture of dosage form

Specific conditions

- Applies to sites of manufacture of the final drug product only, not sites performing in-process steps.
- The product should not be sterile or manufactured under sterile conditions.
- The product should not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.
- 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 drug product sponsor should 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.
- Apart from the change in manufacturing site, there should be no changes to any aspect of the quality data other than changes to manufacturing equipment or method. Where a change in manufacturing equipment or method is made, this should have been validated at the new manufacturing site in accordance with the principles of GMP and/or any relevant guidelines adopted by the TGA.
- Depending on the dosage form of the product, relevant data of the type below should have been generated:
  - All solid dosage forms (for example, tablets, capsules, compressed suppositories and pessaries) should have similar comparative dissolution profiles (that is, the similarity factor, $f_2$, should be between 50 and 100). These data are not required if the API 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.

Note: ‘Comparative dissolution profiles’ means that data should be generated on three recent pre-variation batches and at least one batch of post-variation product as follows:

- At least 12 dosage units (for example, tablets, capsules) of each batch should be tested individually, and mean and individual results reported. The percentage of nominal content released should be measured at a minimum of three suitably spaced time points (excluding zero time point) to provide a profile for each batch (for example, at 5, 15, 30 and 45 minutes, if possible, on the same day). The batches should be tested using the same apparatus and, if possible, on the same day. Test conditions should be those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.
- To demonstrate the similarity of two dissolution profiles, the similarity factor, $f_2$, should be calculated using the equation and conditions stated in Appendix I of the EMA ‘Note for guidance on the investigation of bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The $f_2$ value should be between 50 and 100. In cases where more than 85% of the active substance is dissolved within 15 minutes in all tested batches, dissolution profiles are considered to be similar and the similarity factor does not need to be calculated.

the Australian sponsor for products released for supply overseas. The sponsor does not require a GMP licence to perform this step.
– Insufficient quantities of recently manufactured batches may be available to meet this requirement. In these cases, it is acceptable to test retention batches, and to explain in the test report why this was done, stating the age and storage history of the samples.

– 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 API in suspension. These data are not required if the API 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 metered-dose pressurised inhalations, metered-dose nasal spray solutions, and dry powders for oral or nasal inhalation, the comparative batch data for the drug mass aerodynamic particle size distribution of the aerosol emitted by the drug product should be in the same range as previously approved, as measured by either a multi-stage liquid impinger or a multi-stage cascade impactor (Andersen type). These data are not required if the API 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.

- Comparative batch data should have been generated and should remain within the same range as previously. Note that, for this type of change, the use of retention samples to compare the last three batches manufactured under previous conditions is only allowed in exceptional circumstances, which should be justified by the sponsor.

- Appropriate validation of the manufacturing process at a new site should have been carried out on at least one production-scale batch. The second and third production-scale batches should be subsequently validated.

**Required information**

- The name and address of the new manufacturer.

- Details of the manufacturing step(s) undertaken at the new site of manufacture.

- A summary of the change in manufacturing equipment or manufacturing method at the new site, if relevant.

- A copy of the manufacturer’s Australian licence and/or GMP clearance letter.

**C2 Change to site of packaging and labelling operations**

**Specific conditions**

- A change in, or addition of an alternative, site of primary packaging operations may relate to any product except products that are intended to be sterile or are manufactured under sterile conditions.

A change in, or addition of an alternative, site of secondary packaging operations may relate to any product, including sterile products and products manufactured under sterile 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 drug product sponsor should 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 manufacture.
• Apart from the change in site of manufacture, there should be no changes to any 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**

• The name and address of the new manufacturer.

• Details of the manufacturing step(s) undertaken at the new site of manufacture.

• A copy of the Australian licence and/or GMP clearance letter.

**C3 Change to site of quality control testing, including sterility, microbiological, chemical, physical and bacterial endotoxin/pyrogen testing, and release for supply**

**Specific conditions**

• Applies to sites of manufacture of the final drug product only, not sites performing in-process steps.

• This change is applicable to all medicines, including sterile products and modified-release dosage forms.

• 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 site is overseas, the drug product sponsor should 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 of this document.

• Appropriate technology transfer of the approved test methods to the proposed site should have been carried out.

**Required information**

• The name and address of the new manufacturer.

• Details of the manufacturing step(s) undertaken at the new site of manufacture.

• A copy of the Australian licence and/or GMP clearance letter.

**C4 Cessation of site of manufacture and/or deletion of a step of manufacture at an existing site**

**Specific conditions**

• This change is applicable to all medicines, including sterile products and modified-release dosage forms.

• There should be at least one other site that performs the same steps of manufacture as the ceased site, or that performs the deleted step of manufacture.
**Required information**

- The name and address of the manufacturer to be ceased.
- Details of the manufacturing step(s) to be deleted, as relevant.
- Documentary evidence to show that there is at least one registered site of manufacture performing the same step of manufacture as the ceased site.
D Changes to drug product specifications

The following requests to vary the drug product specifications are self-assessable:

D1 Changes to a non-biological method (assay) for determining the content of the active substance in the drug product

D2 Narrowing of the limits for test requirements within the existing specifications

D3 Adding a new test and limit to the existing specifications

D4 Changes as a result of amendments to pharmacopoeial requirements or requirements of a TGO

D5 Changes to identification tests for the drug substance and/or excipients

D6 Minor changes to existing drug product test methods for physicochemical parameters

D7 Changes to a sterility testing method

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 (ARGPM). Forms for providing CPDs are available on the TGA website.

D1 Changes to a non-biological method (assay) for determining the content of the active substance in the drug product

These specific conditions also apply to changes to assays during dissolution testing, uniformity of content testing, or assaying of excipients such as colours, preservatives or antioxidants in a drug product.

Specific conditions

- The product should not be a radiopharmaceutical.
- If the results obtained using the new method do not agree with the results obtained using an official method, the results from the official method will be deemed to be correct.
- The assay method being varied should not be a biological assay method.
- The assay method being varied should not be a test method for impurities, related substances or degradation products.
- The new method should demonstrably improve at least one of precision, accuracy or specificity, without a reduction in the other 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 assay method.

Required information

- Details of the proposed test method.
- An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).

D2 More stringent limits for test requirements within the existing specifications

Specific conditions

- The proposed limits should be either the same as, or more stringent than, any applicable official standard or accepted guidelines.
- There should be no change in test method other than changes allowed in points D1, D4 or D6 this section.

Required information

- A statement of the current and proposed limits.
- The revised set of drug product specifications at release and expiry.
- An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).
**D3 Adding a new test and limit to the existing specifications**

**Specific conditions**
- Appropriate validation data should have been generated for the test method.
- The proposed limit (release and expiry) of the new test should be based on batch data obtained at product release and on storage for the duration of the shelf life of the product. The limit should be either the same as, or more stringent than, any applicable official standard or accepted guidelines for such a test.

**Required information**
- A statement of the new test and limit, and the revised set of product specifications at release and expiry.
- Details of the test method.
- An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).

**D4 Changes as a result of amendments to pharmacopoeial requirements or requirements of a TGO**

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 products must currently be tested to the existing pharmacopoeial or TGO requirements.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO should continue to be performed.
- There should be no change from the requirements of one pharmacopoeia to those of another, unless such changes are allowed by other sections of this document.
- The new pharmacopoeial monograph or TGO should be suitable for the product and, if necessary, appropriate validation data should have been generated.
- If the change involves updating microbiological test requirements for non-sterile products in accordance with 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.

**Required information**
- The revised set of drug product specifications (release and expiry), if applicable.
- If the change relates to an update to meet TGO 77 requirements, an assurance that the TGA can review the risk assessment report for objectionable microorganisms other than those specified in the order, if required.
• An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).

D5 Changes to identification tests for the drug substance and/or excipients

Specific conditions

• The changes to identification tests:
  – are from a less specific to a more specific identification test—for example, from an ultraviolet/visible spectrophotometric or chromatographic method, such as thin layer chromatography, gas chromatography or HPLC to a conventional infrared (infrared or Fourier transform infrared) spectroscopic method; and/or
  – vary the existing identification test (for example, the existing HPLC method) and demonstrably improve or at least maintain the specificity of the method; and/or
  – include a new identification test in addition to an existing identification test; and/or
  – replace an existing identification test with a near infrared spectroscopic identification test.

• The method should have been validated according to applicable guidelines adopted by the TGA.

• Any additional identification test included should not serve as an alternative identification test (the latter should be submitted as a Category 3 application).

• If near infrared spectroscopy is used, the method development and other data requirements (including data collection, establishment of the spectral reference library, calibration and validation of the method) should comply with the current EMA guideline on use of near-infrared spectroscopy that has been adopted by the TGA.

Required information

• Details of the changes to the existing test or the new identification test.

• The revised set of drug product specifications at release and expiry.

• An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).

D6 Minor changes to existing drug product test methods for physicochemical parameters

Physicochemical parameters include pH, hardness, friability, colour, particle size distribution, particulate matter contamination, density, specific gravity, optical rotation, extractable volume, osmolality, osmolarity and viscosity.

Specific conditions

• The test limit should either remain unchanged or be more stringent.

• The amended method should have been validated.
Required information

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

D7 Changes to a sterility testing method

Specific conditions

- All aspects of the test should comply with the requirements of the internationally harmonised test published in a default pharmacopoeia and as specified in TGO 77.
- The change should comply with the guidelines on particular aspects of the sterility test that are outlined in Appendix 17 of the ARGPM.

Required information

- A summary description of the change and details of the new test method.
- An updated CPD document for the product that incorporates the changes, if applicable (see box 'Note on certified product details [CPD] documents', above).
E Changes to excipients

**Definition and conditions**

An excipient is any component of a drug product other than the active pharmaceutical ingredient.

Except as provided for in Section 4.3 of this document and as specified in E5 below, changes to excipients of biological origin (animal or human source) may not be made as a self-assessable request. For changes to other aspects of excipients that do not require prior approval, see Part 6 of this document.

The following requests to vary excipients are self-assessable:

**E1** Changes to an assay method for excipients

**E2** Narrowing of the limits for test requirements within the existing specifications

**E3** Adding a new test and limit to the existing specification

**E4** Changes as a result of amendments to pharmacopoeial requirements (BP, Ph. Eur. or USP) or requirements of a TGO, or changing between the requirements of one pharmacopoeia to those of another

**E5** Changes in source and/or manufacturing process, or site of manufacture of excipients derived from Category C ruminant tissues

**E1 Changes to an assay method for excipients**

**Specific conditions**

- The new method should demonstrably improve at least one of precision, accuracy or specificity, without a reduction in the other 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 assay method.
E2 Narrowing of the limits for test requirements within the existing specifications

Specific conditions
- The proposed limits should be consistent with any applicable official standard or relevant guidelines adopted by the TGA.

Required information
- The current and revised limits.
- The revised set of specifications for the excipient.

E3 Adding a new test and limit to the existing specifications

Specific conditions
- The new test and limit should not be the result of an altered method of manufacture that alters the excipient’s quality characteristics (such as micronisation).
- Appropriate validation data should have been generated for the test method.
- The limits proposed should be based on batch analytical data and comply with, or be more stringent than, any applicable official standard or relevant guidelines adopted by the TGA.

Required information
- Details of the new test and limit, including the test method.
- The revised set of specifications for the excipient.

E4 Changes as a result of amendments to pharmacopoeial requirements (BP, Ph. Eur. or USP) or requirements of a TGO, or changing from the requirements of one pharmacopoeia to those of another

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 excipient should currently be tested to the existing pharmacopoeial or TGO requirements.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO should continue to be performed.
- The new pharmacopoeial monograph or TGO should be suitable for the product and the excipient.

Required information
- Details of the proposed change.
• The revised set of specifications for the excipient.

**E5 Changes in source and/or 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)*[^1]. 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.

• Either no changes to the specifications of the excipients have been made, or the excipients have been changed as allowed in E1–E4, above.

**Required information**

• Details of the excipients and the proposed changes. Where relevant, CEP issued by the 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 specifications, if changes have been made.

F  Changes to the material of a container/closure system

The following requests to vary the material of a container/closure system are self-assessable:

F1  Bottles, jars and tubes

F2  Blister packs, strip packs and sachets

F3  Increase in thickness of container/closure material

F4  Decrease in thickness of container/closure material: blister packs, strip packs, sachets

F1  Bottles, jars and tubes

Specific conditions

- The product should be a non-sterile solid dosage form (for example, tablets, capsules, compressed pessaries and suppositories) or a non-sterile semi-solid, semi-liquid or liquid (for example, ointment, gel, cream, lotion, oral solution or suspension).
- The material of which the container/closure system (including a reclosable package) is made may be changed from:
  - polystyrene to polyvinyl chloride (PVC), polyethylene (PE), polypropylene or glass; or
  - PVC to PE, polypropylene or glass; or
  - PE to glass or polypropylene with a density of at least 0.89; or
  - PE of one density to PE of a higher density; or
  - glass, metal or PE with a density of at least 0.95 to polypropylene with a density of at least 0.89.
- Any new plastic material used should meet current default standard (BP/Ph. Eur./USP) requirements for materials used for the manufacture of containers, as well as any other guidelines adopted by the TGA.
- If the product is a semi-solid, a semi-liquid or a liquid, it should be water based and should not contain organic solvent.
- If the container and/or closure system is a child-resistant package or is implied by its presentation to be a child-resistant package, data should have been generated to demonstrate that the child-resistant properties of the package and operation of the closure have not been adversely affected by the change in material, in accordance with the current TGO on child-resistant packaging of medicines.
- If the product is a solid dosage form, comparative moisture permeability (water-vapour transmission) data should have been generated on the new and current container/closure system.

Historical document
systems using the current edition of the USP test for containers—permeation (multi-unit containers), and the results should show either equivalent or better moisture protection.

- A stability study using the new container/closure system to verify the product’s shelf life should have started on at least one production-scale batch of the product, and should begin on the second and third batches as they are produced.

- If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority after the failure is detected, and the product in the new container/closure system may be withdrawn from the market at the TGA’s discretion.

- No change should be made to the product’s shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.

**Required information**

- Details of the new container/closure system, including any new material used and the material or container specifications (where relevant).

- If the closure is a child-resistant cap (or is implied by its presentation and construction to be a child-resistant cap), a declaration that the reclosable package meets all of the requirements of the current TGO on child-resistant packaging. The declaration should state, in particular, 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.

- Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.3 of this document.

**F2 Blister packs, strip packs and sachets**

**Specific conditions**

- The product should be a non-sterile solid (such as tablets or capsules) or semi-solid dosage form (such as moulded suppositories and pessaries) in blister packs, strip packs or sachets.

- The plastic component of the container may be changed from:
  - PVC to PVC/polyvinylidine chloride (PVDC) or PVC/polychlorotrifluoroethylene (PCTFE) or PVC/PVDC/PE; or
  - PVC/PVDC to PVC/PCTFE or PVC/PVDC/PE; or
  - polypropylene to PVC/PVDC or PVC/PVDC/PE; or
  - PVC to polypropylene; or
  - any type of plastic material to double aluminium foil blister packs (cold-formed laminated aluminium/aluminium blister packs) or double aluminium foil strip packs.

- Any new plastic material used should meet current pharmacopoeial (BP/Ph. Eur./USP) requirements for plastic materials used for the manufacture of containers.

- Comparative moisture permeability (water-vapour transmission) data should have been generated on the new and current blister-pack or strip-pack system using the current edition of the USP test for containers—permeation (single-unit containers and unit-dose containers), and the results should show either equivalent or better moisture protection.
• A stability study using the new container system to verify the product shelf life should have begun on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.

• If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority, and the product in the new container system may be withdrawn from the market at the TGA's discretion.

• No change should be made to the product's shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.

Required information

• Details of the new container material, including specifications, if relevant.

• Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.3 of this document.

F3 Increase in thickness of container/closure material

Specific conditions

• The product should be a non-sterile solid, semi-solid, semi-liquid or liquid dosage form.

• The container/closure material should be either unchanged or changed in a manner permitted in F1 and F2, above.

• A stability study using the new container/closure system to verify the product shelf life should have begun on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.

• If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority, and the product in the new container system may be withdrawn from the market at the TGA's discretion.

• No change should be made to the product's shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.

Required information

• Details of the change in thickness of the container/closure material, with specifications, if relevant.

F4 Decrease in thickness of container/closure material: blister packs, strip packs or sachets

Specific conditions

• The material that is decreased in thickness should be either the aluminium foil or, in the case of a laminated aluminium foil, the aluminium foil itself or any non-aluminium polymeric material laminated to it.

• The new aluminium foil thickness or the aluminium component of the laminated foil should be at least 20 µm.
• The product should be a non-sterile solid or semi-solid form.
• The container material should be either unchanged or changed in a manner permitted in F2, above.
• A stability study using the new container system to verify the product shelf life should have begun on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.
• If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority, and the product in the new container system may be withdrawn from the market at the TGA's discretion.
• No change should be made to the product's shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.

**Required information**

• Details of the change in thickness of the container material, with specifications, if relevant.
G Changes to the size, shape or components of the container/closure system

The following requests to vary the size, shape or components of the container/closure system are self-assessable:

G1 Container size and shape

G2 Container components (all dosage forms)

G1 Container size and shape

Specific conditions

- The change should not result in a change to the container type.
- The product should be a non-sterile dosage form.
- If the container is a blister pack or strip pack, the change in size or shape (for example, from a blister platform enclosing 7 dosage units to one enclosing 14 dosage units) should not result in an increase in the headspace volume of the blister pack or strip-pack pocket.
- If the container is a reclosable package and is child resistant (or is implied by its presentation to be a child-resistant package), data should have been generated to demonstrate that the child-resistant properties of the package and operation of the closure have not been adversely affected by the change in size and shape.
- If the container is a reclosable package, there should not be an increase in the headspace of the container.
- For solid oral dosage forms, comparative moisture permeability (water-vapour transmission) data should have been generated on the new and current container systems using the current edition of the USP test for containers—permeation (multi-unit or single-unit containers, as appropriate), and the results should show either equivalent or better moisture protection.
- The material and thickness of the container/closure system should be either unchanged or changed in a manner permitted in F1 to F4, above.
- A stability test using the new container/closure system to verify the product shelf life should have began on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.

If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority after the failure is detected, and the product in the new container system may be withdrawn from the market at the TGA’s discretion.

- No change should be made to the product’s shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.
- No change should be made to the quantity of products in the new container/closure system.
**Required information**

- Details of the new container/closure system, with specifications, if relevant.

- If the closure is a child-resistant cap, or implied by its presentation and construction to be one, a declaration that the reclosable package meets all of the requirements of the current TGO on child-resistant packaging. The declaration should state, in particular, 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.

**G2 Container components (all dosage forms)**

Note that, for sterile products, the container components that are being changed are not required to be sterile.

**Specific conditions**

- The change may be:
  - a change to, or addition or removal of, the outer carton or other outer primary pack (including changes to size, shape, colour or material thickness); or
  - a change to, or addition or removal of, components of the container that are not in direct contact with the product (for example, tamper-evident seal, aluminium flip-off crimps on injection vials, plastic dust-cover disc/blanket); or
  - the inclusion or removal of inert wadding from bottles and other containers containing solid dosage forms; or
  - the inclusion of a desiccant in containers of solid dosage forms; or
  - the inclusion of, or change to, an overwrap designed to prevent ingress or egress of moisture, solvent or gases from a container (including changes to size, shape or colour, or increased material thickness).
  
- Other than inert wadding and desiccant, the components should not be in direct contact with the product.

- The label of any outer carton or other primary pack that is added or changed should either remain unchanged, be identical to the container label or be changed as permitted under section K, below, and/or Part 6 of this document.

- Where an existing carton or primary pack is removed, the container label should either remain unchanged or be changed as permitted under section K, below, and/or Part 6 of this document, and should continue to meet all requirements of the existing TGO that relates to labels.

- The removal of inert wadding should have been validated with comparative data to demonstrate that the product’s friability and other physical attributes during normal transport and use have not been adversely affected.

- If an overwrap is introduced or changed, a stability study of the product with the overwrap to verify the product shelf life should have begun on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.
• If the results of the stability study fail to meet the specifications, the TGA should be notified as a priority, and the product in the new container system may be withdrawn from the market at the TGA’s discretion.

• No change should be made to the product shelf life or storage conditions. See subsection J for self-assessable changes to the shelf life or storage conditions.

**Required information**

• Details of the change(s).

• Where a desiccant is included in a container, an assurance that the desiccant is used to improve the existing acceptable stability profile of the product and is not used to overcome stability problems in the existing container.

• Where a desiccant is included in a container, information on the nature of the desiccant, as well as information showing that the desiccant is readily distinguishable from the product, and is appropriately labelled and identified as a desiccant.

• If an overwrap is introduced, the rationale for its inclusion, and details of the material of the overwrap and specification.
H  Change to, or addition of, pack size

A change to, or addition of, a new pack size is self-assessable, but a change in volume of fill of injections or other sterile preparations requires that data are provided for evaluation.

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, with 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 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 a Pharmaceutical Benefits Advisory Committee recommendation (including a larger pack size); or
  - to introduce a smaller pack size; or
  - to delete 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.

• The label for the new pack size should be the same as for the current pack size, except for
quantity of products or other changes allowed under section K, below, and/or Part 6 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 other sections of this document.

**Required information**

• Relevant details regarding the change in pack size.

• A copy of the label for the new pack size.

• Where the proposed change requires an update to the PI, details of changes to the PI, as
outlined in Section 1.3 of this document.
I 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 (including modified-release solid dosage forms).
- There should be no concurrent change to 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.
- Where a change involves product shape, dimension or embossing/debossing, the comparative dissolution profiles of pre-variation and post-variation products should be similar (that is, the $f_2$ value should be between 50 and 100).

Note: 'Comparative dissolution profiles' means that data should be generated on three recent pre-variation batches and at least one batch of post-variation product as follows:

1. At least 12 dosage units (for example, tablets, capsules) of each batch should be tested individually, and mean and individual results reported. The percentage of nominal content released should be measured at a minimum of three suitably spaced time points (excluding zero time point) to provide a profile for each batch (for example, at 5, 15, 30 and 45 minutes, or as appropriate to achieve virtually complete dissolution). The batches should be tested using the same apparatus and, if possible, on the same day. Test conditions should be those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.

2. To demonstrate the similarity of two dissolution profiles, the similarity factor, $f_2$, should be calculated using the equation and conditions stated in Appendix I of the EMA 'Note for guidance on the investigation of bioequivalence' (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The $f_2$ value should be between 50 and 100. In cases where more than 85% of the active substance is dissolved within 15 minutes in all tested batches, dissolution profiles are considered to be similar and the similarity factor does not need to be calculated.
– Insufficient quantities of recently manufactured batches may be available to meet this requirement. In these cases, it is acceptable to test retention batches, and to explain in the test report why this was done, stating the age and storage history of the samples.

**Required information**

- The new product description.
- The revised set of drug product specifications at release and expiry.
- An updated CPD document for the product that incorporates the changes, if applicable (see box ‘Note on certified product details [CPD] documents’, above).
- If relevant, revised labels may be required to provide information on the new appearance.
- Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.3 of this document.
J Changes to product shelf life or storage conditions

Pre-approved stability-testing protocols

Stability-testing protocols can be approved in advance, so that the shelf life of a product can be extended through self-assessment. Such protocols may be submitted with the application for registration of a product or with an application to vary the registration. When a stability-testing protocol is submitted, at least 12 months of stability data should be available for the product (or a closely related formulation) in the marketed container or less protective container.

Any stability-testing protocol proposed for this purpose should include:

- information on the number of batches to be tested (minimum of three production-scale batches) and container/closure to be used
- a statement of the proposed tests and methods
- a matrix indicating the time points at which each of the tests will be conducted, including storage conditions and duration
- acceptance limits for the results for each test. Some test limits (particularly those with quantitative results, such as assay, dissolution/disintegration, and impurities/degradation products) should be more stringent than the approved expiry limits, but not necessarily as stringent as the release limits.

The following requests to vary the product shelf life and storage conditions are self-assessable:

J1 Extension of shelf life according to an approved stability-testing protocol

J2 Decrease in shelf life and/or more restrictive storage conditions

J1 Extension of shelf life according to an approved stability-testing protocol

Specific conditions

This does not apply to the in-use shelf life for multi-dose products.

- A stability-testing protocol should have been previously approved by the TGA through self-assessment, explicitly for the purpose of extending the shelf life.
- At least three production-scale batches of the product should have been tested in accordance with the approved stability-testing protocol.
• The extended shelf life should not be longer than the time for which stability data meeting the approved protocol requirements are available, and should not be longer than five years.

• The extended shelf life should not be based on extrapolation of the stability data generated according to the approved protocol.

**Required information**

• Evidence that the TGA has explicitly approved the protocol for the purpose of shelf life extension through self-assessment.

• The new shelf life and storage conditions.

• Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.3 of this document.

**J2 Decrease in shelf life and/or more restrictive storage conditions**

If changes to shelf life or storage conditions are requested because of a problem with stability, data are required for evaluation, and the variation is not self-assessable.

**Specific conditions**

• Adequate stability data for at least three production-scale batches of the product should have been generated to support the new shelf life and storage conditions.

• Where relevant, product labels and the PI should be changed to reflect the new storage conditions and/or shelf life.

**Required information**

• Reasons for the change.

• Details of the new shelf life and/or storage conditions.

• A copy of the revised product labels.

• Where the proposed change requires an update to the PI, details of changes to the PI, as outlined in Section 1.3 of this document.
K 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*.

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 should 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*, 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 active ingredient in topical preparations
    - addition 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

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)—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 should 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

- changes to names of active ingredients, excipients or dosage forms as a result of changes in the Australian Approved Name, the ingredients database or the code tables in TGA eBusiness Services

  - 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’ or information about a changed appearance of the dosage form.

- addition or deletion of, or change to, the website address of an Australian owned and managed company

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• 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

• 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 should be identified in the request.

• The changes should 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 preferably be of actual size and should indicate the colours to be used. If there are multiple pack sizes or strengths, 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 and their locations on the labels.

• 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 (such as a TGA submission number).
L Changes to pharmaceutical aspects of the product information, including sponsor and/or supplier details

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 Section 4.2 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 API
  - 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 should 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 should 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 1.3 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.
M Other changes

The following further changes are self-assessable:

M1 Changes to medicines and poisons scheduling

M1 Changes to medicines and poisons scheduling

Note that any changes to the Standard for the Uniform Scheduling of Medicines and Poisons signal heading and cautionary statements are matters for the states and territories, and therefore should be handled through state and territory authorities. If a drug 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, 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 1.3 of this document.

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 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 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. 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 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. 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 evaluated.

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.

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

54 <http://www.tga.gov.au/industry/pm-ssp.htm>
56 <http://www.tga.gov.au>
• 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 1.3 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. These fees are subject to change from time to time; current fees 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 should 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 request is taken to have been approved.

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 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 system within 2 weeks of the date of approval. For injectable prescription medicines, the current approved PI should 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.

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 pharmaceutical aspects of the product information

B Changes to the specifications of the active pharmaceutical ingredient

C Changes to the specifications of the drug product

D Changes to the specifications of the excipients, raw materials and starting materials

E Changes in synthetic route or manufacturing process for the active pharmaceutical ingredient

F Changes to the method of manufacture of the drug product

G Changes to the site of manufacture of the active pharmaceutical ingredient

H Changes to the site of manufacture of the drug product

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

J Changes to the container/closure system or container components

K Change to, or addition of, pack size

L Changes to the shelf life or storage conditions of the drug product, or the retest period of the active pharmaceutical ingredient

M Changes to labels

N Changes to other aspects of quality data where the change does not create a separate and distinct good

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.
Comparative batch data

Comparative batch data means a comparison of data between the pre-variation product and the proposed post-variation API or drug product.

Unless otherwise specified in these conditions, these data should compare at least the last three batches that were manufactured under existing conditions (using retention samples, if necessary) and the first batch made under the proposed new conditions, before the first batch is released. The second and third batches manufactured under the new conditions should be reviewed as soon as they become available, and the TGA should be promptly informed of any differences.

For manufacturing changes where multiple strength (three or more) products are involved and the various strengths are either direct scales (that is, the quantity of all excipients increases proportionally with the quantity of active ingredient) or have closely similar formulations, comparative data may be generated for the lowest and highest strengths only.

A Changes to an entry that involve consequential changes to pharmaceutical 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.

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 changes to the PI.
- Details of changes to the PI, as outlined in Section 1.3 of this document.
- Relevant technical data to support the proposed change(s).
B Changes to the specifications of the active pharmaceutical ingredient

Required information

- A copy of the revised specification. This should be consolidated to apply to all sites of API manufacture, where relevant.
- Justification for the proposed changes, including changes to test methods.
- Validation of any changed test methods. Method cross-validation data against alternative or pharmacopoeial methods may also be required, if relevant.
- Certificates of analysis for at least three representative production-scale batches of the bulk API that demonstrate the ability of the API manufacturer and the drug product manufacturer to meet the revised specifications.

C Changes to the specifications of the drug product

Required information

- A copy of the revised specifications at release and expiry.
- Justification for the proposed changes, including changes to test methods.
- Validation of any changed test methods. Method cross-validation data against alternative or pharmacopoeial methods may also be required, if relevant.
- Certificates of analysis for at least two representative production-scale batches of the drug product that demonstrate the product manufacturer's ability to meet the revised specifications. If pilot-scale batches were used for testing, this should be explained and justified. Where appropriate, batch analytical data from aged samples may be necessary—for example, to demonstrate compliance throughout shelf life.

D Changes to the specifications of the excipients, raw materials and starting materials

Note: This type of change includes replacement of one type of starch (for example, wheat starch) with another type in a formulation, or changing the grade of an excipient, with no change in quantity in the formulation.

Required information

- A copy of the revised specifications.
- Justification for any new or changed limits or test methods.
• Validation of any changed test procedures for critical tests.

• Certificates of analysis for at least one representative batch of the excipient that demonstrate the manufacturer’s ability to meet the revised specifications.

• Where necessary (for example, when changing the grade of excipient or changing the type of starch used in a product), relevant validation data, such as comparative dissolution profiles and comparative batch data, that support the changed excipient.

E Changes in synthetic route or manufacturing process for the active pharmaceutical ingredient

This includes increases in batch size, changes to manufacture of key intermediates or redefining a starting material.

**Required information**

• A description (including flow diagram) of the changed manufacturing process, including any changes to manufacturing batch size and in-process controls.

• If redefining a starting material, justification for the choice of the starting material. Provide the pre-starting material synthetic process and details of controls of starting material impurities, including metal catalysts and residual solvents.

• Validation of the process.

• If the API 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 Spongiform Encephalopathies (TSEs). If appropriate, provide assurance regarding self-assessment of TSE risks of such materials (see item E5 in Section 4.2 of this document).

• A description and discussion of any resulting changes in impurities.

• Comparative impurity profile data from three batches of pre-variation material and at least one production batch of post-variation material using a validated test method.

• Comparative particle size distribution data from at least three batches of pre-variation and at least one batch of post-variation API to demonstrate comparability in particle size profile.

• Certificates of analysis for at least one production batch of API manufactured using the new process that demonstrates the manufacturer’s ability to meet the currently approved specifications, including polymorphic form and particle size distribution (using laser diffraction method), if appropriate. An assurance that certificates of analysis for another two batches showing compliance with the currently approved API specifications will be generated should also be provided.

• An updated drug master file (DMF) or Certificate of Suitability (CEP) (refer to Appendix 11 of the ARGPM for further details), if relevant.

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60 As defined in ICH guideline Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

• Where a change is to late stages of synthesis, crystallisation, purification or milling, either relevant comparative data of the dosage form (for example, dissolution, drug mass, aerodynamic particle size distribution) manufactured from at least three batches of pre-variation and at least one batch of post-variation API, or a cogent justification for not providing such data.

• Stability data for post-variation API in accordance with the relevant adopted EMA/ICH guidelines, or a statement of commitment to carry out such studies to verify any applied retest period of the API. Refer to Appendix 14 of the ARGPM for further details. Additional accelerated and long-term stability data for the drug product using the post-variation API may be necessary, in accordance with EMA guidelines.

F Changes to the method of manufacture of the drug product

This includes changes to batch size and equipment. Whether a given change is self-assessable or requires evaluation of data will be assessed on a case by case basis.

Required information

• A detailed description of the changed manufacturing process, including in-process controls.

• Process validation protocols and process validation data for the changed process (including validation of sterile manufacture and sterilisation processes, if applicable) for at least three production-scale batches. If fewer than three batches are process validated, explain why.

• Batch data for representative batches of the drug product manufactured using the current and proposed process. At least one of these batches should be full production scale unless otherwise justified; the other batches should be at least pilot scale but manufactured using full production-scale equipment unless otherwise justified. These data should be compared with at least three batches of recently manufactured pre-variation product. All data should be generated using approved routine quality control methods, unless otherwise justified and details are provided of the non-routine methods used.

• Relevant comparative data of the type listed below for the dosage form manufactured using the new and old manufacturing method or process. At least three recently manufactured batches of the pre-variation product and at least 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 pessaries/suppositories, implants, modified-release dosage forms) and transdermal patches, dissolution profiles using a discriminatory method. For modified-release dosage forms and low-solubility drugs used in conventional dosage form, dissolution testing over a pH range (for example, at pH 1.0, 4.5 and 6.8) should be conducted, unless otherwise justified. Similarity factors ($f_2$) should be calculated, where appropriate.
  – For semi-solid and liquid suspension products, particle size data (microscopic imaging or other methods) and/or dissolution data, as relevant.
For metered-dose pressurised inhalations (oral or nasal), dry powder for inhalation products, and metered-dose nasal spray solutions or suspensions, drug mass aerodynamic particle size distribution data using a multi-stage liquid impinger or a multi-stage cascade impactor of the Andersen type.

- Stability data, or confirmation that stability data will be generated. Relevant stability data should be generated for batches produced using the new process, as required by GMP. The TGA may ask the sponsor to provide accelerated stability data for a particular medicine if stability is known to be a problem or if changes in stability could have clinical consequences. The relevant stability data do not necessarily need to be supplied before the change of process is approved. However, if the data are not supplied, the sponsor should provide written assurance that stability data will be generated, and the TGA should be notified immediately if there are any significant problems, or if the data indicate that the stability of product from the new process is different from that made by the original process to the extent that the shelf life of the medicine would be affected.

- If the changes proposed may affect bioavailability of the product, bioavailability data establishing bioequivalence of product manufactured using the new and currently approved processes, or a justification for a waiver for such data. For further information on this aspect, see Section 3 of Appendix 15 of the ARGPM (Biopharmaceutic studies). If bioavailability data are required and are submitted to support the change, the application becomes a Category 1 application.

G Changes to the site of manufacture of the active pharmaceutical ingredient

Required information

- GMP evidence for the new site (that is, the Australian manufacturing licence for an Australian site or a current GMP clearance letter for an overseas site). The Australian licence or GMP clearance letter should cover the relevant manufacturing steps and should be valid (before expiry) at the time of application.

- Process validation data, including full details of the method of synthesis and relevant flow diagrams, and validation of sterile manufacture and sterile processes, if applicable.

- If the API exhibits polymorphism, relevant data to demonstrate that the approved polymorphic form is produced.

- Comparative impurity profile data from representative batches from current and new sites of manufacture, using a validated test method.

- Comparative particle size distribution data from at least three batches of pre-variation API and at least one batch of post-variation API to demonstrate comparability in particle size profile.

- Validation data that demonstrate the suitability of the API from the new site for use in the dosage form for which it is intended (for example, comparative dissolution profiles for solid dosage forms, drug mass aerodynamic particle size distribution for inhalation products) or justification for not providing such data. Where multi-strength (more than two) products are involved, comparative data for the highest and lowest strengths should suffice if the various strengths are direct scale or their formulations are closely similar.
• A DMF with accompanying letter of access, a CEP with accompanying letter of access, or a declaration that the manufacturing process and quality control are the same as those used at the currently approved manufacturing sites, or a description of any differences between the processes at the different sites (refer to Appendix 11 of the ARGPM for further details).

• Certificates of analysis for at least three production-scale batches manufactured at the new site that demonstrate the manufacturer’s ability to produce material that meets the currently approved specifications, including particle size limits and polymorphic form.

H Changes to the site of manufacture of the drug product

Required information

• GMP evidence for the new site (that is, the Australian manufacturing licence for an Australian site, or a current GMP clearance letter for an overseas site). The Australian licence or GMP clearance letter should cover the relevant manufacturing steps and must be valid (before expiry) at the time of application.

• A declaration that the manufacturing process, including batch size, is the same as that used at the currently approved manufacturing sites, or a description of any differences between the processes at the new and currently approved sites.

• Appropriate validation of the process at the new site for at least one production-scale batch (including validation of sterile manufacture and sterilisation processes, if applicable) to demonstrate that 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 representative batches of drug product that were manufactured at both the currently approved site and the new site. At least one batch from the new site should be full production scale unless otherwise justified; other batches should be at least pilot scale and manufactured using full production-scale equipment.

• Relevant comparative data on the product (see F, above). For modified-release dosage form and follow-on liability drugs used in conventional dosage form, dissolution testing over a pH range (for example, at pH 1.0, 4.5 and 6.8) should be considered, unless justification can be provided for not conducting such testing. Similarity factor, $f_2$, should be calculated, where appropriate.

• Relevant stability data should be generated for batches produced at the new site, as required by GMP. The TGA may ask the sponsor to provide accelerated stability data for a particular medicine if stability is known to be a problem or if changes in stability could have clinical consequences. The relevant stability data do not necessarily need to be supplied before the change of site is approved. However, if stability data are not supplied, the sponsor should provide written assurance that stability data will be generated, and the TGA should be notified as a priority if there are any significant problems, or if the data indicate that the stability of product from the new site is different from that made at the original site to the extent that the shelf life of the medicine would be affected.
I Changes to the source or manufacturing process of excipients of animal origin

*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 the TGA’s *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies [TSEs]*) 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 Appendix 10 of the ARGPM for additional details on requirements for ingredients of human or animal origin.

J Changes to the container/closure system or container components

This includes container shape, size and material, as well as any measuring or delivery system included in the pack, but excludes container type.

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*

- Description and specifications of container/closure system and materials.
- If relevant, biomaterial safety evidence that any new polymeric or rubber container/closure material that will come in contact with the product are free from 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 accordance with GMP requirements. Comparative moisture permeability data of the current and proposed container/closure system may be required.
- Validation data on the changed measuring/delivery system in the pack, if relevant.
- 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 reclosable 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.
For sterile products, sterile manufacture information and sterility testing data, as appropriate, including information such as validation of aseptic processes and preservative efficacy test data.

Revised labelling, instructions for use and any other appropriate information or data that relate to the change, if applicable.

Where the proposed change requires an update to the PI, details of the amended PI, as outlined in Section 1.3 of this document.

For non-sterile multi-dose oral liquid or suspension products, preservative efficacy test data.

**K 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, pre-filled 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 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 requires an update to the PI, details of the amended PI, as outlined in Section 1.3 of this document.

**L. Changes to the shelf life or storage conditions of the drug product, or the retest period of the active pharmaceutical ingredient**

*Required information*

• Stability data generated according to ICH guidelines on at least three production-scale batches to support the change. Data from fewer batches or pilot-scale batches may be acceptable, if justified.

• Revised labelling, if the storage conditions are to be changed.

• Where the proposed change requires an update to the PI, details of the amended PI, as outlined in Section 1.3 of this document.

• For increases in shelf life of multi-dose liquid products, preservative efficacy data, as specified in TGO 77 (see Appendix 16 of the ARGPM).

**M. Changes to labels**

The *Best Practice Guideline on Prescription Medicine Labelling* should be followed where practicable for safe and quality use of 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 to the stated scale.

**N. Changes to other aspects of quality data where the change does not create a separate and distinct good**

*Required information*

• Details of the proposed changes and appropriate supporting data relevant to the change(s) concerned.

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63 [http://www.tga.gov.au/industry/pm-ctd.htm]
4.4 Summary of variations under s. 9D(3)

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

- **No**
  - [s. 9D(1)] Request to correct an ARTG entry
    - See Part 2
  - [s. 9D(2)] Safety-related request to vary an ARTG entry
    - See Part 3
  - [s. 9D(3)] Request for a variation that does not reduce safety, quality or efficacy
    - See Part 4

- **Yes**
  - [s. 23] Application to make a variation that creates a separate and distinct good

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Some variations under s. 23 are self-assessable; others require data to be submitted to the TGA for evaluation.

<table>
<thead>
<tr>
<th>Level of assessment</th>
<th>Application type</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification of details provided by the sponsor</td>
<td>Quality-related variation: self-assessable request</td>
<td>45 working days</td>
</tr>
<tr>
<td>Evaluation of quality data only</td>
<td>Category 3 application: quality-related variation</td>
<td>45 working days</td>
</tr>
<tr>
<td>Full evaluation (combination of clinical, nonclinical, bioequivalence and quality data)</td>
<td>Category 1 or Category 2 application: major variation (streamlined submission process). Refer to the ARGPM for guidance on these application types</td>
<td>255 working days for Category 1; 175 working days for Category 2</td>
</tr>
</tbody>
</table>

ARTG = Australian Register of Therapeutic Goods
5.1 What is a separate and distinct good?

Separate and distinct goods

Under s. 16(1) of the Therapeutic Goods Act 1989, a medicine is a separate and distinct good from another 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; 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.

- **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 should 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 should then apply for approval of the variation, and should 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.

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

The Secretary’s approval under s. 25 is required for applications made under s. 23 of the *Therapeutic Goods Act 1989*[^67]. 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*[^68] (ARTG). However, depending on the nature of the variation, the provisions of the *Therapeutic Goods (Groups) Order No. 1 of 2001*[^69] 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. Information is provided in the following sections about whether the Groups Order applies for the different types of changes that create a separate and distinct good.

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.

5.2 Self-assessable requests

Conditions for self-assessable requests

All self-assessable requests must 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 conditions in this section and all 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 conditions 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) 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, 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 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 conditions

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

The product must be registered in the ARTG.

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71 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. Pilot-scale batch size should be at least 10% of the production-scale batch size. For oral solid dosage forms, the minimum scale is generally taken to be one-tenth that of full production, or 100,000 dose units, whichever is greater.
• 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* 72.

• 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 73.

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 1.3 of this document)

• relevant evidence of GMP (clearance letter if an overseas site of manufacture is involved, or an Australian manufacturing licence), if this is a condition of self-assessment

73 <http://www.tga.gov.au>
• 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 subsection of Section 5.2 of this document. The information should relate only to the specific variation 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 1.4), 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 for 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](http://www.comlaw.gov.au/Series/F1996B00406). These fees are subject to change from time to time; current fees are [available](http://www.comlaw.gov.au/Series/F1996B00406).
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 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 system within 2 weeks of the date of approval. For injectable prescription medicines, the current

75 <http://www.tga.gov.au/about/fees.htm>
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 types of variations 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

### Comparative batch data

Comparative batch data means a comparison of data between the pre-variation product and the proposed post-variation API or drug product.

Unless otherwise specified in these conditions, these data should compare at least the last three batches that were manufactured under existing conditions (using retention samples, if necessary) and the first batch made under the proposed new conditions before the first batch is released. The second and third batches manufactured under the new conditions should be reviewed as soon as they become available, and the TGA should be promptly informed of any differences.

For manufacturing changes where multiple strength (three or more) products are involved and the various strengths are either direct scales (that is, the quantity of all excipients increases proportionally with the quantity of active ingredient) or have closely similar formulations, comparative data may be generated for the lowest and highest strengths only.
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, 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’).
- Any new proprietary excipient to be used must be already entered in the ARTG.
- 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 at least 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 active pharmaceutical ingredient (API) in suspension. These data are not required if the API is in solution at any stage.

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78 <http://www.tga.gov.au/industry/cm-colourings-oral-use.htm>
79 As defined in the Therapeutic Goods (Groups) Order No. 1 of 2001
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 as a priority, 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).

- The new product description or other organoleptic properties of the product if these have changed, incorporated into the revised set of drug product specifications (release and expiry).

- 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).

- If relevant, revised labels may be required to provide information on the new formulation.

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 1.3 of this 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*<sup>80</sup>, this means that the reformulated product is a separate and distinct good from the existing

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product, and requires a new entry in 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 4.2.1 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’<sup>81</sup>) 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, 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 it 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.

- If relevant, revised labels may be required to provide information on the new appearance of the dosage form.

- 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 clear 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 1.3 of this document.

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<sup>81</sup> <http://www.tga.gov.au/industry/cm-colourings-oral-use.htm>
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) 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. 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 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 until it has been lodged.

Further information is also on the TGA website.

What do I need to provide?

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

- a cover letter (see below)

82 <http://www.tga.gov.au/industry/pm-euguidelines.htm>
85 <http://www.tga.gov.au>
• a completed ‘Category 3 application: Quality-related variation under section 23’ form

• the relevant data in the common technical document \(^{86}\) (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 1.3 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 \(^{87}\). These fees are subject to change from time to time; current fees \(^{88}\) 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 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 (which 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, 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 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.

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\(^{86}\) <http://www.tga.gov.au/industry/pm-ctd.htm>


\(^{88}\) <http://www.tga.gov.au/about/fees.htm>
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 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 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.

Data requirements

The following applications to vary an ARTG entry require submission of supporting data to the TGA for evaluation:

A. Formulation changes
B. Changes to container type
C. 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
- does not apply to biological medicines, but does apply to fermentation antibiotics and other products that are produced wholly or partially by fermentation.

### Comparative batch data

Comparative batch data means a comparison of data between the pre-variation product and the proposed post-variation API or drug product.

Unless otherwise specified in these conditions, these data should compare at least the last three batches that were manufactured under existing conditions (using retention samples, if necessary) and the first batch made under the proposed new conditions, before the first batch is released. The second and third batches manufactured under the new conditions should be reviewed as soon as they become available, and the TGA should be promptly informed of any differences.

For manufacturing changes where multiple strength (three or more) products are involved and the various strengths are either direct scales (that is, the quantity of all excipients increases proportionally with the quantity of active ingredient) or have closely similar formulations, comparative data may be generated for the lowest and highest strengths only.
A Formulation changes

The AUST R number can sometimes be retained

Under s. 16(1) of the *Therapeutic Goods Act 1989*, 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, for certain types of formulation changes.

The following formulation changes allow the current AUST R number to be retained:

- removal or addition of fragrance, flavour, ink or colour
- change in existing quantity of excipient (but not total removal).

Any other formulation changes will result in a new AUST R number.

Required information

- A copy of the current and revised formulation, and details of any new manufacturing process and associated validation data.

- 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*).

- Details of the specifications applicable to all the excipients used in the new formulation. If an excipient was not used in the previous formulation, certificates of analysis issued by the drug product manufacturer for two or three representative batches of the excipient should be submitted.

- For excipients that are of ruminant origin:
  - for products that are implanted, injected or given by parenteral, ophthalmic or intratracheal routes of administration, details of excipients derived from Category C tissues from transmissible spongiform encephalopathy (TSE)-relevant ruminant species (including excipients whose manufacture may have exposed them to Category C materials) and measures taken by the manufacturers to minimise TSE risk
  - for products that are given by the oral, topical, vaginal, rectal or inhalation routes that contain excipients derived from Category A or B materials (including excipients whose manufacture may have exposed them to Category A or B materials) from TSE-relevant

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ruminant species, details of all such excipients and measures taken by the manufacturers to minimise TSE risk

- for products given by the oral, topical, vaginal, rectal or inhalation routes that contain only excipients derived from Category C TSE-relevant ruminant materials, details of the excipients and a declaration that the Category C material has been self-assessed and complies with the TGA’s Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs) together with an assurance that the sponsor will maintain a record of compliance for future TGA compliance checks

- 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. 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.

Refer to Appendix 10 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) for additional detail on requirements for ingredients of human or animal origin.

- Relevant comparative data for the proposed new and currently approved drug products to demonstrate that the change in formulation does not lead to changes in the physical characteristics of the product that may affect the absorption and in vivo effect of the medicine. For further guidance, see Section 4.3 F.

- Where the change in formulation involves introduction of, or variation to, a range of values for particular excipients, relevant validation of the manufacture and testing of the product with excipient content at the extremes of the range may be required. Relevant guidance can be found in the current Committee for Proprietary Medicinal Products (CPMP) guidance document 3AQ2a: Manufacture of the Finished Dosage Form adopted by the TGA.

- Certificates of analysis for at least one production-scale batch of the drug product manufactured using the proposed new formulation. Pilot-scale batches are acceptable, if justified.

- Stability data in accordance with relevant EMA/ICH guidelines. For minor formulation changes, the sponsor may justify why relevant stability data need not be provided for review. However, a commitment to carry out stability testing on at least three production-scale batches of the reformulated product is required.

- Comparative bioavailability data may be required to establish bioequivalence of the new and currently approved formulation (for example, if significant changes to the formulation are made and this is likely to affect the bioavailability of the product). However, a justification may be provided to demonstrate why such a study is not required. If bioequivalence data are submitted, the application will be re-categorised as a Category 1 application. (For further information on changes that are unlikely to affect bioavailability and provision of a justification in lieu of bioavailability/bioequivalence data, see Section 3 of Appendix 15 of the ARGPM [Biopharmaceutic studies]).

If the new formulation involves a change to the preservative system, additional data may be required. These may include stability data (including microbial quality and proof of

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92 <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>
93 <http://www.tga.gov.au/industry/pm-argpm.htm>
antimicrobial efficacy of the drug product at expiry) and test methods (with accompanying validation data) for determination of preservative content in the drug product. For additional information, please refer to Therapeutic Goods Order (TGO) No. 77—Microbiological standards for medicines (TGO 77).

- If relevant, revised labels may be required to provide information on the new formulation.
- 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 1.3 of this document.

B Changes to container type

The AUST R number cannot be retained

Under s. 16(1) of the Therapeutic Goods Act 1989, 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.

Required information

- Description and relevant specifications of container/closure system and materials.
- The proposed shelf life and storage conditions in the new container type.
- Stability data (including physical, chemical and microbiological aspects, as applicable) from at least three production-scale batches, to confirm the stability of the product in the proposed new container. Stability data obtained only from pilot scale batches should be justified.
- 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, which is a requirement under regulation 9B of the Therapeutic Goods Regulations 1990.
- For sterile products, information on sterile manufacture, validation of sterilisation processes, preservative efficacy data and sterility testing data, as appropriate.
- If relevant, biomaterial safety evidence may be required. This is assessed on a case-by-case basis.
- For non-sterile products, details of the revised manufacturing process in the new container, together with process validation data, if appropriate.
- Proposed labels for the product in the new container type.

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 1.3 of this document.

C Replacement of trade name

The AUST R number can be retained

Under s. 16(1) of the Therapeutic Goods Act 1989, 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.
- Revised labels.
- 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).
- 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 1.3 of this 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
Part 6
Changes that do not require prior approval
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 handling agent of the active pharmaceutical agent and excipient, including material of biological origin (same site and method of manufacture, specifications and, where applicable, biological source, including geographical origin)

- changes to the supplier or manufacturer of non-sterile container or container components (same material type and specifications) (For other aspects of changes to containers, see also sections 4.2 and 4.3 of this document)

- changes to the manufacturing process and site of manufacture of excipients (same specifications but excluding excipients of animal or human origin) (For other aspects of changes to excipients, see also sections 4.2 and 4.3 of this document)

- 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:
  - change of typeface and increase in font size of print only
  - inclusion or removal of foreign national registration number
  - inclusion or removal of date of manufacture of product
  - inclusion or removal of, or changes to, name and address of supplier in New Zealand
  - inclusion or removal of, or changes to, sponsor or supplier telephone/facsimile number, email address, barcodes (includes 2-D matrix codes but not quick response [QR] codes), Australian Business Number or Australian Company Number, product code number, patent 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 Parts 4 and 5 of this document)
  - change in web address, without a change in the content of the website.
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 (including manufacturers who are also product sponsors) or the manufacturing address, provided the actual site location does not change.

- 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 (including manufacturers who are also product sponsors) or the manufacturing address, provided the actual site location does not change**

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.
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*\(^{97}\) (TG Act).

**active pharmaceutical ingredient (API)**

The therapeutically active component in the final formulation of medicines that are chemical entities. Also known as drug substance.

**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 the Australian Register of Therapeutic Goods (ARTG) entries that create separate and distinct goods under s. 16(1) of the 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**\(^ {98}\) (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)

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**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. Pilot batch size should correspond to at least 10% of the production-scale batch size. For oral solid-dosage forms, the minimum scale is generally taken to be one-tenth that of full production, or 100,000 dose units, whichever is greater.

**category 1, 2 or 3 application**

The type of administrative application made to the TGA to register new prescription medicines or vary existing prescription medicines.

**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 (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 a medicine that is a lyophilised powder that is packaged with an ampoule or vial containing a diluent.

**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. Container types are independent of the material used to make the container, 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’, which are used to specify the quality, method of manufacture and other aspects of therapeutic goods. These are the *British Pharmacopoeia*, the *European Pharmacopoeia* and the *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 prescription medicines. Some exclusions from this requirement are described in specific therapeutic goods orders.

100 <https://www.ebs.tga.gov.au/>
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 types of dosage forms, and their definitions, are listed in the ‘Dosage forms’ table on the TGA eBusiness Services website.

drug master file (DMF) | Data on the manufacture, quality control and stability of active pharmaceutical ingredient used in the manufacture of a medicine.

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 medicines that are chemical entities. Also known as API.

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 (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

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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*[^102]

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 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.

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.


Historical Document
**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 [103](http://www.tga.gov.au/industry/biologicals.htm) (Part 3-2A of the TG Act).

**overage**

Increased content of drug substance or recipient above the target amount, usually due to loss of potency during manufacture or on storage.

**overfill**

Increased volume of drug product to account for loss during delivery.

**packaging material**

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 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

[103](http://www.tga.gov.au/industry/biologicals.htm)
Parliamentary Secretary

The Parliamentary Secretary for Health and Ageing, who assists the Minister for Health in relation to the regulation of therapeutic goods.

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 therapeutic goods, including information regarding 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. A PI’s must comply with the specified form for providing product information104 for a restricted medicine.

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 APIs.

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).105


105 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.
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 separate and distinct goods 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.

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 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 should then make a request or application for approval of the variation, and should 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;\(^{106}\) or
- different directions for use; or
- a different type of container (disregarding container size).

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 this expression is used in this document in relation to a request under s. 9D or an application under s. 23 of the TG Act, it means the person 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.

\(^{106}\) Except for variations to indications under s. 9D(2) of the Therapeutic Goods Act 1989, as described in s. 9D(2A).
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) for 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 an active pharmaceutical ingredient in a medicine.

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.

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).