



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Variations to prescription medicines – excluding variations requiring evaluation of clinical or bioequivalence data

## Process guidance

Version 3.0, July 2019

**TGA** Health Safety  
Regulation



**Copyright**

© Commonwealth of Australia 2019

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

<b>Introduction</b>	<b>5</b>
Other types of variations	6
Contact the TGA	6
<b>1. Legislative basis for varying products</b>	<b>7</b>
1.1 Variations under s.9D of the Act	7
1.2 Changes that do not require prior approval	8
1.2.1 Examples	8
1.3 Separate and distinct goods	9
1.3.1 Retaining an existing AUST R number	9
1.3.2 New AUST R number	9
1.4 Statutory timeframes	9
1.5 TGA requests for further information	10
1.5.1 Section 31 requests	10
1.5.2 Objections	10
1.6 Making an appeal	11
<b>2. Variation category groups and categories</b>	<b>12</b>
2.1 Corrections to an ARTG entry	12
2.1.1 Changes to the product information for corrections to ARTG entries	13
2.2 Notifications	13
2.2.1 Conditions	13
2.2.2 Approval	13
2.3 Quality information	14
2.3.1 Self-assessable requests (SARs)	14
2.3.2 Category 3 requests	15
2.4 Product information	16
2.4.1 Minor editorial changes	16
2.4.2 Safety-related requests (SRR)	17
2.4.3 Extension of indications to align with a reference product	20
2.4.4 Changes to the product information	20
<b>3. How to apply for a variation</b>	<b>24</b>
3.1 Variation types	24
3.1.1 Multiple related changes	24
3.1.2 Multiple unrelated changes	25

---

3.1.3	Associated changes for separate and distinct goods-----	26
3.2	Prior to application submission _____	27
3.3	Variation e-form _____	27
3.3.1	Varying multiple ARTG entries -----	28
3.4	Submitting data _____	29
3.5	Conditions and data requirements _____	29
3.5.1	Validation data -----	30
3.5.2	Comparative batch data - active pharmaceutical ingredient and drug product	30
3.5.3	Comparative dissolution profiles -----	30
3.6	Variations to multi-component products _____	31
3.7	Further information _____	32
<b>4.</b>	<b>Changes not submitted via the Variation e-form</b>	<b>33</b>
4.1	Changes that do not require reporting to the TGA _____	33
4.2	Changes that do not require prior approval _____	33
4.3	Changes to manufacturer names and addresses _____	33
4.4	Mechanism to approve one-off changes to medicines _____	34
<b>5.</b>	<b>Fees for variations _____</b>	<b>35</b>
<b>6.</b>	<b>Processing and approvals _____</b>	<b>37</b>
6.1	Variations with a statutory timeframe _____	37
6.2	Approvals _____	37
6.2.1	Safety-related requests -----	37
6.3	Implementing approved variations _____	38

# 1. Introduction

This guidance describes how to make variations to existing entries for [prescription medicines](#) in the [Australian Register of Therapeutic Goods \(ARTG\)](#). The variations included in this guidance are quality and product information (PI) changes where evaluation of clinical and bio-equivalence data is not required. These applications are not lodged under the [Prescription Medicines Registration Process](#).

This guidance is split into sections:

- [Legislative basis](#) for variations
  - including information about [statutory timeframes](#) and [making an appeal](#)
- [Variation category groups and categories](#)
  - [Corrections](#)
  - [Notifications](#)
  - [Quality information](#)
    - [Self-assessable requests \(SARs\)](#)
    - [Category 3 requests](#) including information on [Category 3 requests that create a separate and distinct good](#)
  - [Product information](#)
    - [Minor editorial changes](#)
    - [Safety-related requests \(SRR\)](#)
    - [Extension of indications to align with a reference product](#)
    - other information on [changes to the product information](#)
- [How to apply for a variation](#)
- [Changes not submitted via the Variation e-form](#)
- [Fees for variations](#)
- [Processing and approvals.](#)

See also:

- Separate guidance that sets out the individual variation types for prescription medicines:
  - [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types – chemical entities](#)
  - [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types – biological medicines](#)
- [Information on dossier requirements](#) and how to submit your dossier to the TGA.

## Other types of variations

Information about other types of variations to prescription medicines that require evaluation of clinical or bioequivalence data are outlined in the [Prescription Medicines Registration Process](#) guidance.

## Contact the TGA

Any questions regarding variations to prescription medicines should be directed to [AET.application.entry.team@health.gov.au](mailto:AET.application.entry.team@health.gov.au).

## 2. 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.

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](#). Penalties may apply, including suspension or cancellation of registration. It is therefore important that sponsors follow the correct procedure when varying registered medicines to avoid breaching the provisions of the Act.



If a sponsor becomes aware that changes have been made to a medicine without the Secretary's approval, they must contact the TGA to determine how the ARTG entry can be updated.

Please email [AET.application.entry.team@health.gov.au](mailto:AET.application.entry.team@health.gov.au).

### 2.1 Variations under s.9D of the Act

To seek the Secretary's approval of a proposed change to a prescription medicine, sponsors must make a request under the provisions of s. 9D of the [Act](#). Four different types of requests can be made under s. 9D. Under each of these subsections, there are several application categories, outlined in the table below.

Legislative basis	Category
<p><b>Subsection 9D(1)</b> allows sponsors to request an update to an ARTG entry that is incomplete or incorrect.</p> <p>The Secretary can also make corrections under ss. 9D(1), if necessary, without the sponsor needing to make a request.</p>	<p><a href="#">Corrections to an ARTG entry</a></p>
<p><b>Subsection 9D(2)</b> allows sponsors to request safety-related variations to an ARTG entry (and consequential changes to the product information).</p> <p>A variation is safety-related if it reduces the patient population (e.g. by removing an indication), or has the effect of adding a warning or precaution (e.g. for an adverse effect or interaction).</p> <p>Under s. 9D(2A) of the 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 Act.</p>	<p><a href="#">Safety-related requests (SRRs)</a></p> <p><a href="#">SRR requiring evaluation of data</a></p>

Legislative basis	Category
<p><b>Subsection 9D(2C)</b> allows sponsors to request certain specified variations to an ARTG entry, that do not affect the established quality, safety and efficacy of the medicine, which under certain conditions must then be approved by the TGA.</p>	<p><a href="#">Notifications</a></p>
<p><b>Subsection 9D(3)</b> 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 Act, provided that the change does not reduce the quality, safety or efficacy of the medicine.</p> <p>Most variations made under s. 9D(3) relate to the quality of registered prescription medicines. Some requests under s. 9D(3) also involve making consequential changes to the Product Information (PI).</p> <p><i>Some PI changes may require evaluation of nonclinical, clinical or bioequivalence data as a Category 1 or 2 application under the <a href="#">Prescription Medicines Registration Process</a>.</i></p>	<p><a href="#">Minor editorial changes (MECs)</a></p> <p><a href="#">Self-assessable requests (SARs)</a></p> <p><a href="#">Category 3 requests</a></p>

## 2.2 Changes that do not require prior approval

These are types of changes that either:

- do not require reporting to the TGA or
- require reporting, but do not have to be approved by the TGA.

If the proposed changes require a consequential change to the approved product information of the medicine, these must be approved by the TGA before they can be implemented.

### 2.2.1 Examples

#### Changes that do not require reporting

- Certain minor changes to labels (e.g. change of typeface and increase in font size of print only)
- Changes to the local handling agent of the active pharmaceutical agent and excipient, including material of biological origin.

#### Changes that must be reported but do not have to be approved

- Certain changes to manufacturers (change in manufacturer's name, or the manufacturing address, provided the actual site location does not change).

See details of variation types in:

- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types – chemical entities](#)
- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data – biological medicines](#)

## 2.3 Separate and distinct goods

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



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;<sup>1</sup> or
- different directions for use; or
- a different type of container (disregarding container size).

If a variation creates a separate and distinct good, the 'new' good must be separately entered in the ARTG. A new AUST R number will be provided upon approval, where the [Therapeutic Goods \(Groups\) Order No. 1 of 2001](#) does not apply.

Variations resulting in separate and distinct prescription medicines cannot be implemented without prior approval by the TGA. Doing so constitutes supply of an unregistered product. It is an offence under s.19B of the Act to supply unregistered prescription medicines.

### 2.3.1 Retaining an existing AUST R number

Depending on the nature of the variation, the provisions of the [Therapeutic Goods \(Groups\) Order No. 1 of 2001](#) may mean that the old AUST R number can be retained for the new product.

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 email to [Application.support.team@health.gov.au](mailto:Application.support.team@health.gov.au).

Once supply of the new product begins, supply of the old product must cease.

### 2.3.2 New AUST R number

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 discuss with the TGA if they intend to supply the old product and the new product concurrently. If the sponsor decides not to supply the new product, they should notify the TGA.

## 2.4 Statutory timeframes

The [Therapeutic Goods Regulations 1990](#) specify statutory processing times for requests and applications relating to prescription medicines. The specified timeframe is known as 'the clock'.

<sup>1</sup> Except for variations to indications under s. 9D(2) of the *Therapeutic Goods Act 1989*, as described in s. 9D(2A).

The length of time depends on the level of assessment required—for example, evaluation of clinical, nonclinical, bioequivalence and quality data has a longer timeframe than an assessment of quality data only or verification of a self-assessable request.

Application category	Level of assessment	Timeframe (working days) <sup>2</sup>
<a href="#">Correction to, or completion of, an ARTG entry</a>	Verification of details provided by the sponsor	No statutory timeframe (TGA processes as soon as possible)
<a href="#">Notification</a> request to vary an ARTG entry	No assessment	No statutory timeframe (automatic approval on submission of e-form and full payment of fee)
<a href="#">Self-assessable request</a> to vary an ARTG entry	Verification of details provided by the sponsor	45 working days
<a href="#">Safety-related request</a>	Verification of details provided by the sponsor	No statutory timeframe (TGA processes as soon as possible)
<a href="#">Category 3 request</a> : variation to ARTG entry	Evaluation of quality data only	45 working days
<a href="#">Safety-related request with data</a>	Evaluation of data submitted to the TGA	No statutory timeframe (TGA processes as soon as possible)
Category 1 application: variation to ARTG entry with consequential PI change.	Full evaluation (combination of clinical, nonclinical, bioequivalence and quality data)	See the <a href="#">Prescription Medicines Registration process</a>

## 2.5 TGA requests for further information

### 2.5.1 Section 31 requests

The TGA may request additional information under s. 31 of the Act, about a proposed variation or to clarify information provided.

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. The clock stops at any time the Secretary is waiting for a response to a s. 31 request for information. There is no limit on the number of clock stops under s. 31.

### 2.5.2 Objections

Alternatively, the TGA may raise an objection to a request or application under Regulation 16F. An objection usually means that the Secretary will ask the sponsor questions about the product

<sup>2</sup> 'Working day' refers to a day that is not any of the following: a Saturday; a Sunday; a public holiday in the Australian Capital Territory; or a day between Boxing Day (26 December) and 1 January.

or the proposed variation (to which the sponsor must respond) that are necessary for a decision to be made about the request.

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 sponsor of the decision.

## 2.6 Making an appeal

Decisions made under s. 9D and s. 25 are ‘initial decisions’ within the meaning of s. 60 of the Act. This means that a person whose interests are affected by the decision can request a review by the Minister for Health.

A request must be made in writing within 90 days of when notice is given of the decision. All requests for reconsideration should be given to the Minister by email:

Email: [minister.hunt.DLO@health.gov.au](mailto:minister.hunt.DLO@health.gov.au) and copied to [decision.review@health.gov.au](mailto:decision.review@health.gov.au)

Where a request for reconsideration includes dossiers (or similar bulk material) that cannot easily be attached to a request made by email, the supporting documentation and original (signed) request for reconsideration can then be sent by express post or registered mail to:

Mail: **Minister for Health**  
**Suite M1 41**  
**c/- Parliament House**  
**CANBERRA ACT 2600**

The request should be titled ‘**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 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 (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](#)). 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.

### 3. Variation category groups and categories

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.

A description of the different category groups and categories of variations is provided below:

- [Corrections to an ARTG entry](#)
- [Notifications](#)
- [Quality information](#)
  - [Self-assessable requests \(SARs\)](#)
  - [Category 3 requests](#)
    - [Category 3 requests that create a separate and distinct good](#)
- [Product information](#)
  - [Minor editorial changes \(MEC\)](#)
  - [Safety-related requests \(SRRs\)](#)
  - [Extension of indications to align with a reference product.](#)

See also:

- The [legislative basis for variations](#) for information about the statutory timeframes for each variation category.
- The individual variation types, with relevant data requirements and conditions:
  - [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types - chemical entities](#)
  - [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types - biological medicines.](#)
- [How to apply for a variation](#)
  - Including information about [variation types](#) and [associated changes](#).

#### 3.1 Corrections 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 from the ARTG entry, including the product information (PI). In some cases, errors in quality-related documentation may need to be corrected.

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

#### Examples

- Correcting typographical errors in quantities of excipients

- Correcting grammatical errors in the records held about a product
- Adding a manufacturing step for a licensed manufacturer that was inadvertently omitted.

### 3.1.1 Changes to the product information for corrections to ARTG entries

Variations under s. 9D(1) can generally include only minimal changes to the PI, for example:

- correcting a typographic error in the street name of the sponsor's address
- adding previously approved text that was inadvertently omitted from the PI—with suitable evidence.

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](#), [minor editorial changes](#), [self-assessable requests](#), [Category 3 requests](#) or Category 1 applications.

## 3.2 Notifications

Notifications are types of variations that have been determined to pose a very low risk. The TGA has concluded that their implementation would not affect the established quality, safety and efficacy of a registered medicine. This conclusion relies on all conditions being met and generation of the appropriate data. If these conditions are not met, the sponsor must make a Category 3 request to the TGA for evaluation of the proposed variation. See further information about [conditions](#) below.

Variations to prescription medicines submitted as a notification are requests made under the provisions of subsection 9D(2C) of the [Therapeutic Goods Act 1989](#). The variation types that can be submitted as 'notifications' are specified in regulations 10AAB and 10AAC of the [Therapeutic Goods Regulations 1990](#) (the Regulations). Regulation 10AAB lists variation types for prescription medicines other than biological medicines and Regulation 10AAC lists those for biological medicines.

### 3.2.1 Conditions

Regulations 10AAB and 10AAC in the [Therapeutic Goods Regulations 1990](#) refer to the TGA guidance [Notifications process: requests to vary biologicals and registered medicines where quality, safety and efficacy are not affected](#). This guidance describes each variation type and the relevant conditions that must be met to allow the request to be processed as a notification.

The electronic application form that must be used to request a 'notifiable' variation will not validate unless the applicant provides assurances that each of the conditions associated with each variation type have been met.

### 3.2.2 Approval

Requests made under ss. 9D(2C) still require an application to the TGA and approval by the Secretary before implementation by the sponsor. However, due to their very low risk, the specified changes do not require evaluation or assessment by the TGA.

Once an application is successfully submitted using the electronic form and the fee paid, the sponsor will be sent an email notifying them that the request has been approved and the relevant ARTG entry will be automatically updated. The Secretary's approval of the variation is made automatically using the TGA Business Services system under the provisions of s. 7C of the *Therapeutic Goods Act 1989*.

### 3.3 Quality information

The categories included within the quality information category group are:

- [Self-assessable requests \(SARs\)](#)
- [Category 3 requests](#).

#### 3.3.1 Self-assessable requests (SARs)

Some variations are considered by the TGA to pose a lower risk and do not require TGA evaluation of data. These include variations where no data are necessary or where the data can be self-assessed by the sponsor.

Where the proposed variation must be validated to demonstrate that safety, quality and efficacy of the medicine have not been reduced, sponsors can assess the supporting data themselves and then make a request to the TGA based on this self-assessment. 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.

It is not mandatory for sponsors to use the self-assessment procedure. Any proposed self-assessable variations to registered medicines may be submitted within a [Category 3 application](#) for evaluation. In this situation, full details should be included in the cover letter and submitted along with the required Category 3 data and evaluation fee. The relevant Category 3 variation type should be selected. The 'Other' Category 3 variation types should only be selected if there is not a relevant Category 3 variation type available. See:

- [Variations to prescription medicines - excluding variations not requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types - chemical entities](#)
- [Variations to prescription medicines - excluding variations not requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types - biological medicines](#).

Requests must meet specific conditions outlined in the Appendix guidance documents to be considered self-assessable. If these conditions are not met, the data must be evaluated by the TGA before the change can be implemented. This means that the sponsor must make a Category 3 request.

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. If evaluation of clinical, nonclinical or bioequivalence data is needed, the application will then become a Category 1 and sponsors will need to resubmit the application in the [Prescription Medicines Registration Process](#).

#### Changes to the PI resulting from an SAR

Some quality-related variations made under ss. 9D(3) will result in a consequential change to the wording in the PI. These will be processed as part of the SARs.

See also:

- [General requirements for changes to the product information](#)

### **Self-assessable requests (SARs) that create a separate and distinct good under s. 23**

Some variations that are considered self-assessable requests result in a separate and distinct good. 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 Act.

See information about separate and distinct goods under the [legislative basis for varying products](#).

#### **3.3.2 Category 3 requests**

Most s. 9D(3) requests are quality related, and require a Category 3 application and evaluation of relevant quality data by the TGA.

The Category 3 variation types listed are representative and are not intended to be an exhaustive list of all quality-related changes requiring evaluation of data by the TGA. They are generally less specific than the notification and SAR variation types; this means that any change that meets the general description can be submitted as a Category 3 request. This includes:

- situations where the conditions and data requirements associated with the lower level request (notification or SAR) cannot be met
- when the sponsor chooses to request that the TGA evaluates the change rather than selecting a SAR or notification when either of those options are applicable
- changes that result in multiple, flow-on amendments to other aspects of the goods – only the single Category 3 variation type is needed, not multiple, individual types. See [how to apply for a variation](#) for an example.

In these situations, a summary of the exact changes being requested should be included in the comments field of the Variation e-form application and the cover letter.

The requirements are essentially the same as for the corresponding section of an application to register a new prescription medicine. The requirements of the [Australian Regulatory Guidelines for Prescription Medicines \(ARGPM\)](#) and relevant [European Medicines Agency \(EMA\)/International Conference on Harmonisation \(ICH\) guidelines adopted by the TGA](#) should be met, as appropriate.

Requests for variations that require evaluation of clinical or bioequivalence data will require a Category 1 application via the [Prescription Medicines Registration Process](#). If a Category 3 application is submitted, but the TGA determines that evaluation of clinical or bioequivalence data is required, sponsors will be informed that the request should be made as a Category 1 application with relevant supporting data.

### **Category 3 requests that create a separate and distinct good under s. 23**

Some Category 3 requests result in a separate and distinct good. All s. 23/s. 25 Category 3 submissions/applications that are approved by the TGA will be documented as new ARTG entries under the provisions of s. 25 of the Act.

See information about separate and distinct goods under the [legislative basis for varying products](#).

## 3.4 Product information

Product information variations are where the only change is to the product information (PI) document. The categories included within the product information category group include:

- [Minor editorial changes \(MEC\)](#)
- [Safety-related requests \(SRRs\)](#)
- [Extension of indications to align with a reference product.](#)



All ARTG entries included in the PI document (and therefore will be affected by a change to the PI) should be selected in the Variation e-form when requesting the variation. If an ARTG entry included in the PI document is not selected, a subsequent variation request will be required to be submitted.

For information about selection of ARTG entries for variations that are a consequence of a quality change see [Consequential changes to the product information](#). Note: changes to the PI that are a consequence of a quality change do not require a separate variation type to be selected in the Variation e-form. These PI changes should be submitted with the quality change request.

See also:

- [Changes to the product information](#)

### 3.4.1 Minor editorial changes

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. All PIs must comply with the specified [form for providing product information](#) for a restricted medicine.

Sponsors can request minor editorial changes under s. 9D(3) of the [Therapeutic Goods Act 1989](#).

#### Examples

- 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.

No new or amended information relating to the quality, safety or efficacy of the product should be proposed as a minor editorial change (see [safety-related requests](#), [self-assessable requests](#) or [Category 3 requests](#)).

#### Related information:

- [General requirements for changes to the product information.](#)

### 3.4.2 Safety-related requests (SRR)

A safety-related request (SRR) is used to vary an entry in the ARTG to either:

- reduce the patient population that can receive the medicine or
- add a warning or precaution.

If, during evaluation of a Category 1 application ([Prescription Medicines Registration Process](#)), proposed changes to the PI are identified as being safety-related, 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.

SRRs are made under s. 9D(2) of the [Therapeutic Goods Act 1989](#). These changes always require changes to the PI.

#### Variations that reduce the patient population

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

##### Examples

- 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)

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

#### Variations that add a warning or precaution



##### Warnings and precautions

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

##### Examples

- Adding a clearly identified warning or precaution
- Adding an adverse effect
- Adding an interaction
- Adding a contraindication
- 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

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.

### Variations that don’t add a warning or precaution

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

Examples of changes to the PI that are not within the meaning of s. 9D(2):

- 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)
  - 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).
- adding information on appropriate medical treatment of overdose, unless recommended by the TGA or [Therapeutic Guidelines](#)
- adding modifying phrases which reduce the impact of a warning (for example, adding a statement such as ‘no causal relationship has been established’)
- adding a statement relating to the efficacy of the medicine.

These types of requests must be made under s. 9D(3) of the Act.



### SRRs requiring evaluation of data

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. The requirement of supporting data will depend on the proposed changes in the safety related request. The request will be processed as a safety-related request with data for evaluation provided it meets the criteria of s. 9D(2).

If the sponsor is unsure if the proposed changes require supporting data, please contact AET prior to submission.

## Examples of safety related changes to PI that may require data for evaluation

- Includes quantitative data (describing values or incidence of certain findings e.g. incidence of an adverse effect)
- Describes a detailed causal relationship, including clinical significance
- Adds detailed information on interactions with other medicines (e.g. describing quantitative changes to AUC or Cmax when drug A is taken with drug B).
- Description of clinical trial or study that adds to a warning or precaution

Requests that involve amendments to the PI and require evaluation of clinical, nonclinical or bioequivalence data will require a Category 1 application in the [Prescription Medicines Registration Process](#). Examples include adding clinical trial information relating to efficacy rather than safety (such as meta-analysis from clinical trials without accompanying safety statements) and updating or adding new dosage directions for patients with renal impairment or due to interactions with other medicines.

## Safety-related variations identified by the TGA



If the TGA identifies the need for a safety-related variation to a sponsor's product, 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 because a signal has been identified during post-market monitoring of the medicine.

The processes and requirements for SRRs, 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 safety related change to a PI is approved, the TGA encourages sponsors to ensure that the approved PIs of all other related products are similarly updated by the same process.

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 reference product.

### ***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 post-market 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 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 approved, along with the consequential change to the PI.

### 3.4.3 Extension of indications to align with a reference product

Extension of indications to align with a reference product is a variation to indications where:

- the proposed indication is identical to one already approved for a prescription medicine where bioequivalence has previously been demonstrated
- regulation 16G of the [Therapeutic Goods Regulations 1990](#) applies and does not require the evaluation of clinical, pre-clinical or bio-equivalence data
- the applicant proposes to group the new medicine (this variation results in a [separate and distinct good](#)) with the existing medicine.

If the variation requires evaluation of clinical, pre-clinical or bio-equivalence data, see [Prescription Medicines Registration Process](#).

#### Related information:

- Extension of indications to align with a reference product in [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types – chemical entities](#).

### 3.4.4 Changes to the product information

As described in [Guidance 8: Product Information](#), a draft PI must be lodged, in a form approved by the Secretary under s. 7D of the 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.

See also:

- [FAQs on reformatting the Product Information document](#)

### 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 Section 3 Pharmaceutical form of the PI to be updated accordingly.



Changes to the PI that are a consequence of a quality change **do not** require a separate variation type to be selected in the Variation e-form. These PI changes should be submitted with the quality change request.

A single PI often refers to multiple ARTG entries (products). If the affected PI refers to additional ARTG entries that are not selected in Variation e-form then these additional ARTG entries should be listed in the application cover letter and comments field of the Variation e-form. A statement should be included requesting that the PI for these additional products is also varied.

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.

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.

See also:

- [Multiple related changes](#) in [How to apply for a variation](#) for an example of submitting changes that result in consequential updates to other aspects of the medicine.

## 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 decision-making by the TGA.

Sponsors should ensure that the information in the entire PI is consistent with the proposed changes. All marked-up text should be in a different colour(s) from the currently approved, unchanged PI text. 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. Any changes made to the currently approved PI should be clearly marked in all tracked versions of the PI.

The table below provides details of the suggested types of marking up.

**Table: Guidance for preparing marked-up product information**

Change to product information	Mark up
Text to be deleted	<p>Use strikethrough font.</p> <p>Text that is proposed to be deleted should be shown in its current position, not in comment boxes in the margins.</p> <p>However, explanatory comments added in the margins may be useful.</p>
Text to be inserted	Use underlined font.
Text to be moved	<p>Use strikethrough font to show where the text is being moved from, and underlined font to show where it is being moved to.</p> <p>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.</p>
Multiple requests in one submission (for example, several changes under the same part of the Act)	<p>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.</p> <p>The Figure below 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.</p>
Reformatting	See <a href="#">FAQs</a> on how to reformat the PI in accordance with the new form.

Clearly distinguishing between PI changes corresponding to different types of variations that have been submitted simultaneously to the TGA will aid decision-making, as different types of changes may be assessed by different TGA delegates.

The figure below shows an example of a marked-up PI.

## Figure: 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.

**Comment [sponsor1]:** Minor editorial change: replace dosage units with full description for clarity.

**Comment [sponsor2]:** Minor editorial change: change wording of sentence about accumulation to increase clarity.

### 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. phenobarbitone, 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*.

**Comment [sponsor3]:** Minor editorial change: paragraph moved to 'Interactions' section, as this is the most appropriate location.

### Presentation and storage conditions

**Transdermal patch 50.** Transdermal patch, 50 mg (releases 50 micrograms of medicine per hour) (square, white patch, marked with trade name and strength in black ink): 5's 2's (carton).

**Comment [sponsor4]:** Self-assessable request: change to PI to reflect request to reduce pack size.

## Other changes to the product information

In some cases, the only proposed variation to an ARTG entry is a change to the PI. Some of these changes do not meet the criteria of a [safety-related request](#) 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.

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 [Prescription Medicines Registration Process](#).

Note: all ARTG entries included in the PI document (and therefore will be affected by a change to the PI) should be selected in the Variation e-form when requesting the variation. If an ARTG entry included in the PI document is not selected, a subsequent variation request will be required to be submitted.

## 4. How to apply for a variation

The information below outlines what you need to consider prior to and whilst applying for a variation. This includes:

- [Variation types](#)
  - including information on [multiple related changes](#), [multiple unrelated changes](#) and [associated changes](#)
- considerations [prior to application submission](#)
- requesting variations using the [Variation e-form](#)
- [Submitting data](#)
- [Conditions and data requirements](#)
  - including information on [validation data](#), [comparative batch data](#) and [comparative dissolution profiles](#).

### 4.1 Variation types

There are specific variation types to describe many possible changes. These are four-letter acronyms with descriptions which are selected during the application process using the [Variation e-form](#). The variation types are listed under variation categories outlined in:

- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types - chemical entities](#)
- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types - biological medicines.](#)

Some variation types require an update to ARTG data. If these variation types are selected in the e-form, a single mandatory provisional ARTG record (PAR) field screen will be displayed. The guidance outlines the PAR fields that you will need to update for each variation type. When an update to ARTG data is required, a change must be made to each of the ARTG records you have selected for the variation type to be applied.

#### 4.1.1 Multiple related changes

In some instances, varying one aspect of a medicine can result in the need to update other information. For example, changing the pack size may involve changes to the label and the product information document. Selecting a separate variation type for each of these changes may result in multiple applications or submissions when, in fact, all the changes should be considered as a consolidated package.



#### Multiple related variations

Read the conditions associated with each variation type to determine if a single variation type can be used. Details of individual changes should be included in the cover letter and in the comments field of the e-form. This ensures that all aspects of a proposed variation are considered at the same time.

### Example – submitting changes that result in consequential updates to other aspects of the medicine

Company S wishes to update the storage conditions for their medicine due to stability concerns. The existing storage conditions are stated on both the medicine label as well as in the PI document. Consequentially, these will need to be updated to reflect the new storage conditions.

Although the change affects multiple aspects of the medicine, in the Variation e-form, Company S will only need to select one Category 3 variation type:

- DSLC: Shelf life - Changes to the shelf life or storage conditions of the drug product.

If this is the only change being made to the label and PI document, Company S does not need to separately select a variation type for the label and PI changes. Company S refers to the Appendix guidance and can see that the conditions and data requirements for DSLC allow for changes to labels and PI.

Company S includes a summary of the changes in the cover letter and the comments field in the Variation e-form.

Company S also check if the PI refers to any other products (AUST Rs) not selected in the Variation e-form (that is goods that are listed in the PI document but do not require the variation to storage conditions). If the PI refers to additional products then Company S also provide a list of these goods and a statement requesting that the PI be updated for these products.



For multiple related changes that require multiple PAR fields to be updated consider if there are [associated changes](#) available for your variation. If there are no 'Associated changes' available, you may need to select separate variation types.

#### 4.1.2 Multiple unrelated changes

Some multiple unrelated changes can be requested by selecting one variation type. For example, with medicine labels, some changes can be made to an approved label as notifications, while others require evaluation by the TGA. If a sponsor wishes to make multiple concurrent changes to a label, and at least one of these requires evaluation, a single Cat 3 request should be submitted. This avoids the automatic approval under ss. 9D(2C) being given for an amended label that includes additional changes that require evaluation.

### Example – submitting unrelated medicine label changes in a single submission

Company T wishes to make the following quality changes to the labels of their prescription medicine, which is available in three strengths:

- alter some colours used in the artwork (Category 3 request)
- change the distributor's name and address (notification)
- remove duplicated information from a side panel (consistent with the conditions that make this a notification)

Although these changes are not related to each other, Company T wants to



submit only one amended label to the TGA. Company T should therefore request all of these changes within one Category 3 application.

In the Variation e-form, Company T will need to select only

- LCDE: Label changes – any changes requiring evaluation (a Category 3 variation type)

and include a summary of the changes within their cover letter.

### 4.1.3 Associated changes for separate and distinct goods

When requesting a change that will result in a new and distinct good, there may be situations where other variations (including changes to PAR fields) need to be included. To prevent unnecessary separate submissions you can select 'Associated changes' to access different PAR fields. If you select these variation types, the changes will only be applied to the new goods. The 'Associated changes' variation types are listed in:

- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types – chemical entities](#)
- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types – biological medicines.](#)

#### **Example – submitting variations with associated changes to other aspects of the medicine for a separate and distinct good**

Company U wishes to update the formulation of their medicine where [Therapeutic Goods \(Groups\) Order No. 1 of 2001](#) does not apply and a new AUST R number is required. The proposed change to the formulation is due to a proposed change to manufacturer site and is therefore 'associated.' There is also a consequential change to visual identification and updates are required to the label and PI.

Company U will select:

- DFNA: Formulation – changes (CE) – New AUST R number

followed by:

- ZFNM: ARTG data – Manufacturer changes associated with DFNA/PFNA or PCCT – For the new AUST R number
- ZFNV: ARTG data – Visual identification changes associated with DFNA/PFNA or PCCT – For the new AUST R number.

This ensures that the associated changes are applied to the new good with the new AUST R number (and not to the existing good).

Company U does not need to separately select a variation type for the label and PI changes. Company U can see that the conditions and data requirements for DFNA allow for changes to labels and PI.

If unrelated changes are required to the new good, Company U will wait until they have received a decision letter stating that their new product has been



approved before applying for a variation to the new good.

## 4.2 Prior to application submission

Prior to submitting an application, gather the data and information that you will require. It is suggested to:

- list all changes
- consider if any of your changes result in a [separate and distinct good](#)
  - consider if the AUST R number can be retained or if a new AUST R number is required
- look for [multiple related changes](#) and [associated changes](#)
- look for Category 3 variations and bundling opportunities (for example [multiple unrelated changes](#))
- lastly, look for unrelated remaining changes that will require separate submissions.

Think about the overall variation outcome that you are trying to achieve. Consider if you are varying an existing good or creating a separate and distinct good. If you are creating a separate and distinct good, consider if a new AUST R number is created. When using the Variation e-form note the following information.

- If you select a variation type that has 'new AUST R number' in the title, a provisional ARTG record is created with a new AUST R number. Your variation is applied to a copy of the existing product at the time that you submit your application. If approved, it will result in a new entry on the register.
  - If you wish to request a further variation to the new product after your application has been submitted, you will need to wait until the good with the new AUST R number has been approved and added to the register.
- If you select any other variation type including those with 'Retaining AUST R number' in the title, your variation will be applied to the existing product. If approved, it will result in an update to the existing entry on the register.

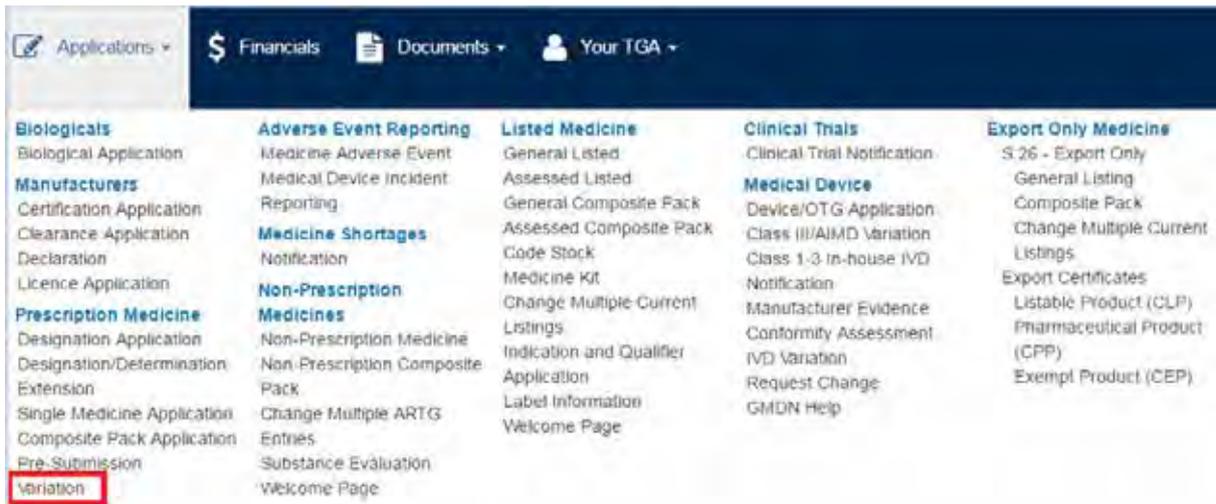
A variation type that requires a new AUST R number cannot be submitted with a variation type that creates a separate and distinct good but retains the AUST R number in the same transaction for the same ARTG record. These variations need to be submitted separately in separate transactions to ensure the ARTG data changes are applied to the correct AUST R number.

## 4.3 Variation e-form

To request variations to prescription medicine entries:

- log onto the [TBS portal](#)

- select **Variation** under Prescription Medicine as per the screenshot below:



- follow the steps in the Variation e-form, including:
  - search and select ARTG entries to vary
  - select the variation category group, category and type
  - ensure the assurances are met
  - include comments (if relevant)
  - update ARTG data (if prompted)
  - provide supporting information
  - complete the declaration.

#### Related information:

- [Guidance on setting up access onto the TBS portal.](#)

### 4.3.1 Varying multiple ARTG entries

The Variation e-form allows multiple ARTG entries with the same active ingredient and sponsor to be selected for a variation request.



All ARTG entries to which the variation applies should be selected when requesting the variation.

If an ARTG entry is not selected for variation and the variation applies to that good, a subsequent variation request will need to be submitted.

For information about selection of ARTG entries for variations to the product information document that are a consequence of a quality change see [Consequential changes to the product information](#) and [Multiple related changes](#).

## 4.4 Submitting data

Data can be submitted by attaching the supporting information to the e-form in either e-submission (eCTD and NeeS) or non-electronic data formats. Attached documents must be submitted as a single zipped file, which can be up to 100 Megabytes (MB) in size.

The application must pass validation under the 'Make variation(s)' step before documents can be attached at the 'Supporting information' step.

If the data are submitted as a sequence in an eCTD or NeeS dossier, sponsors will need to include the print preview at module 1.2.1 as the application form. TGA staff will upload this data into docuBridge. Sponsors do not need to send any information to the TGA e-Submissions address if data are attached to the e-form.

Alternatively, data can be sent separately to the TGA on digital storage media such as CDs/USBs etc. If this option is selected, the e-form will identify that a cover letter has been generated – this document should be downloaded and a paper copy sent to the TGA with the supporting information. The cover letter contains information which allows TGA staff to easily identify the application associated with the data.

The printed cover letter together with the supporting data should be sent by express post or registered mail to:

Mail: **Records Management  
Therapeutic Goods Administration  
PO Box 100  
Woden ACT 2606**

## 4.5 Conditions and data requirements

There are specific conditions and data requirements needed to support variation requests. Different types of requests have different conditions and requirements.

Conditions and data requirements are outlined under individual [variation types](#) in:

- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 1: Variation types – chemical entities](#)
- [Variations to prescription medicines - excluding variations requiring evaluation of clinical or bioequivalence data - Appendix 2: Variation types – biological medicines.](#)

If relevant to the variation request, also provide:

- a clean and [marked-up copy of the approved PI](#)
- a table, provided as an attachment to the letter of request, outlining each of the proposed changes to the PI with brief explanatory text, including justifications
- evidence of GMP (clearance number if an overseas site of manufacture is involved, or Australian manufacturing licence)
- for corrections to the ARTG, details of when the entry became incorrect or incomplete (if possible), preferably including a relevant file or submission number
- a copy of relevant correspondence with the TGA.

## 4.5.1 Validation data

### Validation data

The validation data specified for each individual variation type in the guidance documents are the minimum requirements. Additional validation may be necessary in some instances, for example, to comply with the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme [PIC/S] [Guide to Good Manufacturing Practice for Medicinal Products](#).



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.

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. For chemical entities the pilot-scale batch size should be at least 10% of the production-scale batch size. For biological medicines, the choice of pilot batch size should be justified.

## 4.5.2 Comparative batch data - active pharmaceutical ingredient and drug product

Comparative batch data means a comparison of data between the pre-variation active pharmaceutical ingredient (API)/drug product and the proposed post-variation API/drug product.

- Unless otherwise specified in **individual** 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 products with multiple (three or more) strengths 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.

## 4.5.3 Comparative dissolution profiles

'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 must 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 the 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) [Guideline 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.
- Sufficient quantities of recently manufactured batches may not 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.

## 4.6 Variations to multi-component products

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

The most common multi-component packs are composite packs. 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 composite packs are regulated in a similar way to any other prescription medicine.



**Composite packs** contain two or more therapeutic goods, but do not contain therapeutic devices or medical devices that are included in the ARTG. They are used for a single treatment or a single course of treatment, and the components are either combined before treatment or administered in a particular sequence. The composite pack itself is regulated as a separate and distinct good and must have its own unique AUST R number. Individual components within the pack may or may not have separate registrations or listings.

Examples of composite packs are a blister pack that contains several different types of tablets, for example oral contraceptives, or a vial of medicine that is a lyophilised powder that is packaged with an ampoule or vial containing a diluent.

## 4.7 Further information

For further information related to applying for variations refer to:

- [General dossier requirements](#) including how to submit your dossier to the TGA
- [Fees for minor variations](#)
- [Statutory timeframes](#)
- [Processing and approvals](#).

Any questions regarding variations to prescription medicines should be directed to [AET.application.entry.team@health.gov.au](mailto:AET.application.entry.team@health.gov.au).

## 5. Changes not submitted via the Variation e-form

There are some changes that do not require a Variation e-form submission.

### 5.1 Changes that do not require reporting to the TGA

These changes can be implemented without reporting to the TGA. This does not include any proposed changes that require a consequential change to the approved product information of the registered medicine.

Where these changes affect information within your dossier that had been previously submitted to the TGA, the relevant update can be submitted:

- as part of any subsequent SAR or Category 3 variation, or
- directly submitted to the TGA electronic submission team (following written advice from the TGA).

### 5.2 Changes that do not require prior approval

Certain changes require reporting, but do not have to be approved by the TGA. These changes can be implemented before you inform the TGA of the change. Reporting to the TGA should be made in writing, together with any relevant documentary evidence required in support and the date of implementation advised. No specific form is required. Contact [AET.application.entry.team@health.gov.au](mailto:AET.application.entry.team@health.gov.au).

This process cannot be used if the proposed changes require a consequential change to the approved product information of the registered medicine.

Where these changes affect information within your dossier that had been previously submitted to the TGA, the relevant update can be submitted:

- as part of any subsequent SAR or Category 3 variation, or
- directly submitted to the TGA electronic submission team (following written advice from the TGA).

### 5.3 Changes to manufacturer names and addresses

For [changes to an overseas manufacturer's name or the manufacturing address, provided the actual site location does not change](#), the GMP clearance recording this information should be updated. Details for this process can be found in [GMP Clearance Guidance](#).

Changes to licences to manufacture therapeutic goods (Australian sites only) are arranged by the licence holder.

Changes to GMP clearances and licences will be reflected in the ARTG entries of products when approved.

See also:

- [Manufacturing medicines](#) for more information.

## 5.4 Mechanism to approve one-off changes to medicines

Supplying a medicine which does not comply with all relevant standards, or whose composition, specifications or presentation differs from that authorised by the TGA, is an offence under the Act. However circumstances may arise where the supply of a medicine is appropriate despite not fully complying with all relevant specifications.

Where options such as reworking the batch is not possible and if the sponsor can demonstrate the quality, safety and efficacy of the product is not affected by the non-compliance, TGA may consider permitting the batch to be supplied.

Where the non-compliance relates to a default standard (BP, EP or USP-NF), therapeutic goods order or other legislated standard, a sponsor may request [consent to supply](#) the non-conforming batch(es) from the TGA. This may include quality specifications imposed by the TGA where no specific monograph for the medicine exists, but a general monograph applies.

Where the non-compliance is not derived from a standard, but forms part of the medicine's approval for supply, the sponsor should contact TGA via [pcsinbox@health.gov.au](mailto:pcsinbox@health.gov.au) to discuss an appropriate process and documentary requirements. The data required to be submitted will depend on the nature of the change, but will likely include evidence that the quality, safety and efficacy is not adversely affected and should include any relevant correspondence with TGA.

## 6. Fees for 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 variations to registered prescription medicines.

These fees are subject to change from time to time. Refer to:

- [Schedule of fees and changes](#)
- [Payment options](#)

The e-form will automatically generate an invoice when the variations are submitted via the TBS portal. A single invoice will be generated for all variation types that fall under the same fee item.

See table below for details.

**Table: Relevant submission types for variations**

Submission <sup>1</sup>	Part of Act	Type of application	Level of TGA assessment
2A(a)	s. 9D(1)	<a href="#">Correction of an ARTG entry</a>	Verification of summary provided by sponsor
	s. 9D(2)	<a href="#">Safety-related request (SRR)</a>	
	s. 9D(3)	<a href="#">Self-assessable request (SAR)</a> and <a href="#">Minor editorial change (MEC)</a>	
2AD(a)	s. 9D(2C)	<a href="#">Notification</a>	No assessment
2CA	s. 9D(2)	<a href="#">Safety-related request (SRR) with data</a>	Evaluation of (usually clinical) data
2B	s. 9D(3)	<a href="#">Category 3 request</a>	Evaluation of quality data
2(a) <sup>2</sup>	s. 23	<a href="#">SAR (that creates a separate and distinct good)</a>	Verification of summary provided by sponsor
2(bj) and 4(h)	s. 23	<a href="#">Category 3 request (that creates a separate and distinct good)</a>	Evaluation of quality data

<sup>1</sup>The numbers listed correspond to the relevant item number in Schedule 9 of the Regulations.

<sup>2</sup>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.

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 in 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.

In cases where all entries contain the same active ingredient(s), corrections to ARTG entries, safety-related requests (SRRs) and self-assessable requests (SARs) that do not require TGA evaluation of data can be lodged as a single submission for the purposes of calculating fees payable.

## 7. Processing and approvals

If all the requirements for the variation 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.

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.

The TGA will only review those variations that are described in the application. Any new information will only be accepted if the TGA requests it 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 variations.

### 7.1 Variations with a [statutory timeframe](#)

When all the necessary information has been received by the TGA (including payment), the clock starts on the application. If the Secretary is not able to make a decision, the clock stops while the TGA asks for information under s. 31 of the Act or raises an objection. The clock restarts on receipt of the complete response to the request for information.

### 7.2 Approvals

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 Act. Sponsors should lodge copies of the updated PI and Consumer Medicine Information with the TGA via the [TGA Business 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).

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

The sponsor will be notified of the initial decision in writing. Any notification of a rejection will include reasons. If the Secretary varies an ARTG entry on his or her initiative, a letter will be sent to the sponsor informing them of the decision.

Decisions made under s. 9D and s. 25 are subject to review under s. 60 of the Act.

See also:

- [Making an appeal](#)

#### 7.2.1 Safety-related requests

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.

Processing time 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.

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

### **Request for further information supporting an SRR**

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'.

**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.

If the sponsor has submitted a SRR without data and the Secretary need supporting data to ensure the proposed changes to the PI is accurate and appropriate, the sponsor will need to withdraw the SRR without data and resubmit as SRR with 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 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. In this case, the sponsor should submit an SRR with data.

## **7.3 Implementing approved variations**

Variations to registered prescription medicines cannot be made without approval by 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 to the ARTG entry under s. 9D(3).

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 appropriately.

## Version history

<b>Version</b>	<b>Description of change</b>	<b>Author</b>	<b>Effective date</b>
V1.0	Original publication	Scientific Operations Management Section/Scientific Evaluation Branch	June 2017
V2.0	Introduction of notifications process and minor amendments	Scientific Operations Management Section/Scientific Evaluation Branch	December 2017
V3.0	<p>Amended title</p> <p>Inclusion of Extension of indications to align with a reference product</p> <p>Clarification of process for Notifications, Self-assessable requests and Category 3 requests where multiple variation types could be selected</p> <p>Inclusion of advice regarding advising the TGA of changes made to medicines without the required approval</p> <p>Minor clarifications and corrections to phrasing and layout</p> <p>Clarification of mechanism to approve one-off changes to medicines</p>	Scientific Evaluation Branch	July 2019

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6203 1605  
<https://www.tga.gov.au>

Reference/Publication #D19-5366432