Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

# Notification process

## Requests to vary biologicals and registered medicines where quality, safety and efficacy are not affected

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# Contents

# Introduction

This guidance outlines 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 or included biological.

These requests (known as 'notifications') still require an application to the TGA. These requests do not require evaluation, but legally must still be approved by the TGA before implementation by the sponsor.

The types of variations that can be submitted as 'notifications' are specified in the Therapeutic Goods Regulations 1990 (the Regulations). The conditions for each of these are outlined within the relevant sections below:

- Registered medicines:
  - Non-prescription medicines (OTC and registered complementary medicines)
  - Prescription medicines (non-biological medicines)
  - Prescription medicines (biological medicines)
- Biologicals.

The descriptions of these types of variations are quite specific. If there is no variation code in the Regulations that describes the intended change, or not all of the conditions outlined in the notifications guidance can be met, then that change cannot be made as a notification and will require approval by the Secretary prior to being implemented.

It is a breach of section 28 of the *Therapeutic Goods Act 1989* if a change which requires prior approval from the Secretary is implemented before such approval is given. Penalties may apply if this occurs. Contact the TGA if you are unsure if your change meets the conditions of a notification. General enquiries can be made via the TGA Information line on 1800 020 653 or email info@tga.gov.au and further contact details at www.tga.gov.au/contact-tga.

# Notifications process – registered medicines

Sponsors of registered medicines must:

- submit these 'notification' requests using the approved electronic form, with any relevant supporting information attached, via the TBS portal
- provide relevant assurances, which are included in the form, before lodging the application
- pay the appropriate fee.

Once the form is successfully submitted and the fee paid, the sponsor will be sent an email notifying them that the request has been approved and the relevant Australian Register of Therapeutic Goods (ARTG) entry is being automatically updated. This TGA approval is made automatically through the TGA Business Services system for the Secretary under the relevant provisions of the *Therapeutic Goods Act 1989*.

# Notifications process – biologicals

Sponsors of biologicals must:

- submit these 'notification' requests using the approved electronic form via the TBS portal
- submit a cover letter and supporting information following our general dossier requirements for all submitted supporting information
- pay the appropriate fee.

After successful submission of the application an approval letter will be manually processed.

# A risk-based approach to variations

When applying to register a new medicine or biological, sponsors must submit to the TGA data that assures the quality, safety and efficacy of the good. On the basis of this information, the medicine or biological can be approved by a TGA delegate for registration or inclusion on the ARTG.

Minor variations may be made after goods have been entered on the ARTG. These include, for example, changes to manufacturing processes or updates to product information or labels. Such information would have been relevant at the time the registration decision was made and therefore requests to vary this information must be submitted to the TGA for approval. This helps the TGA to assure the on-going quality, safety and efficacy of the medicine or biological.

Variations to registered medicines and biologicals can range:

- from those that are considered to pose only a very low risk (e.g. ceasing use of a nominated alternative manufacturer)
- to those which may pose a more significant risk (e.g. changes to critical manufacturing methods or proposed extensions to a medicine's shelf-life).

In some instances, data may also need to be submitted to the TGA for evaluation before the variation can be approved. The TGA therefore takes a risk-based approach to assessing and approving minor variations – from the notification process described above to requests that require careful assessment of technical evidence to confirm that quality, safety and efficacy are being maintained.

# Guidance on minor variations

Further information on minor variations and relevant guidance is available on the TGA website:

- Process to change a registered OTC medicine
- Online applications for registered complementary medicines
- Minor variations to prescription medicines
- Varying biological entries on the ARTG

# Notifications for registered non-prescription medicines

## OTC and registered complementary medicines

This guidance outlines the kinds of variations to registered non-prescription medicines that are considered as requests made under the provisions of section 9D(2C) of the *Therapeutic Goods Act 1989* (known as 'notifications'). The conditions outlined below the description of each variation type must be met for the request to be processed as a notification.

Categories:

- Labelling (including package insert) and product detail changes
- Formulation changes - active ingredients
- Formulation changes - excipient ingredients
- Quality control changes - finished product specifications
- Quality control changes - starting material specifications
- Packaging changes
- Manufacturing changes - finished product

## Labelling (including package insert) and product detail changes

### LFT: Font or type size other than change to the type size on the main panel of the label. Does not include change in colour or label copy.

A change to the font, letter height or text size on a label for the medicine, except where the change is to the letter height or text size on the main panel of the label.

#### *Conditions*

- No aspects of the labelling, Product Information (PI), Consumer Medicines Information (CMI), pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## LGM: Movement of graphics provided it remains on the same panel of the label and there is no change to the size, shape or colour of the graphic and does not involve the reformatting of pre-existing text.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## LLN: Introduction of a 'new' or a 'value pack' flash - see LAB for removal of a 'new' or a 'value pack' flash

Introduction of a 'new' or a 'value pack' flash to an approved medicine label, see LAB for removal of a 'new' or a 'value pack' flash

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## LSP: Changes to sponsor details including name and/or logo (inclusion of a logo or change to an existing logo) except where LAB applies

Changes to sponsor details, including logos, stated on the approved medicine label, other than where the sponsor name is part of the approved name of the medicine (except where LAB applies).

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## PLN: Addition of a pack size for liquids/semi solids where the new pack size falls within the pack size range specified in the ARTG entry of the medicine subject to the change. See also PLS.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table (see also PLS)
- The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume.

- The container type (as defined in TGA Approved Terminology for Medicines) is unchanged and container material is unchanged.
- The following are applicable:
  - The changeover has been validated* and the Sponsor is satisfied that the change will not adversely affect the stability of the product; and
  - Stability testing will continue for the full term of the product's shelf life and the TGA advised immediately of any batches not meeting specifications.

* Note: Validation data will be provided during a GMP inspection or upon request by the TGA within 3 months following the request (also see Guidelines on quality aspects of OTC applications).

## PSC: Recommended storage conditions - more restrictive

Change to the recommended storage conditions for the medicine, to make these more restrictive.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## PSD: Pack size - deletion

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## PSN: Addition of a pack size for dosage forms other than liquids/semi- solids (see PLS) or metered dose aerosols (see PMZ) where the new pack size falls within the pack size range specified in the ARTG entry of the medicine subject to the change. See also PSZ.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table. The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume (see PLS. PMZ and PSZ).
- The container type (as defined in TGA Approved Terminology for Medicines) is unchanged and container material is unchanged.

## PSR: Shelf life - decrease

Decrease in the approved Shelf life of the medicine.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## RGN: Removal of a graphic except where this relates to directions on how to use the product or the use of a measuring device or an applicator (see KMD)

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.(see KMD)

# Formulation changes - active ingredients

## AOV: Overage - decrease or removal

Reduction or removal of previously approved overages allowed for the amount of the active ingredient(s) in the medicine.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

# Formulation changes - excipient ingredients

## EST: Type of starch (no change to quantity)

Change to the type of starch used as an excipient ingredient in the medicine, where there is no change to the quantity.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- Neither the existing nor the new material is a modified starch.
- The changeover has been validated.
- Stability data for at least 6 months have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or for at least 3 months at a temperature at least 10°C higher than the maximum recommended storage temperature.

- Stability testing will continue for the full term of the product's shelf life and any batches not meeting specifications will be withdrawn from the market immediately and the TGA notified immediately.

# Quality control changes - finished product specifications

## QFP: Change from one default standard (as defined in the *Therapeutic Goods Act 1989*) to another or from a 'company' or 'in-house' specification to a pharmacopoeial specification.

Changes to the approved finished product specifications to ensure that the medicine complies with the requirements of a default standard (i.e. a monograph in the BP, USP-NF or EP) (see the *Therapeutic Goods Act 1989*).

This may involve a change from a default standard currently identified in the specifications to another; or the adoption a default standard in place of an 'in house' specification.

### *Conditions*

- This includes deletion of the existing pharmacopoeial tests and limits.
- If adding a default standard and consequently removing any tests that are duplicated by this addition, any other tests included in the specifications (e.g. residual solvents in the finished product or friability) must not be deleted or changed.
- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- A copy of the current specification plus a copy of the new specification, with the changes highlighted, have been supplied.

# Quality control changes - starting material specifications

## QSP: Change from one 'default standard' (as defined in the *Therapeutic Goods Act 1989*) to another or from a 'company' or 'in-house' specification to a pharmacopoeial specification.

Changes to the approved starting material specifications such that the material must comply with the requirements of a default standard (i.e. a monograph in the BP, USP-NF or EP) (see the *Therapeutic Goods Act 1989*).

This involves a change from a default standard currently identified in the specifications to another; or adopting a default standard in place of an 'in house' specification. If the latter, any additional non-pharmacopoeial specifications must not be deleted or changed.

### *Conditions*

- This includes deletion of the existing pharmacopoeial tests and limits.

- If adding a default standard and consequently removing any tests that are duplicated by this addition, any other tests included in the specifications (e.g. residual solvents in the finished product or friability) must not be deleted or changed.
- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

# Packaging changes

## KBL: Container material - if the container is a blister pack, the goods are a solid dosage form (e.g. tablet) and the change in material is of a specific type.

Changes to the container material where the container is a blister pack, the medicine is a solid dosage form (e.g. tablet) and the change in material is of a type described below:

- PVC to PVC/PVDC or to PVC/PCTFE or
- PVC/PVDC to PVC/PCTFE or
- the change to the plastic component is to a material with demonstrated lower or equivalent water permeability than the existing material (see for example USP monograph '<671> Containers Permeation').

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- The changeover has been validated and the Sponsor is satisfied that the change will not adversely affect the stability of the product.

It is expected that appropriate validation studies will be performed and that the results will be available on request or during the course of GMP inspections.

Where a manufacturing process has not been fully validated on production scale batches at the time of approval of a new medicine, the sponsor should provide a written assurance that the manufacturing process will be validated, consistent with the requirements of the Code of GMP, for the first two or three production scale batches. The sponsor should also provide an assurance that the manufacturer's validation reports on these batches will be made available, if requested for review by the TGA, within three months of release of the batches. The performance of this validation will be made a condition of registration of the medicine (also see Guidelines on quality aspects of OTC applications).

Stability testing will continue for the full term of the product's shelf life and the TGA advised immediately of any batches not meeting specifications.

- The container type (as defined in TGA Approved Terminology for Medicines) is unchanged.

## KBT: Container material - if the container is a bottle, the goods are a solid dosage form (e.g. tablet) and the change in material is of a specific type

Changes to the container material where the container is a bottle, the medicine is a solid dosage form (e.g. tablet) and the change in material is of a type described below:

- Polystyrene to PVC, polyethylene, polypropylene or glass or
- PVC to polyethylene, polypropylene or glass or
- Polyethylene to glass or polypropylene of density ≥ 0.89 or
- From one density of polyethylene to a higher density or
- Any change between glass, polyethylene of density ≥ 0.95, and polypropylene of density ≥ 0.89.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

Validation data may be reviewed during a GMP inspection or upon request by the TGA within 3 months following the request (also see Guidelines on quality aspects of OTC applications).

- The changeover has been validated and the Sponsor is satisfied that the change will not adversely affect the stability of the product.
- Stability testing will continue for the full term of the product's shelf life and the TGA advised immediately of any batches not meeting specifications.
- The new container/closure system has demonstrated equal or better moisture protection in the USP test for Containers - Permeation (water vapour transmission) to that of the existing container/closure system.
- The container type (as defined in TGA Approved Terminology for Medicines) is unchanged.

## KCL: Closure - other than changes in KCM or MDA

Changes to the container closure other than where the closure also serves as a metering component or the changes refer to the pump or pump components of a metered-dose aerosol.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- The changeover has been validated and the Sponsor is satisfied that the change will not adversely affect the stability of the product.

Validation data may be reviewed during a GMP inspection or upon request by the TGA within 3 months following the request (also see Guidelines on quality aspects of OTC applications).

- Stability testing will continue for the duration of the product's shelf life and the TGA advised immediately of any batches not meeting specifications.

## KMO: Removal of a measuring device where other means of accurately measuring the dose are readily available.

Removal of a measuring device, where other means of accurately measuring the dose are readily available. This change can include the deletion of graphical representation of the device (including associated wording) on the label. The change must not include changes to the directions for use or any other changes to labelling such as reformatting. A copy of current and proposed label must be supplied if the label is changed.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## KRR: Removal of refill pack

Removal of a medicine's refill pack.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

# Manufacturing changes - finished product

## AMS: Addition of steps of manufacture, other than for sterile products where MSS or MST applies

Identification of additional steps in the manufacture of the finished product that can be performed by an approved manufacturer, where the product is non-sterile.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- The nominated manufacturer has acceptable GMP evidence to perform the relevant steps of manufacture of the finished product.

## MMA: Addition of a manufacturer (includes site of manufacture), other than for sterile products where MSS or MST applies

Addition of a new manufacturer approved to perform any or all steps in the manufacture of the finished product, where the product is non-sterile.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- The nominated manufacturer has acceptable GMP evidence to perform the relevant steps of manufacture of the finished product.

## MMD: Deletion of a manufacturer (includes site of manufacture)

Cessation of the use of a manufacturer approved to perform any or all steps in the manufacture of the finished goods at an approved site.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## MSD: Deletion of steps of manufacture

Reduction of the number of steps that can be performed by an approved manufacturer in the manufacture of the finished product.

### *Conditions*

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.

## MSS: For sterile products, the addition of a manufacturer or addition of steps of manufacture involving only one or more of the following steps: release for supply, secondary packaging or testing [chemical and physical or microbial]

For a sterile product:

1. Addition of a manufacturer (includes site of manufacture) involving only one or more of the following steps: release for supply, secondary packaging or testing [chemical and physical or microbial].
2. Addition of steps of manufacture involving only one or more of the following steps: release for supply, secondary packaging or testing [chemical and physical or microbial].

### *Conditions*

- The finished product is sterile.

- No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
- The nominated manufacturer has acceptable GMP evidence to perform the relevant steps of manufacture of the finished product.

# Notifications for prescription medicines (non-biological medicines)

This guidance outlines the variations to non-biological (chemical) prescription medicines that are considered as requests made under the provisions of section 9D(2C) of the *Therapeutic Goods Act 1989* (known as notifications). Conditions that are outlined below the description of each variation type must be met for the request to be processed as a notification.

Categories:

- Active Pharmaceutical Ingredient (API) changes
- Drug product manufacture changes - method, batch size or equipment
- Site of manufacture changes
- Drug product specifications or test changes
- Changes to excipients
- Changes to container/closure system
- Product label changes

## Active Pharmaceutical Ingredient (API) changes

### ACCS: API container - changes to container/closure system of a non- sterile API

Changes to the container or closure system used to store a non-sterile API.

#### *Conditions*

- The API must not be sterile.
- The material of the container/closure must be either unchanged or is changed to a more protective material.
- The thickness of the material must be either unchanged or increased.
- There must either be no change in retest period/storage conditions, or a decrease in retest period and/or more stringent storage conditions are applied in the new container/closure system.

You must submit:

- Details of the new container/closure system.

- Details of the new retest period or storage conditions, if changed. You must generate the following:
- Relevant comparative moisture permeability data for the current and proposed material demonstrating either equivalent or better moisture protection.
- Initial stability testing data of the API in the new container/closure system conducted in accordance with relevant stability testing guidelines.

## ACEP: API Certificate of Suitability (CEP) - A revision for a non-sterile API that is not a synthetic polypeptide or prepared by fermentation

This covers all changes to the data package of the API that have been reviewed by the European Directorate for the Quality of Medicines and Healthcare (EDQM) where the EDQM subsequently issued a revised Certificate of Suitability (CEP), or have declared that a revised CEP is not required.

### *Conditions*

- The API must not be manufactured wholly or substantially by fermentation.
- The API must not be a synthetic polypeptide.
- The API must not be manufactured as a sterile drug substance.
- The current CEP must have been approved previously by the TGA.
- The revised CEP must be the next issued version from that approved by the TGA. Additional consecutive updates can be included if:
  - they follow the 5 year renewal (with no other changes) and/or
  - the changes are for minor administrative updates and/or
  - the drug substance has not been used to manufacture any drug products supplied in Australia.
  - Where changes to the API specification are involved (including test parameters, limits and test methods), the same changes must be adopted by the product sponsor and/or drug product manufacturer, and any new test methods must be validated as suitable for use.
- Where the change to the CEP is a change to the site of API manufacture, the site must have either:
  - a licence to manufacture the API (if the site is in Australia) or
  - sponsor-specific GMP clearance (if the site is overseas) that is valid at the time of the application.

You must submit:

- 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.
- 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 minor changes have been made, a flow diagram or outline of the revised route of synthesis of the API must also be submitted.

A GMP clearance or manufacturing licence is **not** required for the manufacturing site of intermediates or the site of milling/micronisation of the final drug substance. If, however, the milling of the final API occurs in Australia the site will require a GMP licence.

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, including test methods, adopted by the API manufacturer and the drug product manufacturer/product sponsor (as relevant).

You must generate the following data:

- Relevant comparative data 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 micronisation of the final drug substance).
- Comparative data 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 ranges as the pre-change API. Alternatively comparative dissolution profiles must be generated.
- Comparative batch data from at least one production-scale batch of the final drug substance manufactured or tested according to the changed process, which demonstrate compliance with any revised API specification.

## AMBS: API and intermediate manufacture - change to batch size of a non-sterile API (existing site)

Change to the size of a manufacturing batch of a non-sterile API or its intermediates.

### *Conditions*

- Any increase in batch size must be less than 10 fold from that last evaluated by the TGA.
- There must 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 must not be due to unexpected events arising during manufacture or to stability concerns.
- The API must not be a sterile substance.

You must submit:

- Details of the new manufacturing batch size.

You must generate the following data:

- Comparative batch data demonstrating there is no significant difference in the tested parameters, particularly particle size distribution, polymorphism and impurity profiles.

## AMCS: API site of manufacture - cessation

Cessation of an approved site for the manufacture of the API.

### *Conditions*

A GMP clearance or manufacturing licence is required for the principal manufacturing site of the final drug substance. Exceptions are some common inorganic salts and simple organic compounds. For more information see guidance on drug master files (active substance master files).

- There must be at least one other registered site of manufacture for the API.

You must submit:

- The name and address of the manufacturer to be ceased.
- A current TGA Business Services printout for the product or a copy of the TGA approval showing that at least one registered site of manufacture of the API remains to perform the relevant steps of manufacture.

## AMIT: API and intermediate manufacture - addition, revision or deletion of in-process control tests and limits

Addition, revision or deletion of in-process control tests and associated limits applied during manufacture of the API or its intermediates.

### *Conditions*

- The change must be consistent with any applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products.
- The change must not be due to adverse events during manufacture.
- The change must result in equivalent or improved quality of the final isolated material.
- The specifications of the API and/or intermediates may only be changed in ways permitted in other parts of this guidance document or remain unchanged.
- The new test method must not be a biological method.

You must submit:

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

You must generate the following data:

- Appropriate validation data for the in-process control test method.
- Batch analytical data from testing of three batches using the current and proposed methods demonstrating the results are within the same ranges.

## AMMC: API/starting material/intermediate manufacture - minor manufacturing changes not involving sterilising steps (existing site)

Minor changes to the manufacture of the API, starting materials or intermediates (i.e. equipment or process changes to improve efficiency), excluding changes to sterilising steps.

### *Conditions*

- The change must be consistent with any applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products.
- The synthetic route must remain the same, and no new reagents, solvents or catalysts are to be used in the amended process.
- The change must not involve any sterilising steps.
- The specifications of the API, starting materials and intermediates may only be changed in ways permitted in other parts of this document or remain unchanged.

You must submit:

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

You must generate the following data:

- Comparative batch data for the API/starting material/intermediate demonstrating there are no significant differences in the purity profiles or physicochemical properties.

## AMMF: API starting material/intermediate site of manufacture - change to/addition of (for APIs manufactured by multi-step syntheses or fermentation)

Transfer to, or addition of, an alternative site for the manufacture of intermediates for APIs that are manufactured by multi-step synthesis, which may include intermediates prepared wholly or partially by fermentation.

### *Conditions*

- The intermediates must be isolated chemical species and be at least three steps back in the synthetic scheme from the API (purification procedures do not count as steps of synthesis).
- The synthetic route must remain the same, and no new reagents, solvents or catalysts are to be used at the new site.
- The specification limits of starting materials or intermediates must be the same or tighter.
- For intermediates prepared wholly or partially by fermentation:
  - there must be either no change in the strain of the producer organism used or, where there is a change, details of the new producer organism must be provided and the component profiles of the final fermentation broth at harvest made from the new and old strain must be the same.
  - there must be no changes to the scale of operation of the fermentation tank and fermentation processes.
  - there must 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).

You must submit:

- The name and site address of the new manufacturer(s) of the starting material(s) or intermediate(s).
- The route of synthesis of the API.
- The name or code number of the intermediates for which the alternative site of manufacture is sought.

You must generate the following data:

- Comparative batch data (including impurity levels) for the starting material(s) or intermediate(s) manufactured at the current and proposed sites using validated test methods demonstrating that there are no significant differences in purity profiles.
- Comparative batch data for API synthesised using starting material(s) or intermediate(s) from the current and proposed sites demonstrating that there are no significant differences in purity profiles.

## AMTA: API site of manufacture - transfer of/addition to an existing manufacturer's site of a non-sterile API that is not prepared by fermentation

Transfer to, or addition of, an alternative site of manufacture of non-sterile APIs that are not prepared by fermentation, but by chemical synthesis or through isolation from a natural source as pure chemical entities.

### *Conditions*

- The API must be prepared by chemical synthesis or isolated from a natural source as pure chemical entities.
- The API must not be prepared wholly or partially by fermentation, and must not be sterile.
- There must be no change to the existing method of synthesis, including to any intermediates and any solvents or reagents used in the synthesis and purification of the drug substance (the API), or any other aspect of manufacture and specifications.

This change only applies where the sponsor of the drug product or the new API manufacturer knows the **full route of synthesis** and **all other details of manufacture** of the API at both sites.

The manufacturing batch size remains unchanged or smaller.

- The new site must have either:
  - a current manufacturing licence issued by the TGA for this type of manufacture (if the site is in Australia) or
  - a sponsor-specific GMP clearance (if the site is overseas) that is valid at the time of the application for this type of manufacture.

You must submit:

- The name and address of the new manufacturing site and GMP clearance number.
- 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.

You must generate the following data:

- Comparative batch data for three batches of the API from the proposed site. This data must demonstrate that all results (including impurity profiles, particle size distribution and polymorphic forms) are 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.

## ASAM: API/starting material/intermediate specifications - changes to non-biological test methods for assay and/or residual solvents (including water)

Changes to a non-biological method used for assaying or residual solvent testing (including testing for water where this may be present) of the API, starting materials for API synthesis or intermediates created in the synthetic process.

### *Conditions*

- The proposed method must not be a biological method.
- Validation data from the proposed method must demonstrate either**:**
  - an improvement in at least one of precision, accuracy or specificity, without a reduction in the other parameters or
  - an improvement in specificity or accuracy with reduced precision (while precision remains within the specified limits).

You must submit:

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

You must generate the following data:

- Validation data for the proposed method.
- Data for three batches of the API tested using the current and proposed methods demonstrating equivalency of both methods.

## ASDR: API re-test period and storage conditions - decrease to re-test period and/or more restrictive storage conditions

Decrease in the re-test period, or application of more restrictive storage conditions, for APIs.

### *Conditions*

- The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

You must submit:

- Reasons for the change.
- Details of the new retest period and/or storage conditions.
- An assurance that you possess adequate stability data for at least three production-scale batches of the API to support the new retest period and/or storage conditions.

## ASID: API/starting material/intermediate specifications - changes to identification tests

Changes to identification tests used for the API, starting materials for API synthesis or intermediates created in the synthetic process.

### *Conditions*

- The changes to identification tests must:
  - be 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
  - vary the existing identification test (for example, an HPLC test that has been shown to improve or at least maintain the specificity of the method) and/or
  - replace an existing identification test with a near infrared spectroscopic identification test and/or
  - include a new identification test in addition to an existing identification test.
- Any additional identification test must not serve as an alternative identification test.
- For near infrared spectroscopy tests, the method development and other data requirements (including data collection, establishment of the spectral reference library, calibration and validation of the method) must comply with the currently adopted European Medicines Agency (EMA) guideline on the use of near-infrared spectroscopy.

You must submit:

- The revised set of specifications.
- Details of the identification test method.

## ASNL: API/starting material/intermediate specifications - narrowing of limits

Any revision of the specifications for testing of the API, starting materials for API synthesis or intermediates created in the synthetic process must make the limits applied to the test results more stringent.

### *Conditions*

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

The grade of material must not change (for example, unmicronised to micronised material). You must submit:

- The revised set of specifications for the starting materials, intermediates or API (as applicable).

You must generate the following data:

- Data for at least three production-scale batches demonstrating compliance with the proposed test and limits.

## ASNT: API/starting material/intermediate specifications - addition of new test and limit

Addition of a new test and associated limits to the approved specifications for the API, starting materials for API synthesis or intermediates created in the synthetic process.

### *Conditions*

- The change must not result from an altered method of manufacture that changes the material's quality characteristics (such as micronisation).
- The proposed method must be validated.
- Applied limits must be based on batch analytical data, and comply with any applicable official standard or adopted guidelines.
- The change must not involve a genotoxic impurity.

You must submit:

- Details of the new method.
- The revised set of specifications for the starting materials, intermediates or API (as applicable).

You must generate the following data:

- Comparative batch data for at least three commercial batches demonstrating compliance with the proposed test and limit.

## ASPC: API specifications - changes to physicochemical test methods and limits

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

### *Conditions*

- The test limit must either remain unchanged or be more stringent.
- The amended method must have been validated or deemed comparable.
- The test principle must remain unchanged.

You must submit:

- Details of the new method together with a summary description of the change.

You must generate the following data:

- Appropriate validation data or comparison data for the new method.

## ASPT: API specifications - amendments resulting from pharmacopoeial or TGO changes

Changes to the specifications for the API as a result of amendments to requirements in a default standard (i.e. a monograph in the British pharmacopoeia [BP], The United States Pharmacopeia and The National Formulary [USP-NF] or the European Pharmacopoeia [EP]) or relevant requirements in an applicable standard made by the Minister under section 10 of the Act.

### *Conditions*

- The API must already be tested to the existing pharmacopoeial or TGO requirements.
- The requirements applied from one pharmacopoeia must not be changed to another (e.g. changing from the BP to the USP requires the submission of data for evaluation).
- The new pharmacopoeial monograph or amended TGO must be applicable to the API.
- Any tests that were performed in addition to those of the pharmacopoeial monograph must continue to be applied, except where the test was removed going from the old monograph to the new one.

You must submit:

- The revised set of specifications for the API.

# Drug product manufacture changes - method, batch size or equipment

## DMBS: Drug product manufacture - changes to batch size for products that are not modified release dosage forms

Changes to the size of the manufacturing batch of drug products, where these are not modified release dosage forms or sterile products.

### *Conditions*

- The change must not be an increase in batch size for sterile products or products manufactured under sterile conditions.
- For sterile products, a decrease in manufacturing batch size must be either:
  - not accompanied by any change in sterile manufacturing process or
  - where there has been a change in sterile manufacturing process, the specific conditions in DMSE: Drug product manufacture - changes to manufacturing method and/or equipment of sterile dosage forms that are not modified release have been met.
- The product must not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.

- The new manufacturing batch size must be validated in accordance with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products and any relevant guidelines adopted by the TGA.

You must submit:

- Details of the new manufacturing batch size, with the revised batch manufacturing formula.

You must generate the following data:

- Additional validation data as required for the dosage form, as appropriate:
  - For semi-solid/liquid dosage forms, see DMEL: Drug product manufacture - changes to manufacturing method and/or equipment of semi-solid/liquid dosage forms that are not modified release.
  - For oral/nasal inhalation dosage forms, see DMEO: Drug product manufacture - changes to manufacturing method and/or equipment of oral/nasal inhalation dosage forms that are not modified release.
  - For solid dosage forms, see DMES: Drug product manufacture - changes to manufacturing method and/or equipment of solid dosage forms that are not modified release.
  - For sterile dosage forms, see DMSE: Drug product manufacture - changes to manufacturing method and/or equipment of sterile dosage forms that are not modified release.

## DMEL: Drug product manufacture - changes to manufacturing method and/or equipment of semi-solid/liquid dosage forms that are not modified release

Changes to methods or equipment used in the manufacture of semi-solid or liquid products, where these are not modified release dosage forms and are not sterile.

### *Conditions*

- The product must not be a modified-release dosage form (including enteric-coated tablets, enteric capsules and transdermal patches) or sterile.
- The new manufacturing method and equipment must be validated consistent with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products and any relevant guidelines adopted by the TGA on at least one production-scale batch of the product.

You must submit:

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

You must generate the following data:

- Comparative batch data that demonstrates all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- For semi-solid and liquid products (for example, ointments, creams, lotions, oral liquids, moulded suppositories and pessaries), comparative batch data using appropriate current methodology demonstrating 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 for the drug product, or if it is in solution as liquid globules.

## DMEO: Drug product manufacture - changes to manufacturing method and/or equipment of oral/nasal inhalation dosage forms that are not modified release

Changes to methods or equipment used in the manufacture of oral or nasal inhalation products, where these are not modified release dosage forms and are not sterile.

### *Conditions*

- The product must not be a modified-release dosage form (including enteric-coated tablets, enteric capsules and transdermal patches) or sterile.
- The new manufacturing method and equipment must be validated consistent with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products and any relevant guidelines adopted by the TGA on at least one production-scale batch of the product.

You must submit:

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

You must generate comparative batch data:

- That demonstrates all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- For the drug mass aerodynamic particle size distribution of the aerosol emitted by the drug product (for metered-dose pressurised inhalations, metered-dose nasal spray solutions, and dry powders for oral or nasal inhalation) that demonstrates that results are in the same range as previously obtained, as measured by either a multi-stage liquid impinger or a multi- stage cascade impactor (Andersen type).

## DMES: Drug product manufacture - changes to manufacturing method and/or equipment for solid dosage forms that are not modified release

Changes to the manufacturing method or equipment used in the manufacture of solid dosage forms that are not modified release and are not sterile.

### *Conditions*

- The product must not be a modified-release dosage form (including enteric-coated tablets, enteric capsules and transdermal patches) or sterile.
- The new manufacturing method and equipment must be validated consistent with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products and any relevant guidelines adopted by the TGA on at least one production-scale batch of the product.

You must submit:

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

You must generate the following data:

- Comparative batch data that demonstrates all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- All solid dosage forms (for example, tablets, capsules, compressed suppositories and pessaries) must 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 for the drug product, or if it is in solution as liquid globules.

## DMIT: Drug product manufacture - changes to in-process control tests and limits

Addition, revision or deletion of in-process control tests and associated limits applied during manufacture of the drug product.

### *Conditions*

***Parametric release***

The European Pharmacopoeia refers to parametric release in the monograph "methods of preparation of sterile products" as:

When a fully validated terminal sterilisation method by steam, dry heat or ionising radiation is used, parametric release, that is the release of a batch of sterilised items based on process data rather than on the basis of submitting a sample of the items to sterility testing, may be carried out, subject to the approval of the competent authority.

Parametric release can only be applied to products terminally sterilised in their final containers.

- The change must not relate to the parametric release of sterile products.
- The change must be consistent with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products.
- Any changes to in-process control test methods must be validated appropriately.
- The change must result in either improved quality or no change in the quality of the drug product.

You must submit:

- Details of the changes proposed, and the revised set of in-process control tests and limits. Test method details are not required.

You must generate the following data:

- Comparative batch data with the results within the same range as previously obtained.

## DMRO: Drug product manufacture - reduction or removal of API and excipient overages for ingredients that are not antioxidants or similar

Reduction or removal of previously approved manufacturing overages for APIs or excipients, where the excipients may be preservatives but are not antioxidants and where the final drug product is not a modified release dosage form.

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

### *Conditions*

- Any excipient involved must 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 must be appropriately validated.
- The TGA must be notified as a priority if the results of supporting stability data fail to meet the specifications. The TGA reserves the right to withdraw the product from the market if this requirement is not met.

You must submit:

- The revised manufacturing formula.

You must generate the following data:

- Comparative batch data to demonstrate that the results are comparable to those obtained previously (allowing for the reduction in overage).
- Stability data on at least one production batch of the post-variation product (with at least two more production batches to be similarly tested) should have been initiated.

## DMSE: Drug product manufacture - changes to manufacturing method and/or equipment of sterile dosage forms that are not modified release

Changes to methods or equipment used in the manufacture of sterile dosage forms, where these are not modified release dosage forms.

### *Conditions*

- The product must not be a modified-release dosage form.
- The new manufacturing method and equipment must be validated consistent with applicable principles of the Guide to Good Manufacturing Practice for Medicinal Products on at least one production-scale batch of the product.
- 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.

You must submit:

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

You must generate the following data:

- Comparative batch data that demonstrates all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- 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) must not affect the final sterility of the product.
- All of the dosage-specific data requirements described in the following change types must be certified as having been met, as appropriate:
  - For solid dosage forms, see DMES: Drug product manufacture - changes to manufacturing method and/or equipment of solid dosage forms that are not modified release.
  - For semi-solid/liquid dosage forms, see DMEL: Drug product manufacture - changes to manufacturing method and/or equipment of semi-solid/liquid dosage forms that are not modified release.
  - For oral/nasal inhalation dosage forms, see DMEO: Drug product manufacture - changes to manufacturing method and/or equipment of oral/nasal inhalation dosage forms that are not modified release.

# Site of manufacture changes

## DMDM: Drug product site of manufacture - cessation of a site or deletion of a manufacturing step

Cessation of, or deletion of a step in, the manufacture of the drug product at an approved site.

### *Conditions*

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

You must submit:

- 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.

## DMPL: Drug product site of manufacture - change to site of labelling/primary packaging (non-sterile products) or labelling/secondary packaging

Change to the location of a manufacturer, or addition of a new manufacturer, approved for labelling and primary packaging operations for non-sterile dosage forms or labelling and secondary packaging operations for all dosage forms.

### *Conditions*

- A change in, or addition of an alternative, site of **primary packaging** operations may relate to any product except products that are 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.
- The new site must have either:
  - a current manufacturing licence issued by the TGA (Australian manufacturers) for this type of manufacture or
  - a current GMP clearance issued by the TGA and valid at the time of this application (overseas manufacturers) for this type of manufacture.
- Apart from the change in site of manufacture, there must be no change to any aspect of the quality data other than changes to manufacturing equipment.
  - Where a change in manufacturing equipment is made, this must be validated in accordance with the principles of GMP.

You must submit:

- The name and address of the new manufacturer and licence/clearance number.
- Details of the manufacturing step(s) undertaken at the new site of manufacture.

## DMSL: Drug product site of manufacture - change to site of manufacture of non-sterile semi-solid/liquid dosage forms that are not modified release

Change to the location of an approved manufacturer, or addition of a new manufacturer, to make the final drug product, where the products are non-sterile, semi-solid or liquid dosage forms that are not modified release.

### *Conditions*

- Applies to sites of manufacture of the final drug product only, not sites performing in-process steps.
- The product must not be sterile or manufactured under sterile conditions.
- The product must not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.
- The new site must either have:

- a current manufacturing licence issued by the TGA (Australian manufacturers) for this type of manufacture or
- a current GMP clearance issued by the TGA and valid at the time of this application (overseas manufacturers) for this type of manufacture.
- There must be no changes to any aspect of the quality data other than changes to manufacturing equipment or method at the new site of manufacture and
- The changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment or
- The change does not adversely affect the reproducibility of the process and it is not the result of unexpected events arising during manufacture or because of stability concerns.
- Where a change in manufacturing equipment or method is made, this must have been validated at the new manufacturing site in accordance with the principles of GMP and/or any relevant guidelines adopted by the TGA.

You must submit:

- The name and address of the new manufacturer and licence/clearance number.
- 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.

You must generate the following data:

- Comparative batch data demonstrating all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- For semi-solid and liquid products (for example, ointments, creams, lotions, oral liquids, moulded suppositories and pessaries), comparative batch data using appropriate current methodology demonstrating 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.

## DMSO: Drug product site of manufacture - change to site of manufacture of non-sterile oral/nasal inhalation dosage forms that are not modified release

Change to the location of an approved manufacturer, or addition of a new manufacturer, to make the final drug product, where the products are non-sterile oral or nasal inhalation dosage forms that are not modified release.

### *Conditions*

- Applies to sites of manufacture of the final drug product only, not sites performing in-process steps. For changes to the site of manufacture not involving the final product see:
  - EMMP: Excipients (not of animal or human origin) - changes to the manufacturing process and/or site (same specifications) or
  - CSNS: Non sterile container - changes to the supplier or manufacturer if same material and specification.

- The product must not be sterile or manufactured under sterile conditions.
- The product must not be a modified-release dosage form.
- The new site must either have:
  - a current manufacturing licence issued by the TGA (Australian manufacturers) for this type of manufacture or
  - a current GMP clearance issued by the TGA and valid at the time of this application (overseas manufacturers) for this type of manufacture.
- There must be no changes to any aspect of the quality data other than changes to manufacturing equipment or method at the new site of manufacture.
  - Where a change in manufacturing equipment or method is made, this must have been validated at the new manufacturing site in accordance with the principles of GMP and/or any relevant guidelines adopted by the TGA.

You must submit:

- The name and address of the new manufacturer and licence/clearance number.
- 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 declaration that the changes to the manufacturing methods are only those necessitated by scaling-up or down, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns.

You must generate the following data:

- Comparative batch data demonstrating all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- 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 demonstrating that results are in the same range as previously obtained, as measured by either a multi-stage liquid impinger or a multi-stage cascade impactor (Andersen type).

## DMSS: Drug product site of manufacture - change to site of manufacture of non-sterile solid dosage forms that are not modified release

Change to the site of an approved manufacturer, or addition of a new manufacturer, to make the final drug product, where the products are non-sterile solid dosage forms that are not modified release.

### *Conditions*

- Applies to sites of manufacture of the final drug product only, not sites performing in-process steps.
- The product must not be sterile or manufactured under sterile conditions.

- The product must not be a modified-release dosage form. This includes enteric-coated tablets, enteric capsules and transdermal patches.
- The new site must either have:
  - a current manufacturing licence issued by the TGA (Australian manufacturers) for this type of manufacture or
  - a current GMP clearance issued by the TGA and valid at the time of this application (overseas manufacturers) for this type of manufacture.
- There must be no changes to any aspect of the quality data other than changes to manufacturing equipment or method at the new site of manufacture as outlined under Site of manufacture changes.
  - Where a change in manufacturing equipment or method is made, this must have been validated at the new manufacturing site in accordance with the principles of GMP and/or any relevant guidelines adopted by the TGA.

You must submit:

- The name and address of the new manufacturer and licence/clearance number.
- Details of the manufacturing step(s) undertaken at the new site of manufacture.
- A declaration that the changes to the manufacturing methods are only those necessitated by scaling-up or down, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns.

You must generate the following data:

- Comparative batch data demonstrating all results are comparable and within the same range as those obtained previously, as well as meeting currently approved drug product release specifications.
- All solid dosage forms (for example, tablets, capsules, compressed suppositories and pessaries) must 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.

## DMTR: Drug product site of manufacture - change to site performing testing and release for supply

Change to the location of a manufacturer, or addition of a new manufacturer, approved for quality control testing (including sterility, microbiological, chemical, physical and bacterial endotoxin or pyrogen testing) or release for supply of the final drug product.

### *Conditions*

- The change 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.
- The new site must either have:

  - a current manufacturing licence issued by the TGA (Australian manufacturers) for this type of manufacture or
  - a current GMP clearance issued by the TGA and valid at the time of this application (overseas manufacturers) for this type of manufacture.

- There may not be any changes to the existing test methods used for testing the product, whether or not the test methods have been provided to the TGA previously, except where allowed by DMSL: Drug product site of manufacture - change to site of manufacture of non- sterile semi-solid/liquid dosage forms that are not modified release.

You must submit:

- The name and address of the new manufacturer and licence/clearance number.
- Details of the manufacturing step(s) undertaken at the new site of manufacture.

You must generate the following data:

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

# Drug product specifications or test changes

**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 any of the notification requests below result in changes to the product specifications or the non-pharmacopoeial test methods, please provide an updated and complete CPD document in PDF format using the CPD form available on the TGA website.

## DSAM: Drug product specification - changes to non-biological assay method for an active or excipient that is not a radiopharmaceutical

Changes to a non-biological method used for assaying the API or excipients in a final drug product that is not a radiopharmaceutical.

### *Conditions*

- The product must not be a radiopharmaceutical.
- If the results obtained using the proposed method do not agree with the results obtained during TGA testing, using an official method, the results from the official method will be deemed to be correct.
- The proposed method must not be a biological method.
- The proposed method must not be a test method for impurities, related substances or degradation products.
- Validation data from the proposed method must demonstrate either:

  - an improvement in at least one of precision, accuracy or specificity, without a reduction in the other parameters or
  - an improvement in specificity or accuracy with reduced precision (whilst precision remains within the specified limits).

You must submit:

- Details of the proposed test method.

You must generate the following data:

- Appropriate validation data for the proposed method.

## DSID: Drug product specification - changes to identification tests for the active or excipient

Changes to the tests used to identify the API or excipients in the final drug product.

### *Conditions*

- The changes to identification tests must:
  - be 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
  - 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 and/or
  - include a new identification test in addition to an existing identification test.
- The method must be appropriately validated.
- Any additional identification test included cannot serve as an alternative identification test (this 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) must comply with the current EMA guideline on use of near- infrared spectroscopy that has been adopted by the TGA.

You must submit:

- Details of the changes to the existing test or the new identification test.
- The revised set of drug product specifications at release and expiry.

You must generate the following data:

- Appropriate validation data for the identification test.

## DSIP: Drug product specification - changes from an in-house test method to a pharmacopoeial test method

Changes to the specifications to ensure that the drug product complies with the requirements of a default standard (i.e. a monograph in the BP, USP-NF or EP), where previously no default standard applied.

### *Conditions*

- Any changes can be made to assay and/or related substances test methods, but not to a dissolution method which requires TGA evaluation of supporting data.
- The method must be appropriately validated.

You must submit:

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

You must generate the following data:

- Equivalency of the current and pharmacopoeial test method must be established by testing of three batches of the drug product using the current and proposed methods.

## DSNL: Drug product specification - narrowing of test limits

Revision of the approved specifications for testing of the final drug product, to make the limits applied to test results more stringent.

### *Conditions*

- The proposed limits must be consistent with applicable official standards or adopted guidelines.
- There must be no change in test methods other than those allowed under change types:
  - DSAM: Drug product specification - changes to non-biological assay method for an active or excipient that is not a radiopharmaceutical.
  - DSIP: Drug product specification - changes from an in-house test method to a pharmacopoeial test method.
  - DSPT: Drug product specification - changes resulting from pharmacopoeial or TGO requirements.
  - DSPL: Drug product specification - minor changes to physicochemical test methods and limits.

You must submit:

- A statement of the current and proposed limits.
- The revised set of drug product specifications at release and expiry.

## DSNT: Drug product specification - addition of test and limit

Addition of a new test and associated limits to the approved specifications for the final drug product.

### *Conditions*

- The proposed method must be validated.

- The proposed limit (release and expiry) of the new test must be based on batch data obtained at product release and on storage for the duration of the shelf life of the product. The limit must comply with any applicable official standard, TGO or adopted guidelines.

You must submit:

- A statement of the new test and limit.
- The revised set of product specifications at release and expiry.
- Details of the test method.

You must generate the following data:

- Appropriate validation data for the test method.

## DSPL: Drug product specification - minor changes to physicochemical test methods and limits

Minor changes to methods used to test physicochemical parameters of the final drug product.

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

### *Conditions*

- The test limit should either remain unchanged or be more stringent.
- The amended method should have been validated.

You must submit:

- Details of the new method together with a summary description of the change.

You must generate the following data:

- Appropriate validation data for the new method.

## DSPT: Drug product specification - changes resulting from pharmacopoeial or TGO requirements

Changes to the specifications for the final drug product as a result of amendments to requirements in a default standard (i.e. a monograph in the BP, USP-NF or EP) or relevant requirements in an applicable standard made by the Minister under section 10 of the Act.

### *Conditions*

- The products must currently be tested to the existing pharmacopoeial or Therapeutic Goods Order (TGO) requirements.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO must continue to be performed.
- The requirements applied from one pharmacopoeia must not be changed to another, except where the changes are allowed by other sections of this document (e.g. changing from USP to BP is not permitted as a notification).

- The new pharmacopoeial monograph or amended TGO must be applicable to the product and, if necessary, appropriate validation data must be generated.
- If the change involves updating microbiological test requirements for non-sterile products to meet the TGO for microbiological standards for medicines, the product must have undergone a risk assessment for objectionable microorganisms in addition to those specified in the pharmacopoeias that form the basis of the TGO.

You must submit:

- The revised set of drug product specifications (release and expiry), if applicable.
- If the change relates to an update to meet the requirements of the TGO for microbiological standards for medicines, a written assurance that the TGA can review the risk assessment report for objectionable microorganisms other than those specified in the order, if required.

You must generate:

- Appropriate validation data, as required.

## DSST: Drug product specification - changes to sterility test method

Changes to the sterility test methods used for the final drug product.

### *Conditions*

- All aspects of the test must comply with the requirements of the internationally harmonised test published in a default pharmacopoeia and as specified in TGO 77 - Microbiological Standards for Medicines.
- The change must comply with the guidelines on particular aspects of the sterility test that are outlined in Guidance 17 - Microbial quality of prescription and over-the-counter medicines.

You must submit:

- Details of the new method together with a summary description of the change.

# Changes to excipients

## EMRS: Excipient manufacture (from Category IC ruminant tissues) - changes in source (from animal to non-animal) and/or manufacturing process or site

Changes to the source, manufacturing process or site of manufacture of excipients derived from Category IC ruminant tissues (including from animal to plant or non-animal source).

Category IC ruminant tissues are defined in the TGA's Transmissible Spongiform Encephalopathies (TSE): TGA approach to minimising the risk of exposure.

### *Conditions*

- The product must only be intended for oral, topical, vaginal, rectal or inhalation routes, with no potential for cross-contamination with higher risk (Category A or B) tissues.

- The product must not be administered by the parenteral, ophthalmic or intra-tracheal routes.
- The change must be from a ruminant-derived source to a plant or other non-animal source.
- No changes to the specifications of the excipients are permitted, except for the changes allowed within the Changes to excipients section.

You must submit:

- Details of the excipients and the proposed changes.
- Where relevant, CEP issued by the EDQM to the manufacturer of the excipient.
- A declaration that the Category IC material has been self-assessed and complies with the TGA's requirements regarding Transmissible Spongiform Encephalopathies (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.

## ESAM: Excipient specification - change to assay method

Changes to a method used for assaying an excipient.

### *Conditions*

- The proposed method must either:
  - improve at least one of precision, accuracy or specificity without a reduction in the other parameters or
  - the proposed method must improve accuracy or specificity with reduced precision if precision remains within the specified limits.

You must submit:

- Details of the new assay method.

You must generate the following data:

- Appropriate validation data for the proposed method.

## ESIP: Excipient specification - change from an in-house to a pharmacopoeial test method

Changes to the specifications to ensure that the excipient complies with the requirements of a default standard (i.e. a monograph in the BP, USP-NF or EP), where previously no default standard applied.

### *Conditions*

- Change or addition must only be to test methods for physicochemical parameters (e.g. pH, colour, particle size, particulate matter, density, specific gravity, optical rotation, osmolality, osmolarity and viscosity).
- The change must not result from an altered method of manufacture that changes the material's quality characteristics (such as micronisation).

- Applied limits must be based on batch analytical data, and comply with any applicable official standard (TGO or default standard) or adopted guidelines.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO for critical parameters (e.g. particle size, pH, viscosity) must continue to be performed.

You must submit:

- The revised set of specifications for the excipient.
- A summary description of the change and details of the new method.

You must generate the following data:

- Validation data for the method(s), as required.
- Equivalency of the current and pharmacopoeial test method(s) must be established by testing of three batches using the current and proposed methods.

## ESNL: Excipient specification - narrowing of limits

Revision of the approved specifications for testing of excipients, to make the limits applied to test results more stringent.

### *Conditions*

- The proposed limits must be consistent with any applicable official standard (TGO or default standard) or adopted guidelines.

You must submit:

- A statement of the current and proposed limits.
- The revised set of specifications for the excipient.

## ESNT: Excipient specification - new test and limit

Addition of a new test and associated limits to the approved specifications for an excipient.

### *Conditions*

- The change must not result from an altered method of manufacture that changes the material's quality characteristics (such as micronisation).
- Applied limits must be based on batch analytical data, and comply with any applicable official standard (TGO or default standard) or adopted guidelines.

You must submit:

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

You must generate the following data:

- Appropriate validation data for the proposed method.

## ESPT: Excipient specification - changes resulting from pharmacopoeial or TGO requirements

Changes to the specifications for an excipient as a result of amendments to requirements in a default standard (i.e. monograph in BP, USP-NF or EP), or relevant requirements in an applicable standard made by the Minister under section 10 of the Act.

### *Conditions*

- The excipient must be tested to the existing pharmacopoeial or TGO requirements.
- Any tests that are performed in addition to those of the pharmacopoeial monograph or TGO must continue to be performed.
- The new pharmacopoeial monograph or TGO must be applicable to the excipient.

You must submit:

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

# Changes to container/closure system

## CCCA: Container/closure - change to components

Changes to outer packaging, or components of the container, that are not in direct contact with the drug product.

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

### *Conditions*

- The change is restricted to one or more of the following:
  - 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); and/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/top/cap); and/or
  - the inclusion or removal of inert wadding from bottles and other containers containing solid dosage forms; and/or
  - the inclusion of a desiccant in containers of solid dosage forms; and/or
  - the inclusion of, or change to, an outer 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 must not be in direct contact with the product.

- The label of any outer carton or other primary pack that is added or changed must either be identical to the container label or be changed as permitted under:
  - Changes to product labels that are notifications and/or
  - Changes that do not require TGA prior approval (see the TGA minor variations guidance document for chemical entities).
- Where an existing carton or primary pack is removed, the container label must either remain unchanged or be changed as permitted under:
  - Changes to product labels that are notifications and/or
  - Changes that do not require TGA prior approval (see the TGA minor variations guidance document for chemical entities), and must continue to meet all requirements of the TGO that relates to labels.
- No change can be made to the product's shelf life or storage conditions as a notification. For self-assessable (SAR) changes to the shelf life or storage conditions see:
  - DSLE: Shelf life - Extension according to an approved stability-testing protocol and
  - DSLD: Shelf life - Decrease and/or more restrictive storage conditions.
- The TGA must be notified as a priority if the results of supporting stability data fail to meet the specifications. The product in the new container system may be withdrawn from the market at the TGA's discretion.

You must submit:

- 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.

You must generate the following data:

- Where applicable, comparative data to demonstrate the removal of inert wadding has not adversely affected the product's friability and other physical attributes during normal transport.
- If an overwrap is introduced or changed, a stability study of the product with the overwrap to verify the product shelf life must have been initiated on at least one production-scale batch of the product, and should begin on the second and third batches as they are manufactured.

## CCSS: Container/closure - change to size and shape for non-sterile dosage forms

Changes to the size and shape of the container, or closure system, used for drug products that are non-sterile dosage forms.

## *Conditions*

- The change must not result in a change to the container type.
- If the container is a blister pack or strip pack, the change in size or shape must not result in an increase in the headspace volume of the blister-pack or strip-pack pocket.
- If the container is a reclosable package, there must not be an increase in the headspace of the container.
- The material and thickness of the container/closure system must be either unchanged or changed in a manner permitted under change types:
  - CMIT: Container/closure material - increase in thickness for non-sterile solid, semi-solid, semi-liquid or liquid dosage forms and/or
  - CMDT: Container/closure material - decrease in thickness for blister packs, strip packs and sachets for non-sterile solid or semi-solid dosage forms.
- No change can be made to the product's shelf life or storage conditions as a notification. For self-assessable (SAR) changes to the shelf life or storage conditions see:
  - DSLE: Shelf life - Extension according to an approved stability-testing protocol and
  - DSLD: Shelf life - Decrease and/or more restrictive storage conditions.
- No change can be made to the quantity of products in the new container/closure system.
- The TGA must be notified as a priority if the results of supporting stability data fail to meet the specifications. The product in the new container system may be withdrawn from the market at the TGA's discretion.

You must submit:

- 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 must 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.

You must generate the following data:

- If the container is a reclosable package and is child-resistant (or is implied by its presentation to be a child-resistant package), data must 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.
- For solid oral dosage forms, comparative moisture permeability (water-vapour transmission) data must 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 must show either equivalent or better moisture protection.
- A stability study using the new container/closure system to verify the product shelf life must have been initiated on at least one production-scale batch of the product (with at least two more production batches to be similarly tested).

## CCST: Container/closure - changes to specification and test methods

Changes to the specifications for the container or closure system of the final drug product, to include new tests, make specified limits more stringent, delete a test procedure or make minor changes to test methods.

### *Conditions*

- There must be no change to container dimensions or components, other than those specified in:
  - CCSS: Container/closure - change to size and shape for non-sterile dosage forms and/or
  - CCCA: Container/closure - change to components.
- The limits applied must be based on batch analytical data, and comply with any applicable official standard or relevant guidelines adopted by the TGA.
- The packaging components must remain compliant with pharmacopoeial requirements and food standards.
- The change does not result from unexpected events arising during manufacture.

You must submit:

- Updated specifications and test methods.

You must generate the following data:

- Validation data for the proposed method demonstrating that the updated test procedure is at least equivalent to the former test procedure.

## CMDT: Container/closure material - decrease in thickness for blister packs, strip packs and sachets for non-sterile solid or semi-solid dosage forms

Decrease in the thickness of aluminium foil, or laminate material used in laminated aluminium foil, for blister packs, strip packs and sachets containing non-sterile solid or semi-solid drug products.

### *Conditions*

- The product must be a non-sterile dosage form.
- The material that is decreased in thickness must 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 must be
- at least 20 µm.
- The container/closure material must be unchanged.
- No change should be made to the product's shelf life or storage conditions. See self-assessable (SAR) changes to the shelf life or storage conditions.

- The TGA must be notified as a priority if the results of supporting stability data fail to meet the specifications. The product in the new container system may be withdrawn from the market at the TGA's discretion.

You must submit:

- Details of the change in thickness of the container material, with specifications, if relevant.

You must generate the following data:

- Initial stability study data using the new container/closure system to verify the product shelf life must have been initiated on at least one production-scale batch of the product (with at least two more production batches to be similarly tested).

## CMIT: Container/closure material - increase in thickness for non-sterile solid, semi-solid, semi-liquid or liquid dosage forms

Increase in the thickness of the material used for the container or closure system of non-sterile solid, semi-solid, semi-liquid or liquid drug products.

### *Conditions*

- The container/closure material must be unchanged.
- No change can be made to the product's shelf life or storage conditions as a notification. For self-assessable (SAR) changes to the shelf life or storage conditions see:
  - DSLE: Shelf life - Extension according to an approved stability-testing protocol and
  - DSLD: Shelf life - Decrease and/or more restrictive storage conditions.
- The TGA must be notified as a priority if the results of supporting stability data fail to meet the specifications. The product in the new container system may be withdrawn from the market at the TGA's discretion.

You must submit:

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

You must generate the following data:

- A stability study, using the new container/closure system to verify the product shelf life, must have been initiated on at least one production-scale batch of the product (with at least two more production batches to be similarly tested).

# Product label changes

**Requirements for labels**

Mandatory labelling requirements for prescription medicines are set out in the Therapeutic Goods Order (TGO) that pertains to labels, 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.

## LOCI: Label - Consequential change resulting from a change approved under subsection 9D(3) or conditions imposed under subsection 28(3)

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.
- Evidence of the approval of the previous change (such as a TGA submission number).

## LPCL: Label – addition or deletion of, or change to, the company logo or livery

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPCP: Label - addition or deletion of, or change to, the pictogram of a product or its dosage form

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The addition or change of a pictogram of a product or its dosage form must only be designed to clarify information about the medicine which is useful for the patient, to the exclusion of any element of a promotional nature.
- The change must not involve removal of information relating to the safe use of the product.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPCS: Label – addition or deletion of, or change to, the name or address of the Australian sponsor or supplier of the product

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The new name or address must be the same as amended on the register.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPDG: Label – deletion of existing graphics, pictures or diagrams, and any associated text

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The change must not involve removal of information relating to the safe use of the product.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPDR: Label - deletion of repeated text (present elsewhere on a label) from selected side panels provided that the information is not mandatory

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPIA: Label - addition of simple instructional/informational/anti-tampering statements, or information about a changed appearance of the dosage form

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPOP: Label - addition or deletion of, or change to, label text of outer protective pouches or overwraps of the container or primary pack

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The new text must not be confusing, promotional or contradictory to text on the container or primary pack labels.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPPS: Label - adding information either on label or as insert advising of patient support program (PSP)

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- All references to PSPs must have the following disclaimer prominently stated - "Patient Support Program complies with the Medicines Australia code of conduct, however it is not authorised or approved by the Therapeutic Goods Administration".

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPQR: Label - inclusion of QR code

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The link must be to information (e.g. may include CMI or PI documents) that is maintained by an Australian owned and managed company and must not include any element of a promotional nature.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPRP: Label - removal of phrases such as ‘New formulation’, ‘New appearance’ after a period of time.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- There must be a sufficient period of time that has elapsed to advise the market of the new product.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LQAE: Label - addition of excipients

Inclusion of the names of excipients on the medicine label, regardless of whether the substances must be declared on a label to comply with the relevant Ministerial standard.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LQAT: Label - amendment of expression of API content in topical preparations as previously approved

Amendment to the expression of the proportion of active ingredient in a topical preparation.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design

work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LQHI: Label - addition of 'hypotonic', 'hypertonic' and 'isotonic' for large- volume injections

Addition of the terms hypotonic, hypertonic and isotonic on the labels of large-volume injections.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LQRT: Label - addition of a previously approved release rate for transdermal patches

Addition of an approved release rate on the label of medicines that are transdermal patches.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.
- 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).

## LWAH: Label - addition of a warning or cautionary statement where an incorrect route for method of administration is hazardous

Addition of a warning or cautionary statement to a medicine label, to indicate that an incorrect route or method of administration may be hazardous (e.g. ‘Not for injection’, ‘For external use only’ and ‘Not for oral use’).

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LWSR: Label - changes to/addition of a warning or precaution statement resulting from an approved safety-related variation to the PI

Change to, or addition of, a warning or cautionary statement on the medicine label, resulting from or relating to a safety-related variation to the entry in the Register for the product made by the Secretary under subsection 9D(2) of the Act, and an associated variation to the Product Information for the product made by the Secretary under subsection 25AA(4) of the Act.

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.
- 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).

# Notifications for prescription medicines (biological medicines)

This guidance outlines the kinds of variations to biological medicines that are considered as requests made under the provisions of section 9D(2C) of the *Therapeutic Goods Act 1989* (known as 'notifications'). The conditions outlined below the description of each variation type must be met for the request to be processed as a notification.

- Drug substance or excipient changes
- Drug product specification or test changes
- Site of manufacture changes
- In-house reference standard changes
- Purification process changes
- Changes to storage of drug substance
- Changes to storage of drug product
- Fermentation changes
- Plasma fractionation intermediates changes
- Drug product packaging changes
- Product label changes

# Drug substance or excipient changes

**Certified product details (CPD) documents**

For many biological medicines, critical tests are conducted on the drug substance and not repeated on the drug product because of low concentrations of the drug substance or interference by excipients.

If any of the notification requests below result in changes to the drug substance or drug product specifications or the non-pharmacopoeial test methods, please provide a new copy of the entire document, including testing methodology, even if these details have not changed. The CPD document can be provided using the CPD form available on the TGA website.

## ISAM: Drug substance or excipients specifications - change of test method

Change to test method of the drug substance, where it is replaced with a pharmacopoeial method.

### *Conditions*

- The method being changed must not be a viral safety testing method.
- The in-house test method being changed must be replaced with a pharmacopoeial method. If there are differences in specifications between the two methods, the more stringent specifications should apply.
- The stringency of the specifications should not decrease as a result of the change.
- Batch analytical data for at least three commercial batches should have been generated to demonstrate compliance with the new test and limit.

You must submit:

- Details of the new method.
- An updated CPD document, if applicable.

## ISNL: Drug substance or excipients specifications – narrowing of limits

More stringent limits for test results of the drug substance, starting materials, intermediates or excipients in the drug product.

### *Conditions*

- The proposed limits must be consistent with the relevant TGA standards and guidelines.
- Do not change the composition of the substance tested. For example, you cannot narrow the test limits for isoelectric point, as this could alter the substance by resulting in the omission of a charged isoform of a protein.
- The change must not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation application).

- The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
- The change must be within the range of currently approved limits.
- The test procedure remains the same, or changes in the test procedure are minor.

You must submit:

- The revised set of specifications for the substance.
- An updated CPD document, if applicable.

## ISPT: Drug substance or excipients specifications – amendments resulting from pharmacopoeial or TGO changes

Changes resulting from amendments to pharmacopoeial requirements or the requirements of Therapeutic Goods Orders.

If a substance complies with the requirements of an earlier edition of an official pharmacopoeia, such as the British pharmacopoeia [BP], it would be appropriate to substitute the requirements of the current edition of that pharmacopoeia. However, any tests that were performed in addition to those of the pharmacopoeial monograph should continue to be applied.

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.

### *Conditions*

- The change should not involve changing from the requirements of one pharmacopoeia to those of another.
- Any tests that were performed in addition to those of the pharmacopoeial monograph or TGO must continue to be performed.
- The new pharmacopoeial monograph or amended TGO must be applicable to the substance.

You must submit:

- The revised set of specifications for the drug substance.
- An updated CPD document, if applicable.

# Drug product specification or test changes

## PMPL: Drug product specification – minor changes to physicochemical test methods and limits

Minor changes to physicochemical tests.

### *Conditions*

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

You must submit:

- A summary description of the change and details of the new method.
- An updated CPD document.

You must generate the following data:

- Appropriate validation data demonstrating the new test is at least equivalent to former procedure.

## PSNL: Drug product specification - narrowing of test limits

Revision of the approved specifications for testing of the final drug product, to make the limits applied to test results more stringent.

### *Conditions*

- The new limits must be either the same as, or more stringent than, any applicable standard or guidelines.

You must submit:

- The revised set of specifications.

## PSNT: Drug product specification - addition of test and limit

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

### *Conditions*

- The additional test must have been previously evaluated by the TGA.
- The proposed limit (release and expiry) must be based on batch analytical data and comply with, or is more stringent than, any applicable official standard or relevant accepted guidelines for such a test.
- The test method must only be used at a registered quality control testing site that has appropriate GMP clearance.

You must submit:

- Details of the new test method.
- The revised set of drug product specifications at release and expiry.
- An updated CPD document.

You must generate the following data:

- Appropriate validation data for the proposed method.

## PSPT: Drug product specification - changes resulting from amendments to a TGO or pharmacopoeial requirement

Changes resulting from amendments to pharmacopoeial requirements or the requirements of Therapeutic Goods Orders.

### *Conditions*

- The new pharmacopoeial monograph or TGO are suitable for the product.
- The change must not involve changing from the requirements of one pharmacopoeia to those of another.
- Any tests that were performed in addition to those of the pharmacopoeial monograph or TGO must continue to be performed.
- The test method must only be used at a registered quality control testing site that has appropriate GMP clearance.
- If the change involves updating microbiological test requirements for non-sterile products to meet TGO No. 77—Microbiological standards for medicines (TGO 77), the product must have undergone a risk assessment for objectionable microorganisms, in addition to those specified in the pharmacopoeias that form the basis of TGO 77.
- The change must not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a variation application) unless the supporting documentation has been already assessed and approved within another procedure.
- The change must not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
- The change must be within the range of currently approved limits.
- The test procedure must remain the same, or the changes in the test procedure are minor.

You must submit:

- The revised set of drug product specifications at release and expiry.
- An updated CPD document.
- For updating microbiological test requirements for non-sterile products to meet TGO No. 77, an assurance that the report of the risk assessment for objectionable microorganisms is available for review, if required by the TGA.

You must generate the following data:

- Appropriate validation data must have been generated where applicable.

## PSQC: Drug product specification - change to quality control testing equipment

Changes to equipment used for quality control testing of the final drug product (including sterility, microbiological, chemical, physical and bacterial endotoxin or pyrogen testing).

### *Conditions*

- The change must meet any previously approved test method validity criteria.

You must submit:

- A description of the new equipment.
- An updated CPD document.

You must generate the following data:

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

# Site of manufacture changes

## OAMS: Albumin – change of manufacturer's name or contact details

Change in details of albumin manufacturer or supplier.

### *Conditions*

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

You must submit:

- Details of the new manufacturer or supplier.
- Evidence of GMP clearance, showing the changed name.
- An assurance that the albumin still complies with relevant TGO and other standards such as Ph Eur or BP.

## PMRS: Drug product site of manufacture - addition of new site of release- for-supply operations for a registered drug product

Addition of a new manufacturer for release for supply of the final drug product.

### *Conditions*

- The new site must either have:
  - for Australian manufacturers, a current manufacturing licence issued by the TGA for this type of manufacture or
  - for overseas manufacturers, current GMP clearance issued by the TGA and valid at the time of this application for this type of manufacture.

You must submit:

- Details of the new manufacturing site.
- The Australian licence and/or GMP clearance number.

# In-house reference standard changes

## IRSR: In-house reference standard – replacement

Replacement of an in-house reference standard.

### *Conditions*

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

You must submit:

- Details of the new reference standard, including assigned values.
- The reference to the TGA approval of the protocol (that is, TGA submission number).
- The proposed date of implementation, allowing time for TGA approval.
- An updated CPD document.

# Purification process changes

## PPCR: Purification process—column life reduction

Reduction in the approved column life for columns used in the purification process.

### *Conditions*

You must submit:

- A scientific justification for the column life reduction.

## PPHR: Purification process—holding time reduction for a non-plasma- derived product

Reduction in the holding time for the drug substance, or intermediates created during manufacture of the drug substance, where the final drug product is non-plasma derived.

### *Conditions*

You must submit:

- A scientific justification for the holding time reduction.

# Changes to storage of drug substance

## ASRS: Drug substance storage conditions – reduction in shelf life

Reduction in shelf life.

### *Conditions*

- The change must not be due to unexpected events arising during manufacture or because of stability concerns.

You must submit:

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

## Changes to storage of drug product

**Stability testing**

For biological medicine products requiring refrigeration or freezing, stability testing should be in real time at the specified storage temperature, for at least the requested shelf life.

The time out of refrigeration (which also includes time out of the freezer) during normal manufacturing processes, up to the point of return to the fridge or freezer following labelling and packaging, should have been defined and justified. This should be based on worst-case storage scenarios and include storage conditions inherent in the manufacturing process and transport.

From that point onward, all storage and shipping conditions should be justified by the real-time stability data:

- the data for justifying any temperature excursions should include real-time studies of the proposed excursion followed by return to the normal storage conditions for the remainder of the shelf life.

Refer to guidance on Stability testing for prescription medicines for requirements for stability testing of biological medicines.

## PSLD: Drug product storage conditions – reduction in shelf life

Reduction in shelf life.

### *Conditions*

- The change must not be due to unexpected events arising during manufacture or because of stability concerns.

You must submit:

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

## PSET: Drug product storage conditions - changes to excursion temperature during manufacture

Changes to excursion temperature during manufacture.

### *Conditions*

- The change is one of the following:
  - a removal of an excursion temperature
  - a reduction in the time spent out of refrigeration, including time out of the freezer.
- The change must not be due to unexpected events arising during manufacture or because of stability concerns.
- All other changes to the excursion temperature require the TGA to evaluate the data. See PSLC: Shelf life - changes to shelf life or storage conditions of a drug product.

You must submit:

- Details of the change.

## PSAR: Drug product storage conditions – Addition of a restrictive shelf life or storage condition

Addition of a restrictive shelf life or storage condition.

### *Conditions*

- The change should be to a more restrictive shelf life or storage conditions.
- The change must not be due to unexpected events arising during manufacture or because of stability concerns.

You must submit:

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

# Fermentation process changes

## FPFM: Fermentation—change of filter manufacturer

Change to the manufacturer of a filter used in the fermentation process.

### *Conditions*

- Do not change the internal process controls.
- Do not use the filter for steps that require viral safety validation.
- The new filter meets the same acceptance criteria as the previous filter.
- The new internal process controls for the filtrate have not been changed.

You must submit:

- The reason for the change.
- The new manufacturer's details.

## FPNC: Fermentation—more stringent internal process controls

Introduction of more stringent internal controls on the fermentation process.

### *Conditions*

- Do not change the quality characteristics of the product.

You must submit:

- The reason for the change.
- Details of the new internal process controls.

## FPRP: Fermentation—reduction in fermentation period

Reduction in the fermentation period, i.e. the time required to culture and harvest the cell line.

### *Conditions*

- Reducing the fermentation period must not change the batch size.
- Do not change the internal process controls.

You must submit:

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

# Plasma fractionation intermediates changes

## PFCR: Plasma - changes to fractionation intermediates - column life reduction

Reduction in the approved column life for columns used in plasma fractionation.

### *Conditions*

You must submit:

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

## PFSC: Plasma - changes to fractionation intermediates - more stringent internal process control

Introduction of more stringent internal controls on the plasma fractionation process.

### *Conditions*

- Do not change the quality characteristics of the product.

You must submit:

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

# Drug product packaging changes

## PPAT: Packaging – introduction of anti-tamper packaging (materials not in contact with drug product)

Introduction of anti-tamper packaging for the drug product.

### *Conditions*

- The packaging materials must not be in direct contact with the dosage form.
- The change must not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

You must submit:

- Details of the change.

# Product label changes

**Requirements for labels**

Mandatory labelling requirements for prescription medicines are set out in the Therapeutic Goods Order (TGO) that pertains to labels, 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.

## LPCL: Label – addition or deletion of, or change to, the company logo or livery

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPCP: Label - addition or deletion of, or change to, the pictogram of a product or its dosage form

### *Conditions*

- There must be no other changes to the label made under this change request.

- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The addition or change of a pictogram of a product or its dosage form must only be designed to clarify information about the medicine which is useful for the patient, to the exclusion of any element of a promotional nature.
- The change must not involve removal of information relating to the safe use of the product.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPCS: Label – addition or deletion of, or change to, the name or address of the Australian sponsor or supplier of the product

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The new name or address must be the same as amended on the register.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPDG: Label – deletion of existing graphics, pictures or diagrams, and any associated text

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The change must not involve removal of information relating to the safe use of the product.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available,

one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPDR: Label - deletion of repeated text (present elsewhere on a label) from selected side panels provided that the information is not mandatory

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPIA: Label - addition of simple instructional/informational/anti-tampering statements, or information about a changed appearance of the dosage form

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

## LPOP: Label - addition or deletion of, or change to, label text of outer protective pouches or overwraps of the container or primary pack

### *Conditions*

- There must be no other changes to the label made under this change request.
- The changes must ensure continued compliance with the relevant TGO pertaining to labels and not contravene labelling best practice.
- The new text must not be confusing, promotional or contradictory to text on the container or primary pack labels.

You must submit:

- Copies of the existing labels (with tracked changes) and final copies or mock-ups of the amended labels (for each strength, where applicable) which include any logos, design work or graphics. The copies must be to scale and verify the size/dimensions of the labels and indicate the colours to be used. Where there are multiple pack sizes available, one representative label can be provided for each strength, as long as the only difference between the labels is the pack size.

# Notifications for included biologicals

This guidance outlines the kinds of variations to included biologicals that are considered as requests made under the provisions of section 9D(3AC) of the *Therapeutic Goods Act 1989* (known as 'notifications'). The conditions outlined below the description of each variation type must be met for the request to be processed as a notification.

Categories:

- Changes as a result of amendments to an applicable standard
- Biological starting material changes
- Manufacturing process changes
- Manufacturing site changes
- Finished product control changes
- Labelling changes

## Changes as a result of amendments to an applicable standard

### PT: Changes as a result of amendments to an applicable standard (e.g. pharmacopoeial or TGO)

For example, when changes to applicable standards or test methods are published (such as applicable Therapeutic Goods Orders, international standards or pharmacopeial tests), and are introduced into the manufacturing process.

#### *Conditions*

- Is not a change from the requirements of one pharmacopeia to another e.g. USP to BP.
- Any tests that were performed in addition to those of the standard must continue to be applied.
- Appropriate validation has occurred, where necessary.
- TGA has GMP-certified the manufacturing site for that step, where necessary.

You must submit:

- Details of the change.

# Biological starting material changes

## DS: Changes to the donor selection criteria, including the medical and social history questionnaire

Increasing the stringency of donor selection criteria, resulting in rejection of previously acceptable donors, will not require pre-approval by the TGA. Changes to the donor questionnaire that do not affect the information gathered (slight edits to questions, changes to question order etc.) can be introduced without pre-approval of the TGA.

### *Conditions*

- More stringent donor selection criteria (previously acceptable donors would now be rejected).
- In conformity to TGO 108 (or TGO 105 for faecal microbiota transfer (FMT) products);

You must submit:

- Details of the change.

## TK: Changes to infectious disease test kits

When the infectious disease testing facility introduces new test kits for TGO 108-mandated (or TGO 105-mandated) infectious disease tests for donors.

### *Conditions*

- No decrease in specificity, sensitivity, limit of detection and accuracy.
- Performed as per kit instructions, including the intended use.
- Same level of regulatory approval of the kit.
- TGA GMP certification of the testing facility.

You must submit:

- Details of the change.

## SM: Critical material change

This change will apply to critical materials used during the biological material collection manufacturing processes, but does not apply to materials that are biological starting materials, excipients or the primary container.

### *Conditions*

- The critical parameters are equivalent or of greater quality [See note below].
- The containers are not made of a different composition (e.g. different polymer).
- The material is not an excipient.
- The material is not of human or animal origin.

You must submit:

- Details of the change.

**Note**

Changes to some critical materials may have a more significant impact on the product than others and may require evaluation of the supporting data.

For example, a change to the quality of a growth supplement (critical material) can have a significant effect on the culture conditions and would often require re-validation of the manufacturing process; a change to a primary container (critical material) may require re-validation of product stability.

See ARGB Appendix 14: Glossary for more information on critical materials.

# Manufacturing process changes

## MI: Changes to in-process specifications

Increasing the stringency of in-process or release specifications, resulting in rejection of previously acceptable product, will not require pre-approval by the TGA.

### *Conditions*

- More stringent specifications.
- The change did not result from unexpected events identified during manufacture.
- The test procedure remains the same.
- Conforms to any applicable standard.

You must submit:

- Details of the change.

## BR: Removal of a product listed in the entry for a Class 2 biological

The deletion of one of the products that is part of an entry for a Class 2 biological.

### *Conditions*

You must submit:

- Details of the change.

# Manufacturing site changes

## MA: Addition of a new site performing secondary packaging or secondary storage

The addition of new manufacturing sites restricted to product or biological starting material storage, or secondary (non-sterile) packaging steps.

### *Conditions*

- TGA has GMP-certified the manufacturing site for that step.

You must submit:

- Details of the change.

## MT: Changes to site performing testing (including quality control and infectious disease testing)

For example, the addition of a new facility for testing: infectious diseases of donors; or microbial bioburden.

### *Conditions*

- TGA has GMP-certified the manufacturing site for that step.
- There should be no impact on existing method validation.
- The test method has been adequately qualified to generate results comparable to that of the currently approved site(s).
- No modifications to the infectious disease testing algorithms used to determine fate of the product, if applicable.
- An equivalent service agreement is in place with the test facility (TGO 108 9(6) or TGO 105 14(3)).

You must submit:

- Details of the change.

## MR: Removal of a site of manufacturer

The deletion of a manufacturing site that is no longer used will require no specific conditions for pre-approval.

### *Conditions*

You must submit:

- Details of the change.

# Finished product control changes

## BS: Changes to release specifications

Increasing the stringency of release specifications, resulting in rejection of previously acceptable product, will not require pre-approval by the TGA.

### *Conditions*

- More stringent specifications.
- The change did not result from unexpected events identified during manufacture.
- The test procedure remains the same.
- Conforms to any applicable standard.

You must submit:

- Details of the change.

## BT: Reduction in shelf-life of finished product or shipping timeframes

The reduction in proposed product shelf life or acceptable shipping time frames will not require pre-approval by the TGA when the changes do not alter the currently used conditions (shipping configuration, product storage temperatures).

### *Conditions*

- Revised specifications are still within the scope of the TGA approved validation studies.
- No quality or safety concerns triggered the change.

You must submit:

- Details of the change.

# Labelling changes

## LC: Changes to the product labels or supporting documents (e.g. product information, consumer medicine information and patient card)

A limited scope of changes to product labelling is permissible without pre-approval.

### *Conditions*

- The change must be one of the following:
  - Changing the name, address or other details of the sponsor, manufacturer or distributor; or
  - Change to name of active ingredients as a result of changes to the Australian approved name.

You must submit:

- Details of the change.

# Export only biologicals changes

## EX: Changes to the information in the ARTG entry of export only biologicals.

Only applies to export only biologicals included in the ARTG under section 32DCA of the *Therapeutic Goods Act 1989.*

### *Conditions*

- The product is an export only biological included in the ARTG under section 32DCA of the *Therapeutic Goods Act 1989.*

- The change must not result in a separate and distinct export only biological (where the characteristics of the biological differ in respect of any of the following):
  - Active ingredient;
  - Dosage form;
  - Principal manufacturer
- If the change is to add a new manufacturer, the manufacturing site has appropriate TGA GMP certification.

You must submit:

- Details of the change.

# Version history

| Version | Description of change | Author | Effective date |
|---|---|---|---|
| V1.0 | Original publication | TGA | June 2017 |
| V2.0 | Inclusion of second set of notifiable variations to registered medicines.<br>Inclusion of notifiable changes to biologicals.<br>Minor amendments to phrasing to clarify conditions. | TGA | December 2017 |
| V3.0 | Minor amendments to phrasing and typographical errors.<br>Additional guidance on situations where notifications conditions are not met. | TGA | 1 May 2018 |
| V4.0 | Inclusion of export only biologicals | TGA | May 2023 |

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Reference/Publication #