



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for prescription medicines

Appendix 13: Self-assessable changes for biological products

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TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

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

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Appendix 13: Self-assessable changes for biological products

1. Scope

This appendix sets out the circumstances in which sponsors may make certain changes under specified conditions to biological products under a self-assessment procedure. For a general overview of the notification and self-assessment procedure, refer to the Introduction section of Appendix 12 (*Changes to the quality information of registered medicines: Notification, Self-Assessment and prior Approval*). All changes must be notified to the Therapeutic Goods Administration (TGA) unless specified otherwise. Self-Assessable Notifications should be in accordance with the requirements under Appendix 12 Part B, Section 1.6.

These self-assessment provisions apply to:

- products containing materials of biological origin (such as hormones, allergens, blood products, modified animal tissues or vaccines);
- the products of genetic engineering or other newer biotechnological techniques.

The following changes may be made subject to the general conditions in Appendix 12 Part B, Section 1.3 and the specific conditions listed below for each change.

2. Active pharmaceutical ingredient (API) specifications

2.1 Narrowing of the limits for test results within the existing specifications provided this does not lead to a change in the composition of the API. For example, narrowing the range for isoelectric point may result in deletion of an isoform for a protein.

Specific conditions

- 2.1.1 The proposed limits are consistent with any applicable official standard and/or relevant guidelines where applicable.
- 2.1.2 The revised set of specifications for the API must be provided.

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

[Note: A new specification resulting from a change to the method of manufacture that alters the product's pharmaceutical characteristics, for example:

- the introduction of a new limit for particle size following micronisation of the API; or
- a test for leachables following a change in the chromatography resin; or
- a new specification resulting from a safety related concern;

would require prior approval to ensure the test is validated appropriately and is relevant.]

Specific conditions

- 2.2.1 Appropriate validation data have been generated for the test method.
- 2.2.2 Details of the test method are provided.
- 2.2.3 The limits proposed are based on batch analytical data and in compliance with any applicable official standard and/or relevant guidelines where appropriate.
- 2.2.4 The revised set of specifications for the API must be provided.

2.3 Changes which are consequent upon amendments to pharmacopoeial requirements or to requirements of Therapeutic Goods Orders (TGO)¹.

For example, if an API is specified as complying with the requirements of the British Pharmacopoeia 2003 (BP2003), it would be appropriate to substitute the requirements of a later Addendum to the BP2003 when this is published. However any tests which were performed in addition to those of the BP2003 must continue to be applied.

[Note: Changes that require the implementation of a new or amended biological assay **require prior approval** by TGA.]

Specific conditions

- 2.3.1 The suitability of the new pharmacopoeial monograph or amended TGO to the affected API has been examined.
- 2.3.2 The revised set of specifications for the API must be provided.

3. Excipient specifications

3.1 Narrowing of the limits for test results within the existing specifications.

Specific conditions

- 3.1.1 The proposed limits are consistent with any applicable official standard and/or relevant guidelines where applicable.
- 3.1.2 The revised set of specifications for the excipient must be provided.

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

[Note: A new specification that is consequent upon an altered method of manufacture that alters the product's pharmaceutical characteristics, such as micronisation of an excipient, requires prior approval.]

Specific conditions

- 3.2.1 Appropriate validation data have been generated for the test method.
- 3.2.2 Details of the test method are provided.
- 3.2.3 The limits proposed are based on batch analytical data and in compliance with any applicable official standard and/or relevant guidelines where appropriate.

¹ <http://www.tga.gov.au/industry/legislation.htm>

3.2.4 The revised set of specifications for the API must be provided.

3.3 Changes which are consequent upon amendments to pharmacopoeial requirements or to requirements of TGOs.

For example, if an excipient were specified as complying with the requirements of the BP2001, it would be appropriate to substitute the requirements of a later Addendum to the BP when this is published. However any tests which were performed in addition to those of the BP2001 must continue to be performed

Specific conditions

- 3.3.1 The suitability of the new pharmacopoeial monograph or amended TGO to the affected API has been examined.
- 3.3.2 The revised set of specifications for the API must be provided.

3.4 Changes to methods of analysis of non-biological excipients for biological products.

Specific conditions

- 3.4.1 The change must demonstrably improve at least one of precision, accuracy and specificity without a reduction in the others, except that improved specificity and/or accuracy may be associated with reduced precision provided that precision remains adequate in relation to the limits specified.
- 3.4.2 Appropriate validation data have been generated for the proposed method.
- 3.4.3 Details of the new test method must be provided.

4. Finished product specifications

4.1 Narrowing of the limits for test results within the existing specifications.

Specific conditions

- 4.1.1 The proposed limits are either the same as or more stringent than any applicable official standard and/or relevant accepted guidelines where applicable.
- 4.1.2 The revised set of specifications must be provided.
- 4.1.3 An updated Certified Product Details (CPD) document incorporating the new limit must be provided.

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

Specific conditions

- 4.2.1 Appropriate validation data have been generated for the new test method.
- 4.2.2 Details of the test method must be provided together with an updated CPD document incorporating the new test and limit.
- 4.2.3 The proposed limit (release and expiry) is based on batch analytical data and must be in compliance with or more stringent than applicable official standard and/or relevant accepted guidelines for such a test.
- 4.2.4 The revised set of finished product specifications (release and expiry) must be provided.

4.3 Changes which are consequent upon amendments to pharmacopoeial requirements or to requirements of TGOs.

For example, if a finished product is specified as complying with the requirements of the BP2001, it would be appropriate to substitute the requirements of a later Addendum to the BP when this is published. However any tests which were performed in addition to those of the BP2001 must continue to be performed.

[Note: Changes that require the implementation of a new or amended biological assay **require prior approval** by TGA.]

Specific conditions

- 4.3.1 The suitability of the new pharmacopoeial monograph or amended TGO in relation to the product has been examined, and, if necessary, appropriate validation data have been generated.
- 4.3.2 The revised set of finished product specifications (release and expiry) must be provided, and
- 4.3.3 An updated CPD document is also provided.

5. Sites of Product Manufacture

5.1 Changing or adding a new site of secondary packaging operations for an already registered product

[Note: All **other** changes in site of manufacture of biological registered products **require prior TGA approval**. Primary and secondary packaging require different levels of GMP certification. Section 6 of Appendix 12 Part B gives relevant definitions.]

Specific conditions

- 5.1.1 Either the new site has a current manufacturing licence for this type of manufacture issued by the TGA, or if an overseas manufacturer is proposed, the product sponsor has a current GMP clearance letter issued by the TGA's Manufacturer Assessment Section (MAS) for the new manufacturing site and for that type of manufacture, and
- 5.1.2 the TGA is notified of the name and street address of the new manufacturer and a copy of the evidence of manufacturing standard (refer 5.1 above) is provided.

5.2 Deletion of site of manufacture specific conditions

- 5.2.1 The TGA is notified of the name and site address of the manufacturer and the steps of manufacture to be deleted.
- 5.2.2 Evidence in the form of a GMP Clearance Certificate for secondary packing site is provided to show that there is at least one validly registered site of manufacture performing the same step(s) of manufacture as the deleted site.

6. Replacement of in-house reference standard

Specific conditions

- 6.1 The TGA must have explicitly approved the protocol for establishing a replacement standard. The protocol should have been submitted with the application for registration or subsequent category 3 application to change the in-house reference standard.

7. Establishment of new Working Cell Bank

Specific conditions

- 7.1 The new Working Cell Bank (WCB) is derived from the previously approved Master Cell Bank
- 7.2 The TGA must have explicitly approved the protocol for this purpose. The protocol should have been submitted with the application for registration or subsequent category 3 application to change the WCB.
- 7.3 No effects on genetic stability, product yield, adventitious agent safety or quality and purity are evident in the validation study.

8. Quality Aspects of Product Information

Refer to Appendix 12 Part B, Section 16 (*Quality Aspects of PI*).

9. Product Labels

Refer to Appendix 12 Part B, Section 17 (*Changes to Product Labels*).

10. Pack Size

The number of units – vials, syringes, ampoules, cartridges - enclosed in the outer pack may be reduced without prior approval. [Note that a change in the volume of fill of injections requires prior approval.]

Specific conditions

- 10.1 The change in pack size is not accompanied by changes to dosage regimen and/or indications.
- 10.2 The label for the new pack size is the same as for the current pack size except for quantity of goods or other changes allowed under other sections of this document.
- 10.3 The additional or changed pack size is consistent with the treatment recommendations in the product information.

Historical document

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 02 6232 8444 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #