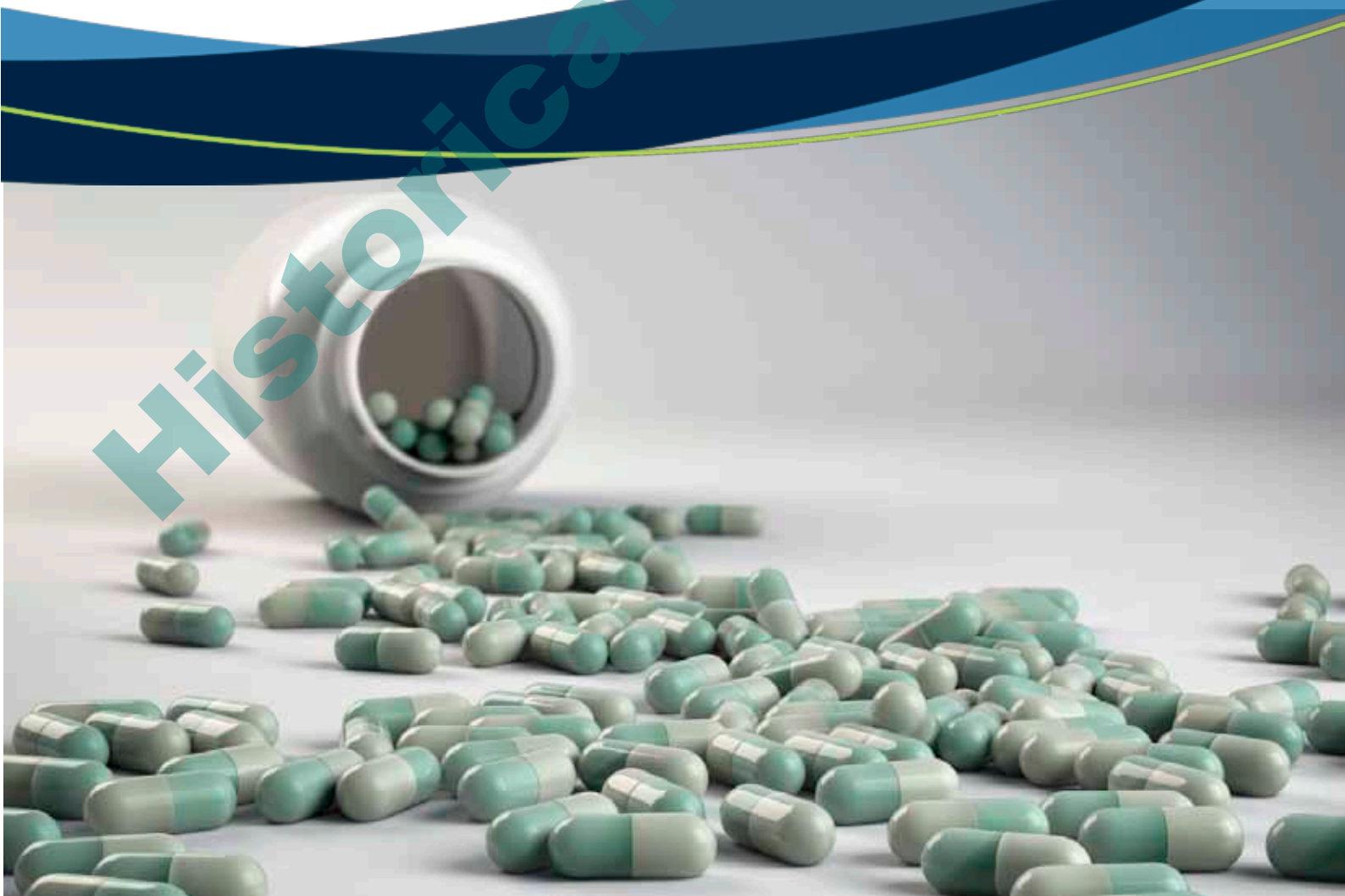
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for prescription medicines

Appendix 12: Changes to the quality information of registered medicines: notification, self-assessment and prior approval

June 2004

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.

Contents

Introduction

This guidance document applies only to the quality information aspects of registered medicines. It is divided into Parts A, B and C, dealing with, respectively:

- changes that only require notification to the Therapeutic Goods Administration (TGA) on implementation or no notification at all;
- changes that are self-assessable by the sponsor and do not require approval before implementation;
- changes that require approval before implementation.

After a medicine has been granted registration in the Australian Register of Therapeutic Goods (ARTG), the standard conditions of registration state *inter alia*

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

This means that it is a condition of registration that, with limited exceptions, no changes may be made to information of registered medicines without the prior approval of the Secretary. The exceptions are safety-related changes and certain minor editorial changes to Product Information (PI) (see Sections 4.4.5.1 and 4.4.5.3 of the *Australian Regulatory Guidelines for Prescription Medicines*, ARGPM) and changes described in Parts A (non-assessable changes) and B (self-assessable changes) of this Appendix. Part C of the document gives guidance on the type of supporting data required to be submitted in any application to support changes that require prior approval. Generally, such an application would be a Category 3 application (see Sections 2.5.3, 3.5.3 and 4.4.2 of the ARGPM).

Where a specific change is not listed in Parts A or B, prior approval is generally required via a Category 3 application. Sponsors should note that implementation of a change which requires prior approval from the Secretary before such approval is given is in breach of the provisions of section 28 of the *Act* and penalties may apply. It is therefore important that sponsors follow the correct procedure when making changes to registered medicines so as to avoid breaching the provisions of *the Act*. If a sponsor is unclear as to which procedure to follow in a particular case, clarification should be sought from the Drug Safety and Evaluation Branch (DSEB).

Self-assessable changes (see Part B for details) are subject to certain general conditions and specific conditions, all of which must be met before the change can be implemented. Where the required specific conditions cannot be met or the validation data generated for self-assessment show a difference between pre- and post-variation batches, the change must not be implemented. Prior approval via a Category 3 application should be obtained if the sponsor still wishes to make the change.

For any change, whether requiring prior approval or not, the general principles of validation according to the code of Good Manufacturing Practice (GMP) apply.

Where a particular change comes within more than one category, such as a change of synthetic route for an active pharmaceutical ingredient (API) and a simultaneous change of site of synthesis, the more stringent requirements apply.

The sponsor should disclose fully all intended change(s) in an application letter or a notification. Any undisclosed additional change(s) that are embedded in the data submitted or in other accompanying documents, including any flow-on changes, such as to PI and/or product labels, are not approved. For this reason and to avoid any misunderstanding, all Category 3 applications (including self-assessable changes) should be accompanied by the following declaration:

No aspects of the quality information have been changed, including manufacturing procedures and equipment and raw material and finished product specifications, other than the changes nominated in this application.

In some instances, notification may lead to a request for further information and the TGA reserves the right, where appropriate and necessary, to request that a notifiable or a self-assessable change not be proceeded with.

Applications and notifications must be accompanied by any relevant fee applicable at the time of submission.

Part A: Non-assessable changes

The following general type of changes and requirements apply to all registered medicines, including biologicals except where specifically excluded (see Appendix 13: *Self-Assessable Changes for Biological Products*).

1. Changes not requiring notification to, or prior approval from, the TGA

1.1 Local handling agent of API and excipient, including material of biological origin (same site/method of manufacture, specifications and, where applicable, biological source including geographical origin).

1.2 Supplier/manufacturer of non-sterile container and/or container components (same material type and specifications). [Note: For other aspects of changes to container, see also Parts B and C of this Appendix].

1.3 Manufacturing process and site of manufacture of excipients (same specifications but excluding excipients of animal or human origin). [Note: For other aspects of changes to excipients, see also Parts B and C of this Appendix].

1.4 The following changes to product labels **with strictly no other changes** and where minimum letter height requirements of Therapeutic Goods Order (TGO) pertaining to labels are observed:

- Change of typeface and increase in font size of print only;
- Inclusion/removal of date of manufacture of product;
- Inclusion/removal of foreign national registration number;
- Inclusion/removal of or changes to name and address of supplier in New Zealand;
- Inclusion/removal of or changes to sponsor or supplier telephone/facsimile number, barcodes, ABN/ACN, product code number, recycle logo and associated text, trademark and other such symbols (eg. â , ã and ä);
- Change to Aust R number following an approved change requiring a new Aust R number, eg new formulation.

[Note: For other aspects of changes to product labels, see also Parts B and C of this Appendix].

2. Changes requiring notification to the TGA

The following changes must be notified to the TGA. Notification, together with any relevant documentary evidence required in support, must be made in writing and the date of implementation advised. No specific form is required but any applicable fee should accompany the notification. The Self-Assessable Change notification proforma (see Part B) should **not** be used for this purpose.

2.1 Change to sponsor name and/or address where the sponsor is not also a product manufacturer. Notification, together with a list of the affected products, must be sent to:

The Information Technology Section (ARTG Unit)
Business Management Branch
Therapeutic Goods Administration
PO Box 100,
Woden ACT 2606

with a copy to the Director of the DSEB. In accordance with provisions of regulation 10A of the *Therapeutic Goods Regulations 1990*, a change in sponsor name must be notified to the Secretary within 3 months of its occurrence. The notification allows the client database of the ARTG to be updated and new Certificates of Registration to be issued.

2.2 Change to manufacturer's name only (including those who are also product sponsors) but not the actual manufacturing site address. Notification, together with valid GMP evidence of the company with the new name, must be sent to:

The Head
Manufacturer Assessment Section
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

for the issue of a new GMP clearance letter. A copy of the notification together with the new GMP clearance letter should be to the Director of the DSEB. Such a change should also be notified to the Information Technology Section (ARTG Unit) of the TGA as soon as possible upon occurrence so that relevant client databases and the ARTG entries of affected products can be updated. Note that the above procedure must be followed by every sponsor whose products are manufactured by the affected manufacturer.

2.3 Change to drugs and poisons scheduling. Notification, together with relevant evidence, such as National Drugs and Poisons Schedule Committee (NDPSC) meeting minutes/resolutions, must be sent to:

The Director
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Attention: Application Entry Team (ARTG Unit)

Where a Schedule 2 or 3 drug has been re-scheduled to Schedule 4 or 8, relevant changes to product labels and PI may be necessary and this should be done either as a Category 3 application or through self-assessment as appropriate (see relevant sections in Parts B and C of this Appendix). Note that any changes to the SUSDP signal heading and cautionary statements are State and Territory matters and should be dealt through the State and Territory authorities. If a drug has been down-scheduled from Schedule 4 or 8 to Schedule 2 or 3, then any necessary changes to the product should be handled

according to the Australian Regulatory Guidelines for OTC Medicines (ARGOM) where appropriate. For those products which, despite their new lower scheduling status, continue to be the responsibility of the DSEB, any necessary changes to product labels and PI are handled as stated in the first sentence of this paragraph.

Part B: Self-assessable changes

1. Introduction

As stated in the Introduction to this Appendix, changes to information of registered medicines generally require prior approval from the TGA. The legal provisions for applications to make changes to already registered products reside in sections 9D (3) and 28(3) of the *Act*. For changes to information on the quality aspects of registered medicines, a Category 3 application is normally required. However, certain types of changes are considered by the TGA to be minor in nature and if appropriately validated, are unlikely to have a deleterious effect on the quality, efficacy and safety of a product. Indeed, some proposed changes may even result in assurance of a better quality product than the existing one. For such changes, self-assessment by the sponsor of any data generated to support the change is allowed.

This Part of the Appendix is thus intended to provide in detail the range of changes that may be made to quality information of registered products without approval from the TGA before implementation. For each type of change, certain specified conditions must be met and any data generated to validate the change is self-assessed by the sponsor without reference to the TGA, hence the term *self-assessment* procedure.

Notwithstanding that this Part deals primarily with self-assessable changes, it also provides guidance in some cases on data requirements for changes which require prior approval, for example, Section 5 *Variations in Content of Excipients*.

1.1 Scope

The self-assessment provisions in this document apply to all registered medicines, including antibiotics and other products whose APIs are prepared wholly or in part by fermentation, but **do not apply** to:

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

other than as provided for in Appendix 13 (*Self-Assessable Changes for Biological Products*).

1.2 Self-Assessment Procedure

To take advantage of this self-assessment option, the general conditions listed below and all of the specific conditions listed for each type of change must be complied with.

All self-assessable changes **must be notified to the TGA** following procedures detailed in point 1.6 below.

The TGA reserves the right, however, to:

- request copies of the experimental (validation) data at its discretion;
- follow up the validation during an audit of the manufacturing site.

The validation data specified in this document are minimal and any additional necessary validation, as for example which would follow from the code of GMP, must also be conducted. Where validation data are required to be generated to support a change, such data may be generated using either pilot plant scale or full production batches of the product (see Note N.3), except for changes involving batch size variations when the data should be generated from full production scale batches.

Where validation tests show a difference between pre-and post-variation batches, unless otherwise allowed in this document or agreed to by the TGA in a particular case, the change must not be implemented. Prior approval is required through an appropriate application to make the change, at which time, depending on the nature of the change and the significance of the differences in results, additional data such as studies on bioavailability or clinical safety and/or efficacy may be needed.

For changes not covered by this document and/or where all of the specified conditions are not complied with, approval must be obtained before implementation.

Sponsors are advised that use of the self-assessment procedure to make changes allowed in this guideline is not mandatory. Any proposed changes to registered medicines may be submitted as a formal Category 3 application. However, if the decision is to seek prior approval for the change, then the normal data requirements (see Part C of this document) and evaluation fee, as well as the applicable statutory timeframe, will apply.

1.3 General Conditions

The following general conditions always apply to changes made by self-assessment and sponsor must ensure that they are complied with:

- the product is validly registered in the ARTG;
- no change that requires prior approval is made concurrently;
- a date of implementation is advised (this should be a date in the future)
- all of the validation data specified for each proposed change have been generated;
- experimental (validation) data will be supplied to the TGA, if requested, within one month of the request;
- validation data generated in Australia will be provided upon request during a GMP inspection.

1.4 Amended Validation Requirements

If a sponsor believes that the validation requirements in this document are excessive for a particular product, there are two options:

- Submit a Category 3 application to make the variation in question and include the validation data the sponsor believes are necessary, together with appropriate argument. In this case, any subsequent change of the same nature to the product can no longer be done through self-assessment and would require prior approval;
- Submit a written proposal through a Category 3 application that, in the general case, variations defined in this document as self-assessable may be made **to this particular product** on the basis of amended validation procedures, stating the validation amendments that are proposed. An example might be the generation of single point dissolution data rather than profiles for a particular product. Factors that the TGA would consider in making a decision on such an application or proposal would include:
- the likelihood that the amended validation procedures would detect a real change in the product;
- the likely clinical consequences of a failure to detect a real change.

1.5 Separate and distinct goods

Note that section 16(1) of *the Act* deems that a change to the formulation of a product renders the product a separate and distinct good that must be separately included in the ARTG. It follows that those changes to formulation which are self-assessable according to these guidelines (see sections 14 and 15 below) must be notified to the TGA in advance of the change so that the new good can be registered and, if necessary, a new Aust R number assigned. However, depending on the nature of the formulation change,

the *Therapeutic Goods (Groups) Order No. 1 of 2001*[1] allows retention of the old Aust R number for the new product.

1.6 Self-Assessable Notifications

Notifications should be accompanied by all of the following:

- a statement that no changes have been made to the product other than:
- those specified in this notification, or
- those which do not require either prior approval or notification as provided for in Part A of this Appendix;
- a statement that all of the general conditions in section 1.3 and all of the applicable specific conditions have been complied with;
- the date of implementation of the change (preferably an estimated future date);
- relevant evidence of GMP (clearance letter if an overseas site of manufacture is involved or Australian manufacturing licence) where this is a condition of self-assessment.

Notification to the TGA should be made by completing all sections in the Proforma for *Notification of Self-Assessable Changes to the Quality Information* (SAN proforma). This proforma is available on the TGA website. The completed hard copy of the proforma should be signed by the person taking responsibility for ensuring that all of the general and specific conditions relevant to the proposed change have been complied with and any specified validation data have been generated and self-assessed by the company as being acceptable. The proforma, together with any covering letter and relevant fee, should be sent to:

The Director
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Attention: Application Entry Team

Note that any validation/experimental data that are required to be generated for self-assessment purposes should not be submitted with the notification. However, such data may be requested by the TGA for review at a later date [see point 1.3 above].

Where a self-assessable change according to this guideline has already been implemented, notification to the TGA must be made prior to its occurrence [see *point 1.3* above]. Late notification of a self-assessable change is not acceptable. If this occurs, a Category 3 application with payment of any applicable evaluation fee will be required to regularise the change, at which time the full validation data will be required for evaluation. **Self-assessment is not a means of regularising unauthorised changes made to registered medicines.**

All acceptable self-assessable changes notified to the TGA will be acknowledged as approved variations to the product under the provisions of sections 9D(3) and 28(3) of *the Act*. Where a notified change in accordance with this Part of the Appendix is deemed not to be a self-assessable change, the sponsor will be advised of the reason(s) and of the need to submit a formal application for approval to make the change. Breaching of the conditions of registration of a product can result in penalties being imposed and/or cancellation of the registration of the product by the Secretary under section 30(2) of *the Act*.

[1] http://www.tga.gov.au/industry/legislation-groups.htm

2. Changes to the API

2.1 Changes to method for determining the content of the active substance (assay) and/or residual solvents (including water)

[Note: Any changes to biological methods of assay (such as those used for antibiotics) and any changes to the test method for determining impurities, related substances and degradation products require prior approval.]

Specific conditions

2.1.1 Appropriate validation data have been generated for the proposed method.

2.1.2 The changes, must demonstrably improve at least one of precision, accuracy and specificity without 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, and

2.1.3 details of the new method are provided.

2.2 Narrowing of the limits for test results within the existing specifications

Specific conditions

2.2.1 The proposed limits are consistent with any applicable official standard and/or relevant guidelines where applicable.

2.2.2 Narrowing of the limits must not be such as to result in a different grade of material being produced, for example, from unmicronised to micronised material (see also 2.3).

2.2.3 The revised set of specifications for the API are provided.

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

[Note: If the new test and limit is added because of an altered method of manufacture which changes the material's quality characteristics, such as micronisation, then the change would require prior approval.]

Specific conditions

2.3.1 Appropriate validation data have been generated for the test method.

2.3.2 Details of the test method must be provided.

2.3.3 The limits applied are based on batch analytical data and in compliance with any official standard and/or relevant guidelines where applicable.

2.3.4 The revised set of specifications for the API is provided.

2.4 Changes which are consequent upon amendments to pharmacopoeial requirements or requirements of a TGO

For example, if an API is specified as complying with the requirements of a particular edition of the British Pharmacopoeia (BP), it would be appropriate to substitute the requirements of a later edition of the BP when this is adopted by the TGA. However, any tests that were performed in addition to those of the pharmacopoeial monograph must continue to be applied. Note that changing from the requirements of one pharmacopoeia to those of another, such as from the United States Pharmacopeia (USP) to the BP, is not covered by this section and therefore may not be self-assessable.

Specific conditions

2.4.1 The suitability of the new pharmacopoeial monograph or amended TGO to the affected API has been examined.

2.4.2 The revised set of specifications for the API are provided.

2.5 Changes to identification tests

Changes to identification tests as follows:

- from a less specific to a more specific identification test, for example, from a UV/Visible spectrophotometric and/or chromatographic method (TLC, GC or HPLC) to normal infra-red (IR) spectroscopic method;
- include an additional identification test to an existing identification test;
- vary the existing identification test method, eg an HPLC test, which demonstrably improves or at least maintain the specificity of the method;
- replace existing identification test(s) with a near infra-red (NIR) spectroscopic identification method (applicable only if specific condition 2.5.4 is met).

Specific conditions

2.5.1 Applicable to organic APIs only.

2.5.2 the method must have been validated for specificity and details of the method provided, and

2.5.3 Any additional identification test included must not serve as an alternative identification test.

2.5.4 If NIR is used, the site of testing must have a previously TGA-approved standard operating procedure (SOP) for introducing NIR as an identification test for APIs (see Note N.6).

2.5.5 The revised set of specifications must be provided.

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

[Note: The above change does not apply to APIs prepared wholly or partially by fermentation.]

Specific conditions

2.6.1 There is no change to the method of synthesis including any solvents used in the purification of the final product (the API) or to any other aspect of manufacture and specifications, whether or not these have been previously provided to the TGA. Given this condition, it follows that changes to the site of manufacture of APIs may not be made without TGA approval unless either the finished product sponsor or the new API manufacturer knows the route of synthesis at both sites.

2.6.2 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 finished 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.

2.6.3 The TGA is notified of the name and address of the new manufacturer and a copy is supplied of the Australian licence and/or GMP clearance letter (see 2.6.2 above).

2.6.4 Comparative batch analytical data of the API have been generated (see Note N.4) and all results, but in particular, impurity profiles, particle size distribution and polymorphic forms, are either within the same range as previously (no new impurities must be present) or remain unchanged.

2.7 Deleting an existing site of manufacture

Specific conditions

2.7.1 The name and site address of the manufacturer and the steps of manufacture to be deleted are notified, and

2.7.2 Evidence (eg. current ARTG print out, TGA approval letter or other documentary evidence) is provided that there is at least one validly registered site of manufacture of the API remaining to perform the relevant step(s) of manufacture.

2.8 Change in or addition of an alternative site of manufacture of intermediates or starting materials in API manufactured by multi-step synthesis, including intermediates prepared wholly or partially by fermentation

Specific conditions

2.8.1 The intermediates/starting materials must be isolated chemical species and must be at least three steps back in the synthetic scheme (purification procedures count as one step only).

2.8.2 no change in the overall synthetic route of the API, including that of the intermediates/starting materials; and

2.8.3 either no change or improvements in the specifications of the intermediates/starting materials; and

2.8.4 Comparative batch analytical data have been generated using validated test method(s) (in particular impurities levels) on the intermediate and on the API before and after the change, and results showed no significant difference in purity profile.

2.8.5 The name and site address of the new manufacturer(s) of the intermediates are notified for file record purposes only, but GMP evidence is not required. The sponsor or purchaser of the intermediates/starting materials is responsible for supplier qualification, and

2.8.6 for intermediates/starting materials prepared wholly or partially by fermentation:

- there is either no change in the strain of the producer organism used or where there is a change, details of the new producer organism are provided and the component profiles of the final fermentation broth at harvest made from the new and old strain have been shown to be the same;
- there must be no changes to the scale of operation of the fermentor tank and fermentation processes;
- there must be no changes to the nature of the media ingredients, particularly precursors, activators or components of biological and/or animal origin, although changes to the quantities used are acceptable provided they are not a result of a change in scale of operation.

2.9 Decrease in manufacturing batch size

Specific conditions

2.9.1 There is no change in route of synthesis including solvents used in the final purification of the API other than any necessary adjustment to processing conditions and/or use of different equipment.

2.9.2 Comparative batch analytical data (see Note N.4) have been generated and the results showed no significant difference in the tested parameters, in particular, particle size distribution (for an insoluble API) and impurity profiles.

3. Replacement of One Type of Starch by Another

Where starch is an excipient in a formulation, the type of starch specified (for example, wheat starch) may be replaced by the **same quantity** of another type (for example, maize starch) through self-assessment. A new Aust R number is not required for such a change. Prior approval is required if a different quantity of the new starch is used.

Specific conditions

3.1 The TGA is notified of the change, including the specifications of the new starch.

3.2 The changeover has been validated, which includes demonstration that the comparative dissolution profiles are similar, that is, the similarity factor, f_2, value is between 50 and 100 (see Notes N.1 and N.4), and

3.3 At least 6 month stability data on a minimum of two pilot scale batches have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 months data under accelerated conditions at 40°C/75 % relative humidity and the results are comparable to those of the existing product.

3.4 Stability testing continues for the full term of the product's shelf-life and on the first three production scale batches of the product, and any batches not meeting specifications are voluntarily withdrawn from the market immediately and the TGA notified.

3.5 Neither the existing nor the new material is a modified starch.

4. Changes to Manufacturing Method, Manufacturing Batch Size and Manufacturing Equipment for Finished Products

These changes may be made to any medicines (including sterile products) covered by this Part of the Appendix through self-assessment except for those product types specifically excluded under each change, and any modified release dosage forms (including enteric-coated tablets and capsules, and trans-dermal patches).

4.1 Change in manufacturing method and/or equipment.

Conditions 4.1.4 to 4.1.6 do not apply where the drug is in solution at any stage during

manufacture of the finished product, or if it is in solution in the finished product or is present as liquid globules.

Specific conditions

4.1.1 In relation to sterile products, the new method of manufacture (including sterilisation of containers and/or container components) and/or manufacturing equipment do not impact on the final sterility of the product; and

4.1.2 Comparative batch analytical data showed that all results are comparable and within the same range to those obtained previously and meet currently approved finished product release specifications (see Note N.4).

4.1.3 Validation of the new manufacturing method and equipment has been carried out in accordance with relevant parts of the code of GMP.

4.1.4 For all solid dosage forms, including for example tablets, capsules, compressed suppositories and pessaries, it is demonstrated that the comparative dissolution profiles are similar, ie the similarity factor, f_2, value is between 50 and 100 (see Notes N.1 and N.4); or

4.1.5 For semi-solid and liquid products (for example, ointments, creams, lotions, oral liquids, moulded suppositories and pessaries etc), it is demonstrated using appropriate methodology that there has been no change to the particle size distribution and polymorphic form of the API in suspension in the product (see Note N.4); or

4.1.6 For metered dose pressurised inhalations and dry powders for inhalation for oral or nasal application and metered dose nasal spray solutions, the comparative drug-mass aerodynamic particle size distribution of the aerosol emitted by the finished product, as measured by either a multi-stage liquid impinger or a multi-stage cascade impactor (Andersen type), is shown to be in the same range as previously (see Note N.4).

4.1.7 For sterile dosage forms, all of the above specific conditions apply as appropriate. Other changes, as they relate to assurance of sterility, are permitted provided:

- the technology to be used already exists at the manufacturing site and is in use for other 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.

  For example, a manufacturer using both conventional aseptic filtration /filling and Form Fill Seal (FFS) may, from the sterility view point, change the filling of a particular product from one to the other through the self-assessment procedure. However, the introduction of FFS to a particular site which had previously only utilised filtration/filling of sterile products would require prior approval.

4.1.7 The TGA is provided with the revised method of manufacture together with any relevant flow-diagram of the new process.

4.2 Reduction in, or removal of, previously approved manufacturing overages of active substance and excipients

(includes preservatives but excludes anti-oxidants and other ingredients which function at least in part by being “consumed” over time).

[Note: Since manufacturing overages are not recorded on the ARTG, such a change is not regarded as a change in product formuation.]

Specific conditions

4.2.1 Appropriate validation of the manufacture of the new product has been carried out.

4.2.2 Comparative batch analytical data have been generated to demonstrate that, having allowed for the reduction in overage, the results are comparable to those obtained previously (see Note N.4).

4.2.3 Stability testing on at least one production batch of the post-variation product has begun and at least two more production batches will be similarly tested and any failure to meet finished product specifications during the stability trials is immediately notified to the TGA which reserves the right to withdraw the product from the market at its discretion.

4.2.4 The revised manufacturing formula is provided.

4.3 Change in manufacturing batch size

A decrease or increase in manufacturing batch size is self-assessable except for the following:

- an increase in batch size for sterile products or products manufactured under sterile conditions;
- an increase in batch size for micro-dose products containing less than 2 mg per unit dose or less than 2% of the total unit dose mass of the active substance.

Specific conditions

4.3.1 The new manufacturing batch size has been validated in accordance with the principles of GMP, appropriate to the specific dosage form involved.

4.3.2 Depending on the dosage form of the product, relevant validation data as detailed in 4.1.2 and 4.1.4 - 4.1.6 above have been generated.

4.3.3 For sterile products, a decrease in manufacturing batch size is either not accompanied by any change in sterile manufacturing process or, where there has been a change, the specific conditions 4.1.1 or 4.1.7 above are also simultaneously met.

4.4 Change (addition, deletion or revision) to in-process control tests and limits during product manufacture

Changes relating to parametric release of sterile products require prior approval.

Specific conditions

4.4.1 The change is consistent with any applicable principles of the code of GMP.

4.4.2 The change results in either an enhancement or maintenance of the quality of the finished product with no change in finished product specifications.

4.4.3 Comparative batch analytical data have been generated and the results are within the same range as previously (see Note N.4).

5. Variation in Content of Excipients

The following guidance is provided to sponsors/manufacturers to allow the occasional minor departure from the registered nominal formulation to occur during manufacture of a specific batch of a product. **It is stressed that the inclusion of this section in this Part of the Appendix does not mean that a permanent change in formulation, other than those provided for under sections 14 and 15 (see later), is self-assessable, nor does it mean that any proposed inclusion of a range in excipient content for a registered product is a self-assessable change. Such changes require prior approval.**

5.1 Principles

5.1.1 In accordance with the principles of GMP and with the goal of minimising batch to batch variation in stability and bioavailability, all batches should ideally be manufactured to a nominal formula with nil variations. To this end:

- thorough process validation studies should be conducted at the development stage;
- appropriately tight specifications should be set for raw materials as far as possible, including where relevant physical properties such as particle size and bulk density.

Validation studies are discussed in detail in 5.3 below. The quantities of some excipients may need to be varied with every batch and there is no nominal quantity, such as liquids for pH adjustment.

5.1.2 However, even when a manufacturer has gone to some lengths to validate processes and, where necessary, tighten excipient specifications, there may occasionally be a batch for which minor variations in certain excipients are necessary for production purposes (for example, the volume of granulating fluid) or to achieve specified properties of the formulation (for example, a colouring agent in a tablet coating).

5.1.3 If a manufacturer considers that there is good reason to vary the content of a nominated excipient, a range may be proposed at the time of the registration application. Appropriate validation data should be provided. These ranges, or a modification of them as agreed during evaluation, then become a part of the substantive formulation and companies are free to vary

the quantities of excipients within these bounds. Separate approval is required only if a batch or batches are manufactured outside the agreed formula and ranges.

5.1.4 For products which have not been subject to registration evaluation by the TGA in respect of quality data or where no ranges were approved at the time of registration, sponsors may vary formulations according to the guidelines outlined below (5.2 and 5.4 to 5.6) without prior approval, subject to the general conditions in section 1.3 above and subject to conduct of all of the validation specified below.

Prior approval is required only if a batch or batches are manufactured outside the ranges specified in 5.2 below or outside the ranges approved at the time of registration approval, as the case may be.

5.1.5 Where the need for variation outside the allowed ranges becomes more than occasional, resulting in several applications to the TGA, it is in the interests of both the sponsor and the TGA that sufficient development work be conducted to validate a reformulation for submission.

5.1.6 The TGA does not accept that it is either necessary or appropriate to set permitted ranges for all excipients without reason, for example, an arbitrary ± 10% for each excipient.

5.2 Ranges for which a lesser level of validation is deemed necessary

The following is a guide as to the ranges whose validation requires only (1) compliance with quality control specifications and (2) comparative dissolution profiles. Proposals to make variations outside these guidelines will require additional validation and cogent argument as to why the range is essential. Outside of these ranges, prior approval is required unless the range has been approved at the time of registration.

5.2.1 In liquid formulations, it will not normally be necessary to specify ranges for pH adjusting fluids or for the quantity of a fluid used to make up a given volume. For these cases, respectively "q.s." or "to 1000L" or similar is normally acceptable. It will not normally be necessary to validate variations in the quantities of pH or volume-adjusting fluids.

5.2.2 For tablets and compressed suppositories, pessaries and implants other than modified release products (see 5.2.7 below).

5.2.2.1 It is not normally necessary to vary flavours, sweetening agents, binders, fillers and wetting agents. (However see 5.2.2.3 below when these materials are included in granulating fluids.)

5.2.2.2 It may be necessary to vary slightly the amount of colour and of other ingredients in a film-coating solution but not that in the body of a tablet. It will not normally be necessary to validate small variations in the quantity of colouring agent in a tablet coating.

5.2.2.3 The total quantity of solid ingredients in a batch of granulating fluid should not be varied, but the quantity of solvent may be. For example if the nominal quantity is 10 litres of 1% povidone, then 12.5 litres of 0.8% povidone is also likely to be acceptable.

Alternatively, the quantity of a granulating fluid of fixed composition may be varied by ±10%. Variations greater than this may be applied for on a batch to batch basis or at the time of registration, supported by validation data and cogent argument.

5.2.2.4 It is acceptable to vary the quantity of disintegrant by up to + 25%, even if the excipient serves more than one function in the formulation, such as a disintegrant/binder.

5.2.2.5 The quantities of coating solutions may need to be varied between batches and even between lots, but the solutions themselves should always be of the same composition from batch to batch and from lot to lot (but see 5.2.2.2 concerning colours).

5.2.2.6 Variations in the content of talc and water-soluble lubricants/glidants of -25% to +100% may be acceptable subject to validation.

5.2.2.7 Except for talc, water-insoluble lubricants/glidants such as magnesium stearate and stearic acid may be varied by up to ±25% subject to validation. It should be noted that changes to mixing

times after addition of lubricants to granules in the preparation of capsule fill and tablets have been shown to affect dissolution rate and must be validated.

5.2.3 For **hard gelatin capsule formulations other than modified release products**, the same principles apply as for tablets (see 5.2.2), with the following addition:

- the content of filler (bulking agent) in hard gelatin capsules may be varied by up to ±10% in order to achieve the required volume of fill.

5.2.4 In **liquids and semi-solid products**, the content of ingredients whose function is to contribute to viscosity may be varied by up to ±10%. Variations greater than this may be applied for on a batch to batch basis or at the time of registration, supported by validation data and cogent argument.

5.2.5 **Variation in weight of active per batch and consequent change in content of an excipient.** For some substances, the weight of raw material drug used in a batch may vary according to its moisture content and in some cases, particularly antibiotics, according to its potency.

Generally speaking, batch to batch differences in moisture content will be reduced when granules are dried to a constant level of hydration so that the **proportions** of excipients will remain reasonably constant from batch to batch.

However, where the potency varies, the fluctuations in quantity of raw material may affect the proportions of excipients present in the finished product relative to the nominal formula. In some situations, the manufacturer may opt to compensate for the fluctuations in the weight of raw material active added by adjusting the amount of a nominated excipient in order to maintain a target weight for the batch. Such variation will be taken into account during the evaluation, and separate batch-to-batch approval is not required. However the formulation given in the registration application should have an annotation indicating that the actual weight of active substance will be varied according to (as appropriate) estimated potency and/or water content, and a formula should be provided showing how the amount of adjustment will be calculated. There should be an indication of which other excipients will be varied correspondingly, if any, and within what limits.

5.2.6 With the exception of variations mentioned in 5.2.1 to 5.2.5 above, it should not normally be necessary to depart from the nominated formula.

5.2.7 For modified release formulations, variations to the nominal formulation will not normally be acceptable. Any application for variation from the nominal formulation (normally that with which bioavailability, safety and efficacy studies were conducted) must be accompanied by either appropriate bioavailability data or a justification as to why such data are not necessary (see note N.2). This applies both to approval of allowable ranges at the registration stage and batch by batch approvals. Spray coating of non-pareil seeds to a pre-determined dissolution performance is a case where batch-to-batch variation in content of excipients may be allowable. The ranges for cure and coating composition of these controlled release products must be approved at the time of registration. The pre-determined dissolution limits may not be altered without approval.

5.3 Validation studies

Two levels of validation are recognised, A and B.

A: For **variations within the guidelines** in 5.2, that is self-assessable variations, validation should comprise:

- compliance with routine quality control specifications;
- validation as for 4.1.4 to 4.1.6, as appropriate.

B: For **variations outside the guidelines** in 5.2, prior approval is required and validation should include:

- all of the studies required for A;

- stability data;
- either comparative bioavailability data or a justification as to why such data need not be provided (see Note N.2);
- a cogent argument as to why the range is essential.

In the context of this document, validation studies should include pilot plant scale (see note N.3) or full-scale production batches containing at least the upper and lower amounts of the excipient it is intended to vary Where it is intended to vary more than one excipient, more than two batches should be selected for testing. These should be chosen so as to represent the likely extremes of finished product properties, both physical and chemical, including dissolution rate.

5.4 Stability studies

5.4.1 Stability studies should be conducted according to the guidelines on stability testing (see Appendix 14: *Stability testing*).

5.4.2 Where approval is sought to release a batch which is outside the ranges approved during the registration evaluation, the TGA may require that the batch be placed on a stability test and that the company provide an assurance that, if at any stage the batch is outside expiry limits, it will be recalled. Stability studies are very likely to be required where the quantity of water-insoluble lubricant/glidant is 50% more than the nominal quantity.

5.5 Use of residues from earlier batches

5.5.1 The *Australian Code of Good Manufacturing Practice For Medicinal Products* (August 2002)[2] makes the following statements in regard to rejected, recovered and returned materials (Chapter 5 Production, sections 5.62 - 5.64):

> The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.
>
> The recovery of all or part of earlier batches, which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.
>
> The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.5.2 If use of residues amounting to more than 10% of final batch weight is to be included in the Master Formula, this must be approved at the time of the registration application and will require validation data. Incorporation of residues up to 10% of final batch weight is permissible without TGA approval provided quality control results, particularly for dissolution rate, are in the same range as for previous batches and the above requirements of the *Australian Code of Good Manufacturing Practice for Medicinal Products* are met.

5.5.3 Radiopharmaceuticals

Use of residues from earlier batches should not be routine for radiopharmaceuticals. Nonroutine addition of up to 10% of the final batch activity would be acceptable provided:

- an SOP exists to cover this eventuality;

[2] http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm

- the radionuclidic purity of the incorporated residue meets the specifications of the radionuclidic purity, specific radioactivity and the chemical and radiochemical purity of the chemical form of the raw material radionuclide.

5.6 Reworking (or reprocessing) of whole batches

5.6.1 Refer to section 5.5.1 above in regard to *Australian Code of Good Manufacturing Practice for Medicinal Products* requirements for reworked or reprocessed batches.

5.6.2 A quantity of water-insoluble lubricants/glidants such as magnesium stearate may be added to reworked batches up to 25% of the quantity in the original batch. Variations greater than this may be applied for on a batch by batch basis, supported by validation data and cogent argument.

5.6.3 Reworked batches of solid dosage forms must be tested for dissolution rate before release, even if such a test is not a part of routine quality control. Provided the dissolution profile is in the same range as for previous batches, TGA approval is not required.

If a dissolution rate test is not a part of routine quality control, it will be necessary to test retention samples to provide a comparison with previous batches.

5.7 Summary of Validation of Variation in Content of Excipients

Table 1: Validation when ranges are proposed at the stage of Application for Registration

Proposed ranges are within guidelines in 5.2

(1) Pilot or full-scale batches at extremes of ranges must:
- comply with qc specifications
- show comparative dissolution profiles in the same range as previously

(2) Stability data not required

Proposed ranges are outside guidelines in 5.2

(1) Pilot or full-scale batches at extremes of ranges must:
- comply with qc specifications
- show comparative dissolution profiles in the same range as previously

(2) Provide stability data at extremes of ranges
(3) Provide either comparative bioavailability data or justification as to why not
(4) Provide cogent argument as to why range is essential

Table 2: Validation for a Proposed Change to an already Registered Medicine

Proposed ranges or variations are within guidelines in 5.2 (self-assessable change)

(1) Pilot or full-scale batches at extremes of ranges must:
- comply with qc specifications
- show comparative dissolution profiles in the same range as previously

(2) Stability data not required
(3) Prior approval not required
(4) Notification not required

Proposed ranges are outside guidelines in 5.2 (prior approval required)

(1) Pilot or full-scale batches at extremes of ranges must:
- comply with qc specifications
- show comparative dissolution profiles in the same range as previously

(2) Provide stability data at extremes of ranges
(3) Provide either comparative bioavailability data or justification as to why not
(4) Provide cogent argument as to why range is essential
(5) Prior approval is required

6. Change in or Addition of Alternative Site of Manufacture of Finished Products

Definitions

Change in site of manufacture of finished medicines, for the purpose of this Appendix, is generally taken to imply a change in the location of the manufacturing premises. The change in location may or may not involve changes in the manufacturing equipment used.

Secondary packaging means any packaging or labelling, including repackaging and labelling, over-labelling, or supplementary labelling, where the drug or device is already in the primary container and that package is not opened, breached or modified in the secondary packaging process.

Primary packaging means any other type of packaging operation.

Note that primary and secondary packaging require different levels of GMP certification.

Self-assessment of the change in site of manufacture is applicable to all registered medicines covered by this Part of the Appendix **except** for products that are intended to be sterile and products which are modified release administered by whatever route, unless otherwise allowed.

6.1 Site of manufacture of dosage form and other steps of manufacture

Specific conditions

6.1.1 **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 finished product sponsor has a current GMP clearance letter issued by the TGA's MAS for the new manufacturing site and for that type of manufacture.

6.1.2 The TGA is notified of the name and address of the new manufacturer and a copy of the Australian licence and/or GMP clearance (see 6.1.1 above) is be provided, and

6.1.3 Details of the manufacturing step(s) undertaken at the new site of manufacture are stated.

6.1.4 Apart from the change in site of manufacture, there are no changes to any other aspect of the quality data other than changes to manufacturing equipment. Where a change in manufacturing equipment is made, this has been validated prior to implementation in accordance with the principles of GMP.

6.1.5 Depending on the dosage form of the product, the change has been validated as in 4.1.4 to 4.1.6 above as appropriate.

6.1.6 Comparative batch analytical results have been generated and are comparable and within the same range as previously (see Note N.4).

6.2 Site of packaging operations

Self-assessment of change in or addition of an alternative site of packaging operations is acceptable as follows:

- secondary packaging: applicable to all products, including sterile products and modified release dosage forms;
- primary packaging: applicable to all products except products intended to be sterile.

Specific conditions

6.2.1 **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 finished product sponsor has a current GMP clearance letter issued by the TGA's MAS for the new manufacturing site and for that type of manufacture.

6.2.2 The TGA is notified of the name and address of the new manufacturer and a copy of the Australian licence and/or GMP clearance letter (see 6.2.1 above) is provided, and

6.2.3 Details of the manufacturing step(s) undertaken at the new site of manufacture are provided.

6.2.4 Apart from the change in site of manufacture, there are no changes to any other aspect of the quality data other than changes to manufacturing equipment. Where a change in manufacturing equipment is made, this has been validated prior to implementation in accordance with the principles of GMP.

6.3 Site of quality control testing, including sterility and bacterial endotoxin/pyrogen testing

Applicable to all medicines, including sterile products and modified release dosage forms.

Specific conditions

6.3.1 **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 finished product sponsor has a current GMP clearance letter issued by the TGA's MAS for the new manufacturing site and for that type of manufacture.

6.3.2 The TGA is notified of the name and address of the new manufacturer and a copy of the Australian licence and/or GMP clearance letter (see 6.3.1 above) is provided, and

6.3.3 Details of the manufacturing step(s) undertaken at the new site of manufacture are provided.

6.3.4 There are no changes to the test methods used for testing the product, whether or not such test methods have been provided to the TGA previously. For sterility testing, the method used at the new site must be that of the BP or the European Pharmacopoeia (Ph Eur) and guidelines on particular aspects of the sterility test, for example, the interpretation of test results and incubation periods, are those provided in Appendix 17 (*Microbial quality of medicines*).

6.4 Deletion of site of manufacture

This change is applicable to all medicines.

Specific conditions

6.4.1 The TGA is notified of the name and site address of the manufacturer and the steps of manufacture to be deleted.

6.4.2 Evidence (eg. current ARTG print our, TGA approval letter or other documentary evidence) is provided to show that there is at least one validly registered site of manufacture performing the same step of manufacture as the deleted site.

7. Changes to Finished Product Specifications

7.1 Change to the method for determining the content of the active substance (assay) in the finished product

(including assay of the active substance during dissolution testing and/or uniformity of content testing) and assay of the content of essential excipients such as preservatives/anti-oxidants.

Sponsors should note however, that should there be a dispute of test results obtained using the new assay method and an official assay method (generally, the BP compendial method or a method prescribed in a TGO), the result obtained using the latter method alone is official.

[Note: Any changes to biological methods of assay (such as those used for antibiotics) and any changes to the test method for impurities, related substances and degradation products require prior approval.]

Specific conditions

7.1.1 The new method demonstrably improves 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.

7.1.2 appropriate validation data have been generated for the proposed assay method; and

7.1.3 details of the test method are provided, together with an updated Certified Product Details (CPD) document for the product incorporating the new assay method (see Note N.7).

7.2 Narrowing of the limits for test results within the existing specifications

Specific conditions

7.2.1 The proposed limits are either the same as or more stringent than any applicable official standard and/or relevant accepted guidelines where applicable; and

7.2.2 there is no change in test method other than those allowed by points 7.1, 7.4 or 7.7 of this Part, and

7.2.3 the revised set of finished product specifications are provided; and
7.2.4 an updated CPD document incorporating the new limit is provided.

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

Specific conditions

7.3.1 Appropriate validation data have been generated for the test method.

7.3.2 Details of the test method must be provided together with an updated CPD document (see Note N.7) incorporating the new test and limit; and

7.3.3 The proposed limit (release and expiry) is based on batch analytical data and must be in compliance with or more stringent than any applicable official standard and/or relevant accepted guidelines for such a test.

7.3.4 The revised set of finished product specifications at release and expiry must be provided.

7.4 Changes which are consequent upon amendments to pharmacopoeial requirements or to requirements of a TGO.

For example, if a finished product is specified as complying with the requirements of the current edition of the BP (inclusive of tests, limits and test methods), it would be appropriate to substitute the requirements of the new edition of the BP when this is formally adopted by the TGA. However, any tests which are performed in addition to those of the pharmacopoeial monograph must continue to be performed. Note that changing from the requirements of one pharmacopoeia to those of another, such as from the BP to the USP, is not covered by this section and therefore may not be self-assessable.

Specific conditions

7.4.1 The suitability of the new pharmacopoeial monograph or TGO in relation to the product has been examined and, if necessary, appropriate validation data had been generated.

7.4.2 The revised set of finished product specifications (release and expiry), if applicable, must be provided with the notification.

7.4.3 An updated CPD document is provided.

7.5 Changes to sterility testing method.

[Note: Change(s) involving compliance with the USP requires prior approval because some elements of the USP sterility test remain unacceptable to the TGA. Changes to other forms of biological testing, such as pyrogen or bacterial endotoxin tests, also require prior approval.]

Specific conditions

7.5.1 All aspects of the test are in accordance with the requirements of the internationally harmonised test published in the BP or Ph. Eur.; and

7.5.2 Guidelines on particular aspects of the sterility test, for example, interpretation of results and incubation periods, are those provided in Appendix 17 of the ARGPM.

7.5.3 Details of the test method(s) are included in the updated CPD document which must be provided.

7.6 Change to identification test

Changes to identification test as follows:

- from a less specific to a more specific identification test, for example, from a UV/Visible spectrophotometric and/or chromatographic method (TLC, GC or HPLC) to normal infra-red (IR) spectroscopic method;
- vary the existing identification test, for example, HPLC test, which demonstrably improves or at least maintain the specificity of the method;
- the inclusion of an additional identification test to an existing identification test;
- replace existing identification test(s) with a near infra-red (NIR) spectroscopic identification method (applicable only if specific condition 7.6.3 is met).

Specific conditions

7.6.1 The method must have been validated in accordance with applicable guidelines; and

7.6.2 Any additional identification test included must not serve as an alternative identification test; and

7.6.3 If NIR is used, the site of testing must have a previously TGA-approved SOP for introducing NIR as an identification test in finished products (see Note N.6).

7.6.4 The details of the revised identification test method(s) and the revised set of finished product specifications are provided in an updated CPD document.

7.7 Minor changes to existing finished product test methods for physico-chemical parameters such as for pH, density/specific gravity, optical rotation, extractable volume, osmolality/osmolarity and viscosity

Specific conditions

7.7.1 The test limit either remains unchanged or has been tightened; and
7.7.2 The amended method has been validated; and
7.7.3 The revised method has been incorporated into an updated CPD document which is provided with the notification.

8. Changes to Excipients

[Note: Except as provided for in Appendix 13 (*Self-Assessable Changes to Biological Products*) and as specified in 8.5 below, changes to excipients of biological origin (animal or human source) are not self-assessable. For changes to other aspects of excipients not requiring prior approval, see Part A of this Appendix.]

For the purposes of this section, *excipients of biological origin* means materials sourced from animal or human such as hormones, allergens, vaccines or modified animal tissues including blood products, and products of genetic engineering or other newer biotechnological techniques

8.1 Changes to assay method for excipients (where there is an assay for the excipient)

Specific conditions

8.1.1 the new method must 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; and

8.1.2 appropriate validation data have been generated for the proposed method; and
8.1.3 details of the new method are provided.

8.2 Narrowing of the limits for test results within the existing specifications

Specific conditions

8.2.1 The proposed limits are consistent with any applicable official standard and/or relevant accepted guidelines if applicable.

8.2.2 The revised set of specifications for the excipient must be provided.

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

Note that a new specification which is consequent upon an altered method of manufacture which alters the excipient's quality characteristics, such as micronisation, would require prior approval.

Specific conditions

8.3.1 Appropriate validation data have been generated for the test method.

8.3.2 Details of the test method must be provided.

8.3.3 The limits proposed are based on batch analytical data and are in compliance with or more stringent any official standard and/or relevant accepted guidelines if applicable.

8.3.4 The revised set of specifications for the excipient must be provided.

8.4 Changes which are consequent upon amendments to pharmacopoeial requirements or to requirements of a TGO and changing from one pharmacopoeial requirements to those of another.

For example, if an excipient is specified as complying with the requirements of the current edition of the USP, it would be appropriate to substitute the requirements of the new edition of the USP when this is published. However, any tests which were performed in addition to those of the USP must continue to be performed. Note that changing the excipient specifications from the BP/Ph.Eur. requirements to those of the USP or vice versa is also acceptable as a self-assessable change but any extra tests must continue to be performed and the limits applied.

Specific conditions

8.4.1 The suitability of the new pharmacopoeial monograph or TGO has been examined.

8.4.2 The revised set of specifications for the excipient is provided.

8.5 Change in source and/or manufacturing process of animal-derived (in particular ruminant) excipients classified as Category IV in TGA's *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)* [3] may be self-assessed if

- the change is from an animal source to a plant or other non-animal source; or
- the excipient is used in products given only by the oral, topical, vaginal, rectal or inhalation routes.

Specific conditions

8.5.1 Details of the excipients and the proposed changes must be provided.

8.5.2 Either no changes to the specifications have been made, or they are changed as allowed in sections 8.1-8.4 above.

8.5.3 A declaration has been provided that the Category IV material has been self-assessed and that it complies with the TGA's requirement cited above regarding TSE risks.

8.5.4 An assurance has been provided that records will be maintained of compliance for future TGA compliance checks.

9. Changes to the Material of Which a Container is Made

9.1 Bottles

For products which are non-sterile solid dosage forms (for example, tablets, capsules, compressed pessaries and suppositories) and non-sterile semi-solids and liquids (for example, ointments, creams, lotions, oral solutions and suspensions), self-assessment of the following changes in the material of which the bottle and/or closure system (a re-closable package) are made is allowed:

- polystyrene to PVC, polyethylene, polypropylene or glass;
- PVC to polyethylene, polypropylene or glass;

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

- polyethylene to glass or polypropylene of density of at least 0.89;
- from polyethylene of one density to polyethylene of a higher density;
- any change between glass, metal, polyethylene of density of at least 0.95, and polypropylene of density of at least 0.89.

Specific conditions

9.1.1 Any new plastic material used must meet the requirements of the BP (see Appendix XX of the BP *Materials Used for the Manufacture of Containers*).

9.1.2 If the product is a semi-solid or a liquid, it must be water-based and contain no organic solvent.

9.1.3 Where the bottle and/or closure system is a child-resistant package or is implied by its presentation as a child-resistant package, data have been generated to demonstrate that the child-resistant properties of the package and operation have not been adversely affected by the change in material.

9.1.4 Comparative moisture permeability (water-vapour transmission) data have been generated using the current edition of the USP test for *Containers-Permeation* (Multi-Unit Containers) on the new and the current bottle/closure systems, and the results showed either equivalent or better moisture protection.

9.1.5 A stability test in the new bottle/closure system has been commenced on at least one production batch of the product and will be commenced on a second and third batch as they become available to verify the product shelf-life.

9.1.6 In the event of a verified failure to meet specifications in the stability study, the TGA will be notified within one week of the failure being detected, and the product in the new bottle/closure system may be withdrawn from the market at the TGA's discretion; and

9.1.7 Either no change is made to the product's shelf-life and storage conditions or the shelf-life has been reduced and the storage conditions made more stringent.

9.1.8 If relevant, details of the new product shelf-life and storage conditions are stated, and any consequential changes made to the PI and/or product labels are notified (see later under sections 16 and 17).

9.2 Blister packs and strip packs

For products which are non-sterile solid dosage forms and non-sterile semi-solids such as moulded suppositories and pessaries in blister or strip packs, the following changes to the plastic component of the container is self-assessable

- PVC to PVC/PVDC or PVC/PCTFE or PVC/PVDC/PE;
- PVC/PVDC to PVC/PCTFE or PVC/PVDC/PE;
- PP to PVC/PVDC or PVC/PVDC/PE;
- PVC to PP
- any type of plastic material to double aluminium foil blister packs (cold-formed A1/A1 blister packs) or strip packs

Specific conditions

9.2.1 Any new plastic material used must meet the requirements of the BP (see Appendix XX of the BP: *Materials Used for the Manufacture of Containers*), and

9.2.2 Comparative moisture permeability (water-vapour transmission) data have been generated using the current edition of the USP test for *Containers-Permeation* (Single-Unit Containers and Unit-Dose containers) on the new and the current blister/strip pack systems, and the results showed either equivalent or better moisture protection.

9.2.3 A stability test in the new container system has been commenced on at least one production batch of the product and will be commenced on a second and third batch as they become available to verify the product shelf-life.

9.2.4 In the event of a failure to meet specifications in the stability study, the TGA will be notified immediately of failure being detected, and the product in the new container system may be withdrawn from the market at the TGA's discretion.

9.2.5 Either no change is made to the product's shelf-life and storage conditions or the shelf-life has been reduced and the storage conditions made more stringent.

9.2.6 If relevant, details of the new product shelf-life and storage conditions are stated and any consequential changes made to the PI and/or product labels notified (see later under sections 16 and 17).

9.3 Increase in container material thickness

Applicable to non-sterile solid dosage forms, non-sterile semi-solids and liquid products.

[Note: A decrease in container material thickness requires prior approval except that where aluminium foil is used in blister or strip packs, a reduction in the aluminium foil thickness to a minimum of 20mm is permitted as a self-assessable change.]

Specific conditions

9.3.1 Details are provided of the change in container material thickness.

9.3.2 The container material is either unchanged or is changed in a manner permitted in sections 9.1 and 9.2 above; and

9.3.3 A stability test in the new container system has been commenced on at least one production batch of the product and will be commenced on a second and third batch as they become available to verify the product shelf-life.

9.3.4 In the event of a failure to meet specifications in the stability study, the TGA will be notified immediately of failure being detected, and the product in the new container system may be withdrawn from the market at the TGA's discretion.

9.3.5 Either no change is made to the product's shelf-life and storage conditions or the shelf-life has been reduced and the storage conditions made more stringent.

9.3.6 If relevant, details of the new product shelf-life and storage conditions are stated and any consequential changes made to the PI and/or product labels notified (see later under sections 16 and 17).

Changes to Container Size, Shape and Components

[Note: For changes to other aspects of container not requiring prior approval, see Part A of this Appendix.]

10.1 Container size and shape

Applicable to non-sterile dosage forms only.

Specific conditions

10.1.1 Details of the new container system are provided.

10.1.2 Where the container is a re-closable package and is child-resistant or is implied by its presentation as a child-resistant package, data 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, and

10.1.3 For solid oral dosage forms, comparative moisture permeability (water-vapour transmission) data have been generated using the current edition of the USP test for *Containers-Permeation* (Multi-Unit or Single-Unit Containers procedures, as appropriate) on the new and the current container systems, and the results showed either equivalent or better moisture protection.

10.1.4 The container material is either unchanged or is changed in a manner permitted in sections 9.1 to 9.3 above.

10.1.5 A stability test in the new container system has been commenced on at least one production batch of the product and will be commenced on a second and third batch as they become available to verify the product shelf-life.

10.1.6 In the event of a verified failure to meet specifications in the stability study, the TGA will be notified within one week of failure being detected, and the product in the new container system may be withdrawn from the market at the TGA's discretion.

10.1.7 Either no change is made to the product's shelf-life and storage conditions or the shelf-life has been reduced and the storage conditions made more stringent.

10.1.8 If relevant, details of the new product shelf-life and storage conditions are stated and any consequential changes made to the PI and/or product labels must be notified (see later under sections 16 and 17).

10.1.9 No change is made to the quantity of goods in the new container system except as permitted in section 11 below.

10.2 Container components

Changes of the following types are self-assessable and applicable to all products provided that the affected container components are not required to be sterile:

- change to or addition/removal of the outer carton or other outer primary pack but **excluding** outer over-wraps designed to prevent ingress or egress of moisture/solvent/gases from a container; or
- change to or addition/removal of components of the container that are not in direct contact with the product (eg tamper-evident seal, aluminium flip-off crimps on injection vials, plastic dust-cover disc/top/cap, etc); or
- inclusion or removal of inert wadding from bottles and other containers containing solid dosage forms; or
- inclusion of a desiccant in bottles containing solid dosage forms.

Specific conditions

10.2.1 Details of the change are provided.

10.2.2 Other than inert wadding, the components are not in direct contact with the product.

10.2.3 The label of any outer carton/other primary pack that is added or changed either remains unchanged, is identical to the container label or is changed as permitted under section 17 and/or Part A (section 1.4) of this Appendix; or

10.2.4 where an existing carton/primary pack is removed, the container label must either remain unchanged or is changed as permitted under section 17 and/or Part A (section

1.4) of this Appendix and it must continue to meet all requirements of the existing TGO pertaining to labels; or

10.2.5 the removal of inert wadding has been validated with comparative data to demonstrate that in normal transport and usage of the product, its friability and other physical attributes have not been affected adversely (see Note N.4); or

10.2.6 where a desiccant is included in bottles, an assurance is provided that its use is for enhancement of the existing acceptable stability profile of the product and not due to stability problems in the existing container, the nature of the desiccant is identified and is readily distinguishable from the product and/or it is appropriately labelled and identified as a desiccant.

11. Change to Pack Size

Change to or addition of a new pack size is self-assessable but a change in volume of fill of injections or other sterile preparations require prior approval.

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

- for products presented as discrete dose units, such as tablets and capsules, the number of such units in the container; or
- for non-sterile solid, powder, semi-solid and liquid products, the weight or volume of the container contents, or
- for injections and other sterile preparations, the number of ampoules/vials/pre-filled syringes/bags/bottles, etc per primary pack (carton); or
- for trans-dermal patches, the number of patches per primary pack (carton); or
- for pressurised metered-dose preparation or dry powder inhaler, the number of doses in the container; or
- for non-pressurised metered-dose preparation, the minimum number of doses in the container.

Specific conditions

11.1 The change either is consequent to a Pharmaceutical Benefits Advisory Committee (PBAC) recommendation or is a change to a smaller pack size.

11.2 The change in pack size is not accompanied by changes to dosage regimen and/or indications.

11.3 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 section 17 or Part A (section 1.4) of this Appendix; and

11.4 The additional or changed pack size is consistent with the treatment recommendations in the PI; and

11.5 The container material, size and shape is unchanged or is changed in a manner permitted in sections 9 and 10 above.

[Note: if a new pack size is added to the Australian Government's *Schedule of Pharmaceutical Benefits*, sponsors whose products are not listed in the Schedule may also add the new pack size without prior approval, subject to all of the general and specific conditions above.]

12. Dimensions, Shape, Embossing and Debossing of Solid Dosage Forms

Applicable to all solid dosage forms, including modified release, such as tablets and compressed pessaries and suppositories. Embossing/debossing refers in this context to raised or depressed identifying markings on the product formed by special tooling, but not printing, used during product manufacture. For changes involving inked imprints, refer to section 15 below.

Specific conditions

12.1 There must not be a concurrent change to formulation except as allowed in section 14 of this Appendix.

12.2 No change in scoring, whether deletion, addition or variation, has occurred.

12.3 It is demonstrated that the comparative dissolution profiles of pre- and post-variation products are similar, ie f_2 value between 50 and 100 (see Notes N.1 and N.4).

12.4 The new product description is provided.

12.5 The revised set of finished product specifications (release and expiry) and an updated CPD document must be provided.

13. Changes to Product Shelf-Life and Storage Conditions

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

The shelf-life of a product may be extended through self-assessment in accordance with a stability testing protocol which was approved explicitly for this purpose. Such protocols may be submitted with the application for registration or subsequent to registration through a Category 3 application. It is normally necessary that, at the time of submission of the stability testing protocol, at least 12 month stability data be available on the product in question, or on a closely related formulation, in the marketed container or one which is less protective.

Any stability testing protocol proposed for this purpose must include:

- information on the number of batches to be tested (minimum of three batches);
- a statement of the proposed tests and test methods;
- a matrix indicating the time stations at which each of the tests will be conducted;
- acceptance limits for the results for each test, some of which, particularly those with quantitative results such as assay, dissolution/disintegration, and impurities/degradation products, should be set somewhat tighter than the approved expiry limits although not necessarily as tight as the release limits.

[Note: see also Section 8 of Appendix 14 (*Stability Testing*)]

Specific conditions

13.1.1 Evidence is provided that the TGA had explicitly approved the protocol for the purpose of self-assessable shelf-life extension.

13.1.2 All quality aspects of the product, including its immediate container and closure and labelled storage conditions, are either identical to those approved at the time the stability testing protocol was approved or where changes have occurred, they have been

implemented following either prior approval, self-assessment or notification in accordance with the provisions of this Appendix.

13.1.3 At least three production batches of the product have been tested in accordance with the approved stability testing protocol.

13.1.4 The extended shelf-life is not longer than the time for which stability data meeting the approved protocol requirements are available on three production batches, and in any case is not longer than 5 years.

13.1.5 The new shelf-life is notified to the TGA, and any consequential change resulting from this, such as to the PI is also notified to the TGA if relevant (see section 16).

13.2 Decrease in shelf-life and/or more restrictive storage conditions

Specific conditions

13.2.1 Details of the new shelf-life and/or storage conditions are provided.

13.2.2 Adequate stability data are available to support adoption of the new shelf-life and/or storage conditions.

13.2.3 Any consequential changes required resulting from this change, such as to product labels and PI (see sections 16 and 17) are also notified to the TGA; and

13.2.4 no change in container other than allowed in sections 9 and 10 of this Part.

14. Formulation Change Relating to Colouring Agent, Flavour or Fragrance

Changes to, addition or deletion of colouring agents, flavour and fragrance of a product may be made through self-assessment. It should be noted that such a change in formulation, being a change under section 16(1) of *the Act*, requires a new ARTG entry. However, the provisions of the *Therapeutic Goods (Groups) Order No. 1 of 2001* allow retention of the Aust R number of the existing product for the new product if the new product replaces the existing product.

Specific conditions

14.1 The colouring agent (or lake thereof), fragrance or flavour is present in the formulation at not more than 2% w/w or w/v and they contain only substances already present in the ARTG.

14.2 Any new colour is listed in the current TGA list of colours permitted in medicines for oral use, and complies with the specifications in the same list (see Appendix 22: *Colourings permitted in medicines for oral use*); and

14.3 Any new proprietary ingredient to be used must have been listed already on the ARTG and the ARTG number for the new proprietary ingredient is provided.

14.4 The new product formulation is provided.

14.5 The new product description is provided, if this is changed.

14.6 Depending on the dosage form of the product**,** the change has been validated as required in either point 4.1.4 or 4.1.5 above; and

14.7 A stability test on the reformulated product has been commenced on at least one production batch and will be commenced on the second and third batch as they become available.

14.8 In the event of a failure to meet specifications in the stability study, the TGA will be notified immediately of the failure being detected and the re-formulated product may be withdrawn from the market at the TGA's discretion.

14.9 If relevant, the revised set of finished product specifications (release and expiry) incorporating the new product description must be provided in an updated CPD document for the new product.

14.10 The product is only supplied

- if a Consumer Medicine Information (CMI) document exists for the product ;
- if the new product has been registered (see Note N.5).

14.11 Any consequential changes required resulting from this change, such as to product information (PI) (see section 16) are also notified to the TGA.

15. Addition, Deletion or Variation to an Inked Imprint

An inked imprint (marks made by printing with an ink during product manufacture) on a solid dosage form may be added, deleted or varied through self-assessment. It should be noted that addition, deletion or change in formulation of an ink is a change under section 16(1) of *the Act* and requires a new entry on the ARTG (see Note N.5). However, the provisions of the *Therapeutic Goods (Groups) Order No. 1 of 2001* allow retention of the Aust R number of the existing product for the new product if the new product replaces the existing product.

Note that specific condition 15.7 below does not apply if the change is to the inked markings only using the existing ink.

Specific conditions

15.1 Any new colour or dye of an ink is listed in the current TGA list of colours permitted for use in medicines for ingestion (Appendix 22: *Colourings permitted in medicines for oral use*), and complies with the specifications specified in the same list; and

15.2 Any new proprietary ingredient to be used must have been listed already on the ARTG and the ARTG number for the proprietary ingredient provided; and

15.3 The new product formulation is provided, if relevant.

15.4 The revised product description is provided if this has changed, together with the revised set of finished product specifications (release and expiry) incorporating the new product description.

15.5 An updated CPD document for the new product is provided, if relevant.

15.6 Any consequential changes required resulting from this change, such as to the PI (see section 16), are also notified to the TGA.

15.7 If the change results in a new formulation for the product, it is only supplied

- if a CMI document exists for the product;
- if the new product has been registered (see Note N.5).

[Note: For the current TGA list of approved colours see Appendix 22 (*Colourings permitted in medicines for oral use*)]

16. Quality Aspects of PI

The following types of changes to the quality aspects of the PI document of a product are self-assessable:

- the changes put into effect the guidelines in sections 3.1 to 3.3 and 3.5 of Appendix 20 (*Supplementary Guidelines for Radiopharmaceuticals*); or
- changes to the PI of radiopharmaceuticals which specifically:
- gives instructions and information relating to the enhancement of radiation protection and safety of the user and the patient. These may include radiation shielding data, decay charts, procedures to minimise radiation doses to staff and unwanted dose to patients and references to guidelines and codes of practice relating to radiation protection;
- gives instructions to users that the patient dose should be measured by a suitable radioactivity calibrator immediately before the administration;
- the change is to add the names of excipients in the product, whether or not those excipients are referred to in the TGO pertaining to labels;
- the change is consequent to the implementation of a self-assessable change allowed in this Appendix;
- the change is consequent to a TGA-approved change following a Category 1 or Category 3 application;
- the change is consequent to the implementation of a change allowed in Part A of this Appendix;
- the change is consequent to an approval under section 9D(1) of the *Act* to correct ARTG information of the product; or
- the change is consequent to a change in terminology used in the PI to comply with the current edition of the TGA's *Approved Terminology for Medicines*[4], including changes to the name of APIs, name of excipients, routes of administration and container type name;
- the change is to include the CAS number, the chemical structure, molecular formula, molecular weight and/or the chemical name/nomenclature of the API.

Specific conditions

16.1 Copies of the existing PI, with clear annotations of the changes made, and a clean copy of the amended PI are provided, together with an assurance that there have been no other changes to the PI.

16.2 If the PI already has a TGA approval date, the same date must be retained but with the revised document annotated *Date of most recent amendment* as the date of the notification letter to the TGA. If it does not already have one, a TGA approval date must not be added to the PI as a consequence of the self-assessable change.

16.3 All names and terminology used in the amended PI must comply with the current edition of the *TGA Approved Terminology for Medicines*.

16.4 Any included technical information is accurate and is obtained from recognised reference sources.

[4] http://www.tga.gov.au/medicines-approved-terminology.htm

16.5 For consequential changes to the PI of the type listed under dot points four to seven above, appropriate evidence is provided of the approval or notification.

17. Changes to Product Labels

It is the responsibility of sponsors to ensure that their product labels meet any State and Territory requirements.

Product labels are as defined by the TGO Number *69*[5] *General Requirements for Labels for Medicines* as from time to time amended. Self-assessment of proposed changes to product labels is allowed, but only of the types detailed below. Sponsor should not use the self-assessment procedure to revise labels for compliance with the TGO pertaining to labels other than as allowed below. Refer also to Part A of this Appendix for other types of changes to labels that do not require prior approval.

17.1 Addition of the names of excipients, whether or not the excipients are referred to in the TGO pertaining to labels.

17.2 Addition of the release rate for trans-dermal patches.

17.3 Amendment of the means of expressing the proportion of active ingredient in topical preparations.

17.4 Addition or amendment of the terms hypotonic, hypertonic and isotonic in the labels of large volume injections.

17.5 Addition of or changes to a warning or precaution statement resulting from a change to PI pursuant to section 9D(2) of *the Act* (Safety Related Changes to PI) and which has been notified to the TGA.

[Note: Amendments to warning statements resulting from changes to the Poison Standard or to the standard that applies to the medicines require prior approval.]

17.6 Amendments which, pursuant to section 9D(1) of *the Act*, correct an incomplete or erroneous entry in the ARTG, and which have been approved by the TGA.

17.7 Addition of a new TGA-approved route of administration for injectables.

17.8 Amendments which are consequent to the implementation of a self-assessable change in this document and which have been notified to the TGA.

17.9 Changes which are consequent to a change approved by the TGA following a Category 1 or Category 3 application.

17.10 Changes which are consequent to the implementation of changes allowed in Part A of this Appendix and which have been notified to the TGA.

17.11 Changes to the colour, design or layout of labels with no change to content.

17.12 Addition/deletion of or change to the name and/or address of the Australian sponsor or supplier of the product.

17.13 Addition/deletion of or changes to the company logo/livery.

17.14 Deletion only of existing graphics/pictures/diagrams and any associated text.

17.15 Addition/deletion of, or changes to, simple instructional/informational/anti-tampering statements such as *CMI enclosed*, *Break security seal before opening*, *Push tablets through blister foil*, *Do not accept if security seal is broken*, and other similar statements.

[5] http://www.tga.gov.au/industry/legislation.htm

17.16 Addition of warning/cautionary statements where an incorrect route or method of administration may be hazardous, such as *Not for injection, For external use only* and *Not for oral use* or similar statements.

17.17 Addition/deletion of or changes to Australian-owned and managed company website address.

17.18 Change to method of expression of content of active ingredient and/or excipient in accord with the current TGO pertaining to labels, such as 0.5mg to 500 micrograms.

17.19 Addition/deletion of or change to the *Country of Origin/Manufacture* statement for imported products as required by other relevant Australian legislations.

17.20 Addition/deletion of or changes to label text of outer protective pouches or over-wraps of the container or primary pack where the text is not confusing, promotional or contradictory to text on the container or primary pack labels.

17.21 Changes to labels consequent to product re-scheduling (following from changes to *Standard for the Uniform Scheduling of Drugs and Poisons*, SUSDP), such as to directions for use and statement of purpose(s) of the product that are in accord with the approved PI. See section 2.3, Part A of this Appendix for more information.

17.22 Changes which must be made to currently approved labels which are in compliance with TGO No. 48 (*General requirements for labels for drug products*) to ensure compliance with TGO No. 69 (*General requirements for labels for medicines*). Note that updating old labels which have not previously been evaluated and approved by the TGA is not self-assessable.

Specific conditions

17.23 The changes must ensure continued compliance with the relevant TGO pertaining to labels.

17.24 Copies of the existing labels and final or mock-up of the amended labels which include any logos, design work or graphics are provided. The copy should be to scale and should indicate the colours to be used. If there are multiple strengths and/or pack sizes, one representative label or copy will be sufficient provided that the only difference between the labels is the pack size or strength. If batch number and expiry date are printed on during packaging, a statement to this effect should be provided.

17.25 For the addition of or changes to a company website address (point 17.17 above), the following conditions must also be satisfied:

- the website has an Australia address, ie must end with *.au* or other justified suffixes which still reflect Australian ownership of the address; and
- an assurance is provided that the website is Australian owned and operated;
- an assurance is provided that the sponsor has full control over the content of the site.

17.26 For consequential changes to labels of the type 17.5 to 17.10 and 17.21, appropriate evidence is provided of the approval or notification.

Part C: Changes requiring prior approval

Parts A and B of this Appendix provide details of the types of changes to the quality information of already registered medicines which may be implemented without prior approval from the TGA. All other types of changes, or for those products for which changes are intended that are not covered by the provisions in Parts A or B will require prior approval. As stated in the Introduction section, generally a Category 3 application is required for such approval. However, depending on the data requirements, some changes may require submission of a Category 1 application.

The data required to support a Category 3 application to make changes to the quality information of the types detailed are essentially the same as those required for the corresponding section of an application to register a new medicine. The requirements of the relevant Committee for Medicinal Products for Human Use (CHMP)/International Conference on Harmonisation (ICH) guidelines adopted by the TGA should be met, as appropriate.

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

- a clear description of the currently approved information;
- the proposed changed information;
- the rationale and/or justification for the change(s);
- technical data to support the proposed change(s) (see below);
- a declaration that:

> "No aspects of the quality information have been changed, including manufacturing procedures and equipment and raw material and finished product specifications, other than the changes nominated in this application."

Depending on the nature of the proposed change(s), the following supporting technical data should be provided and, if not provided, may be requested by the evaluator. Sponsors should be aware that the types of changes listed below are not exhaustive and the technical data required represent the minimum data necessary for assessment. The TGA reserves the right to request data/information additional to those required below, if deemed appropriate.

A Category 3 application should be formatted according to the Common Technical Document (CTD) format (see section 1.6 of the ARGPM), however, the sponsor needs only to submit a single copy of any supporting data relevant to the application.

The guidance provided below does not apply to biological products although it is applicable to fermentation antibiotics and other products produced wholly or partially by fermentation.

1. Change to PI: quality aspects

- A copy of the current PI with annotations of where changes have occurred and a clean copy of the revised PI.
- A declaration that no other changes have been made to the PI other than those identified in the application.

- Relevant technical data to support the proposed change(s).

2. Formulation changes

- A copy of the current and revised formulation and details of any new manufacturing process and associated validation data.
- Details of the specifications applicable to all the excipients used in the new formulation. Where an excipient was not used in the previous formulation, Certificates of Analysis issued by the finished product manufacturer for 2 or 3 representative batches of the excipient should be submitted.
- For excipients that are of animal origin, especially ruminant, such as cattle, sheep and goat, that are classified as Category IV in the TGA's *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)*[Error! Bookmark not defined.], the following are required:
- For products that are implanted or given by parenteral, ophthalmic or intra-tracheal routes of administration, details of such excipients (including excipients whose manufacture may have exposed them to Category IV materials) and measures taken by the manufacturers to minimise TSE risk.
- For products given by the oral, topical, vaginal, rectal or inhalation routes, provide details of the excipients and a declaration that the Category IV material has been self-assessed and that it complies with the above TGA requirements together with an assurance that the sponsor will maintain record of compliance for future TGA compliance checks.
- Relevant comparative data for the proposed new and currently approved finished products to demonstrate that the change in formulation does not lead to changes in the physical characteristics of the product that may impact on the absorption and *in vivo* effect of the medicine. For further guidance, see below under *Method of manufacture: finished product*. [Note that where the change in formulation is considered significant (see below), *in vivo* data may be required to support the change.]
- Certificates of Analysis for at least one production batch of the finished product manufactured using the proposed new formulation. Pilot scale batches are acceptable, if justified.
- Stability data in accordance with relevant adopted CHMP/ICH guidelines. For minor formulation changes (such as those discussed in Section 5.2 under *Variations in content of excipients*, Part B of this Appendix), the sponsor may provide a justification as to why up-front stability data need not be provided for review. However, a commitment to carry out stability testing on at least three production-scale batches of the reformulated product is nevertheless required.
- Comparative bioavailability data (if the changes are likely to affect bioavailability of the product) establishing bioequivalence of the new and currently approved formulation or a justification for a waiver. Note that, if bioequivalence data are submitted in support, the application will be re-categorised as a Category 1 application. (For further information on changes considered unlikely to affect bioavailability, see Section 5.2 under *Variations in content of excipients*, Part B of this Appendix, and Section 3 of Appendix 15 (*Biopharmaceutic Studies*).
- If the formulation involves a change to the preservative system, then additional data may be required such as stability data (including microbial quality and proof of anti-microbial efficacy of the finished product at expiry) and test methods (with accompanying validation data) for determination of preservative content at finished product at release.

- Clean copy of the revised PI (if appropriate) together with a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.

3. Specifications: API

- A copy of the revised specifications.
- Justification for the proposed changes, including to test procedures.
- Validation of any changed test procedures (including microbiological tests, if applicable).
- Certificates of Analysis for representative batches (2 or 3) of the bulk API demonstrating the ability of the manufacturer to meet the revised specifications.

4. Specifications: finished product

- A copy of the revised specifications.
- Justification for the proposed changes, including to test procedures.
- Validation of any changed test procedures (including microbiological tests, if applicable).
- Certificates of Analysis for representative batches (2 or 3) of the finished product demonstrating the ability of the manufacturer to meet the revised specifications. Where appropriate, batch analytical data from aged samples may be necessary.

5. Specifications: excipients

- A copy of the revised specifications.
- Justification for any new or changed limits or test procedures.
- Validation of any changed test procedures for critical tests.
- Certificates of Analysis for representative batches (2 or 3) of the excipient demonstrating the ability of the manufacturer to meet the revised specifications.

Synthetic route/manufacturing process change: API

- Description (including flow-diagram) of the changed manufacturing process, including any changes to manufacturing batch size, and in-process controls.
- Validation of the process.
- If the API is made entirely by fermentation, provide details of any material of animal origin that is used during the process and which is classified as Category IV in the TGA's *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)*[Error! Bookmark not defined.]. If appropriate, provide the necessary assurance regarding self-assessment of TSE risks of such materials.
- A description and discussion of any resulting changes in impurities.
- Comparative impurity profile data from three batches of pre-variation material and at least one production batch of post-variation material using a validated test method.

- Certificates of Analysis for at least one production batch of active ingredient manufactured using the new process and demonstrating the ability of the manufacturer to produce material that meets the currently approved specifications, including polymorphic form and particle size distribution (use laser diffraction method), if appropriate.
- If relevant, an updated drug master file (DMF) or Certificate of Suitability (CEP) may be submitted.
- Where a change is to late stage(s) of synthesis, crystallisation and purification, or milling, either relevant comparative data of the dosage form (for example, dissolution, drug mass aerodynamic particle size distribution, etc) manufactured from pre- and post-variation active ingredient or data to demonstrate compliance with relevant particle size limits or polymorphic form.
- Stability data of post-variation API in accordance with the relevant adopted CHMP/ICH guidelines or a statement of commitment to carry out such studies.

7. Method of manufacture (including batch size changes): finished product

- A detailed description of the changed manufacturing process including in-process controls.
- Where the change includes variation to the content of excipients, such as the introduction of a range for specific excipients, see *Variations in content of excipients* (section 5 of Part B of this Appendix) for more information on data requirements.
- Process validation data for the changed process (including validation of sterile manufacture and sterilisation processes, if applicable).
- Batch analytical data for representative batches of finished product manufactured using the proposed process. At least one batch should be full production scale unless otherwise justified, while the other batches should be at least pilot scale manufactured using full production scale equipment unless otherwise justified.
- Relevant comparative data of the type listed below for the dosage form manufactured using the new and old methods. At least three recently manufactured batches of the pre-variation product and one production batch of the post-variation product should be tested preferably at the same time and using the same method. The second and third batches manufactured under the new conditions, if unavailable at the time of application, should be tested and the results reviewed by the sponsor as soon as they become available post-approval and any differences brought immediately to the TGA's attention.

  For all solid dosage forms (for example, tablets, capsules, compressed pessaries/suppositories, implants) and transdermal patches, dissolution profiles data using a discriminatory method are required. For low solubility drugs, dissolution testing over the pH range 1.0 to 7.5 should be considered.

  For semi-solid and liquid suspension products, particle size data (microscopic imaging or other methods) and/or dissolution data, as relevant.

  For metered-dose pressurised inhalations (oral or nasal), dry powder for inhalation products and metered-dose nasal spray solutions or suspensions, drug mass aerodynamic particle size distribution data using a multi-stage Liquid Impinger or a multi-stage Cascade Impactor of the Andersen type.
- Stability data or confirmation that stability data will be collected. Relevant stability data must be generated for batches produced using the new process as required by GMP. The TGA may

request the sponsor to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to approval of the change of process. However, if the data are not supplied, the company must provide written assurance that stability data will be generated and the TGA notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new process is different from that made by the original process to the extent that the shelf-life of the medicine would be affected.

- Comparative bioavailability data establishing bioequivalence of product manufactured using the new and currently approved processes if the change is likely to affect bioavailability, or a justification for a waiver. (For further information on changes considered unlikely to affect bioavailability, see Section 3 of Appendix 15 (*Biopharmaceutic Studies*).

8. Site of manufacture: API

- GMP evidence for the new site, ie either the Australian manufacturing licence for a local site or current GMP clearance letter for an overseas site.
- Comparative impurity profiles data from representative batches of current and new sites of manufacture using a validated test method.
- Validation data demonstrating the suitability of the active from the new site for use in the dosage form for which it is intended, eg comparative dissolution profiles for solid dosage forms, drug mass aerodynamic particle size distribution for inhalation products, or a justification for not providing such data. Where multi-strength products are involved, comparative data for one representative strength should suffice if the various strengths are either direct-scale or their formulations are closely similar to each other.
- A DMF with accompanying *letter of access*, or a CEP with accompanying *letter of access*, or a declaration that the manufacturing process and quality control are the same as those used at the currently approved manufacturing sites, or a description of any differences between the processes at the different sites.
- Certificates of Analysis for representative batches manufactured at the new site and demonstrating the ability of the manufacturer to produce material that meets the currently approved specifications, including particle size limits and polymorphic form.

9. Site of manufacture: finished product

- GMP evidence for the new site, ie either the Australian licence for a local site or a current GMP clearance letter for an overseas site.
- A declaration that the manufacturing process is the same as that used at the currently approved manufacturing sites, or a description of any differences between the processes at the new and currently approved sites.
- Appropriate validation of the process at the new site (including validation of sterile manufacture and sterilisation processes, if applicable) to demonstrate that product manufactured at the new site meets the currently registered requirements for in process controls and the finished product specifications.
- Description and validation of quality control test methods where there is a change in test procedures or where the laboratory testing the product (site of quality control testing) has changed.

- Certificates of Analysis for representative batches of finished product manufactured at both the currently approved site and the new site. At least one batch from the new site should be full production scale unless otherwise justified, while other batches should be at least pilot scale manufactured using full production scale equipment.
- Relevant comparative data on the product (see above under *Method of manufacture: finished product*).
- Relevant stability data must be generated for batches produced at the new site as required by GMP. The TGA may request the sponsor to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to approval of the change of site. However, if stability data are not supplied, the sponsor must provide written assurance that stability data will be generated and the TGA notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new site is different from that made at the original site to the extent that the shelf-life of the medicine would be affected.

10. Source and manufacturing process change of excipients of animal origin

- For Category IV excipients [see TGA's Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)**Error! Bookmark not defined.**] used in products that are implants or products given by the parenteral, ophthalmic or intra-tracheal routes:
    - Details of the excipients and the proposed changes, and
    - Measures taken by the manufacturer to minimise TSE risks
- For Category IV excipients used in products that are given by the oral, topical, vaginal, rectal or inhalation routes, such changes are self-assessable and must be notified (see section 8 in Part B of this Appendix).
- For Category IV excipients used in any products and where the change is from an animal source to a plant or other non-animal source, the change is self-assessable and must be notified as per section 8 in Part B of this Appendix.

11. Packaging (including container shape, size and material as well as any measuring/delivery device included in the pack but excludes container type)

- Packaging and packaging materials specifications.
- If relevant, evidence that any new polymeric/rubber packaging materials used and in contact with the product are free from any leachable toxic impurities and comply with BP/Ph Eur/USP and Australian requirements for polymeric materials used in packaging of medicines.
- Up-front stability data if the packaging may be expected to be less protective than the currently approved packaging or the change may have an effect on the stability of the product. Otherwise, a commitment to generate such data according to relevant stability guidelines and in accord with GMP requirements.
- Validation data on the changed measuring/delivery device in the pack.

- Revised labelling, instructions for use and any other appropriate information/data pertinent to the change, if applicable. Revised PI, if applicable and a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.
- For sterile products, sterile manufacture information and sterility testing data, as appropriate, including, for example, validation of aseptic media fills and preservative efficacy test data.

12. Additional/Change in pack sizes

- Revised labelling, if applicable. A clean copy of the revised PI, if applicable, and a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.

13. Shelf-life and/or storage conditions

- Stability data on at least three production-scale batches to support the change. Data from a lower number or from pilot-scale batches may be acceptable if justified.
- Revised labelling, if the storage conditions are to be changed.
- A clean copy of the revised PI, if it requires changing, and a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.

14. Labelling

- Copies of both the currently approved labelling and the changed labelling.

15. Other aspects of quality data

- Appropriate supporting data relevant to the change(s) concerned.
- A clean copy of the revised PI, if changes in the text are required, and a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.

16. Change to container type

- Container specifications.
- Stability data (including physical, chemical and microbiological aspects, as applicable) from at least three production-scale batches to confirm the stability of the product in the new type of container.
- Revised labelling, if applicable.
- A clean copy of the revised PI, if changes in the text are required, and a declaration that no changes have been made to the text of the PI other than that affected by the changes requested in the application, together with a copy of the current PI with annotations of where changes have occurred.

- For sterile product, sterile manufacture information, validation of sterilisation processes, and sterility testing data as appropriate.

17. Change to trade name

- Labelling. A copy of the revised or new PI, as applicable, with a declaration that no changes have been made to the PI other than the trade name, and any other consequent changes (for example, strengths to be marketed) requested in the application, as well as a copy of the current PI with annotations of where changes have occurred.

Notes

N.1 Comparative dissolution profiles

When *comparative dissolution profiles* or a similar term is used in this document, data should be generated as follows:

- At least **12 dosage units** (for example, tablets, capsules) of each batch are tested individually and mean and individual results reported. The percentage of nominal content released is measured at a number of suitably spaced time points (minimum of three, excluding zero time point) providing a profile for each batch, for example, at 5, 15, 30 and 45 minutes, or as appropriate to achieve virtually complete dissolution. The batches are tested using the same apparatus and if possible on the same day. Test conditions are normally those used in routine quality control or, if dissolution is not part of routine quality control, any reasonable, validated method.
- To demonstrate the similarity of two dissolution profiles, the similarity factor, f_2, must be calculated using the equation and conditions stated in Appendix II of the CHMP *Note for Guidance on the investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98)[6]. The f_2 value must be within 50 to 100. In cases where more than 85% of the active is dissolved within 15 minutes in all tested batches, dissolution profiles are accepted as similar without the calculation of the similarity factor.
- Under some circumstances, insufficient recently manufactured batches may be available to meet the requirement. It would then be acceptable to test retention batches, and to explain in the test report why this was done, stating the age and storage history of the samples. See also Note N.4.

N.2 Justification as to why data on bioavailability are not required

A justification as to why data on bioavailability/bioequivalence are not required should address all the dot points under Section 4 of Appendix 15 (*Biopharmaceutic Studies*).

N.3 Pilot production batch or pilot plant scale batch

A pilot production batch or pilot plant scale batch is defined as:

[6] http://www.tga.gov.au/industry/pm-euguidelines-quality.htm

The manufacture of either active drug substance or product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale. For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full production or 100,000 tablets or capsules, whichever is the larger.

N.4 Comparative studies of changed products

Where this document requires the provision of comparative batch data (ie a comparison be made of pre- and post-variation batches), the batches compared should be at least the last three manufactured under existing conditions (using retention samples if necessary) and the first batch made under the proposed new conditions before the first batch is released. The second and third batches manufactured under the new conditions should be reviewed as soon as they become available and any differences brought to the TGA's attention promptly.

Where multiple strength products are involved and the various strengths are either direct-scales or have closely similar formulations, comparative data from just one representative strength will suffice.

N.5 Registering a separate and distinct good on the ARTG

Where a self-assessable minor formulation change is made to a product under either section B14 or B15, a new ARTG entry may be required. This means that the new product has to be registered as a separate and distinct good on the ARTG. However, due to the nature of such changes and the new formulation is intended as a replacement for the old formulation, under the provisions of the *Therapeutic Goods (Group) Order No. 1 of 2001*[1], the old Aust R number may be retained for the new product.

As soon as supply of the old product has ceased, the sponsor should advise the TGA, by writing to:

The Manager
Application Entry Team (ARTG Unit)
Drug Safety and Evaluation Branch
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Please note that the old product may not be supplied once supply of the new product commences. Should it be decided that supply of the new product will not proceed, notification in writing to this effect should be provided to the TGA.

N.6 TGA policy on use of Near Infra Red (NIR) spectroscopy

Where NIR is to be used as an identification test in either APIs or finished products, details of the requirements can be found in CHMP guidance document, CPMP/QWP/3309/01, entitled *Note for Guidance on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations.*

N.7 Provision of updated CPD

In this Appendix, the provision of an updated CPD document is generally required when a change is made to some aspects of the finished product specifications, such as to test requirements, limits of acceptance and/or test methods, for example, sections B7, B12, B14 and B15 above. Where a self-assessable change to product specifications does not involve a change to test methods, it is acceptable to the TGA to not submit details of test methods in the updated CPD document since the test methods will be assumed to be the same as those provided in the current version. However, a declaration to this effect in the relevant part of the updated CPD document must be made.

However, if this is not the case or if a current version of the CPD does not exist, then details of all test methods used must be provided with the updated CPD document.

Therapeutic Goods Administration

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Reference/Publication #