

TGA **THERAPEUTIC
GOODS
ADMINISTRATION**

PO Box 100 Woden ACT 2606 Australia
Telephone: (02) 6232 8444 Facsimile: (02) 6232 8241
ABN 40 939 406 804



Commonwealth Department of
**Health and
Ageing**

GUIDELINES ON STANDARD OF OVERSEAS MANUFACTURERS

**13th Edition
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Guidelines for the submission of an application for GMP clearance of overseas manufacturers, using evidence of the standard of manufacture and quality control of therapeutic goods manufactured outside, and imported into, Australia

Introduction

The *Therapeutic Goods Act 1989* (the Act) requires that the standard of manufacture and quality control of therapeutic goods manufactured outside Australia be taken into consideration for the registration or listing of those therapeutic goods¹ on the Australian Register of Therapeutic Goods (ARTG), unless the goods are exempt² from this requirement by the Act.

A sponsor applying to the Therapeutic Goods Administration (TGA) for registration or listing of a therapeutic good manufactured outside Australia must provide an acceptable form of evidence to show that the manufacture of the goods is of an acceptable standard³, referred to as **GMP clearance of overseas manufacturers**.

This guideline document is intended to provide information on what is regarded by the TGA as an acceptable form of evidence, and guidance for sponsors and manufacturers on the submission of that evidence to the TGA for assessment. It is not intended to provide a definitive list of forms of evidence that are considered acceptable or unacceptable.

Evidence of the standard of manufacture submitted will be reviewed by the Manufacturer Assessment Section (MAS) of the TGA and information on the standard of each manufacturing site operated by overseas manufacturers will be kept on a computer database.

The term "Manufacture" is defined in the Act to mean:

- (a) to produce the goods; or
- (b) to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

Current sponsors of therapeutic goods manufactured outside Australia will be requested on a periodic basis to provide evidence that the standard of manufacture of those therapeutic goods continues to be acceptable. It is a standard condition of registration or listing to provide this evidence when requested. Failure to supply this information may result in the product's registration/listing being cancelled.⁴

Sponsors should note that therapeutic goods being supplied under an ARTG entry may only be manufactured by the manufacturer(s) specified in the registration or listing of the products recorded on the ARTG. GMP approval is required for any additional manufacturer to be added to an existing registration or listing on the ARTG. Please note that the TGA will not accept a request from a sponsor to access GMP evidence previously submitted by or obtained for another sponsor without written authorisation from that sponsor.

Sponsors are reminded that evidence of the standard of overseas manufacturers of therapeutic goods solely for export may be requested. Sponsors should also note that TGA reserves the right to request an audit⁵ (inspection) of any overseas facility.

¹ Therapeutic Goods Act 1989 Subsections 25(1)(g) and 26(1)(g)

² Therapeutic Goods Act 1989 Subsections 25(2)(2D) and 26(2)(2C)

³ Therapeutic Goods Act 1989 Subsections 25(2)(a) and 26(2)(a)

⁴ Therapeutic Goods Act 1989 Subsection 30(2)(c)

⁵ The term "audit" is used in Australia, whereas overseas regulatory agencies tend to use the term "inspection". These two terms may be used interchangeably where appropriate.

General Information

How does GMP clearance help my application?

Many applications for registration or listing of a therapeutic good on the ARTG are either delayed or rejected due to a lack of acceptable evidence of the standard of manufacture of the therapeutic goods. Therefore, sponsors are requested to obtain GMP clearance of overseas manufacturers prior to submitting an application for registration, listing, or variation of a product.

Please note however that GMP clearance approval is required prior to submitting an application for registration, listing, or variation of a product in the following categories:

- **Listing of medicines using the Electronic Lodgement Facility (ELF);**
- **Category 3 applications for prescription medicines in which changes include overseas manufacturing sites. Sponsors are advised that because a Category 3 application has only a short statutory timeframe for completion, it will not be accepted for evaluation unless GMP clearance, where relevant, has been obtained prior to submitting the application; and**
- **Self-Assessable Notifications submitted to the Drug Safety and Evaluation Branch involving changes to or addition of new overseas manufacturing sites allowed in Appendix 8 of the Australian Guidelines for the Registration of Drugs (AGRD) Vol.1, 1994 edition or its successors.**

How do I obtain GMP clearance?

To apply for a GMP clearance of an overseas manufacturer, sponsors must complete an Overseas Manufacturer Clearance Application Form for each manufacturing site, attach the relevant evidence of the manufacturing standard (if available) and forward it to the TGA as instructed on the form.

The application form is available on MAS webpage at www.tga.gov.au/docs/html/gmphome.htm#forms. Please note that sponsors are required to only use the Dosage Forms Codes as appear in the Code Tables of SIME available at www.tgasime.health.gov.au when completing Section 5 of the application form.

The GMP clearance application and GMP evidence submitted will be assessed in accordance with the current edition of this guideline. A response detailing the result of the assessment will be returned to the sponsor. If approved, a GMP clearance letter will be issued confirming the manufacturing site address, product type according to the Corporate Codes and the manufacturing steps in manufacture, and a date prior to which new evidence must be submitted to continue the clearance approval. The sponsor should submit a copy of the GMP clearance approval letter with any relevant application to the TGA for registration, listing or variation of a medicinal product. The same GMP clearance approval letter may be used by the same sponsor to whom it is issued for other applications where the scope of manufacture is the same, provided the validity date is still current.

It is expected that applications for GMP clearance will be processed within 15 working days of receipt by MAS, provided that the correct form, information and acceptable GMP evidence are submitted.

Where the sponsor is unable to provide documentary evidence or the evidence supplied is insufficient, the sponsor may request MAS to liaise with the regulatory agency or conformity assessment body of the country in which the manufacturer is located to confirm the status of the manufacturer. A fee is payable for this service (refer Attachment 1). Sponsors should only make this request if all other options have been exhausted. Sponsors should also note that where the TGA is requested to obtain GMP evidence from an overseas regulator, the target time for GMP approval is 10 weeks, as under the Mutual Recognition Agreements (see page 6), those agencies have up to 8 weeks to respond to TGA's requests.

Other reasons why you need to obtain a GMP clearance

- Manufacturer name change.
- New site.
- Alternative manufacturer(s) for registered or listed products on the ARTG.
- New steps in manufacture for an existing product that is listed/registered on the ARTG where the overseas manufacturer has current GMP clearance approval that does not include the new steps.
- New products to be included on the ARTG if different to the clearance already obtained, eg current GMP clearance is for the manufacturing of effervescent tablet but the sponsor now wishes to include a soft gel capsule on the ARTG.

The sponsor needs to submit an application for GMP clearance setting out any of the reasons listed above, supported by current GMP evidence from an overseas regulator from one of the countries listed on page 6 of this document and the documents needed to satisfy the requirements set out on page 5. In the case where GMP documentation has not yet been issued to the manufacturer, a letter from the overseas regulator (country of origin), confirming they have been informed of the changes and that a new document will be issued in the near future, will be accepted by the TGA.

After obtaining a new GMP clearance approval, the sponsor must notify the relevant product regulator of the TGA in writing of the change. The sponsor may submit a copy of the GMP clearance approval letter with appropriate application or notification to the product regulator for approval of the change(s) made to the manufacturing site.

Other information

- Where an overseas manufacturer changes its name, evidence of the name change can be in the form of:
 - An original letter from the health authority in the manufacturer's country (being a country that Australia recognises as having a standard of GMP inspections at least equivalent to that of Australia) to certify that the manufacturer's name has changed from XXX to YYY; or
 - An original declaration from the manufacturer that its name has changed from XXX to YYY, authenticated by the health authority of that country (being a country that Australia recognises as having a standard of GMP inspections at least equivalent to that of Australia).

Where GMP evidence is not current or is about to expire, new GMP evidence should also be submitted.

- If a sponsor no longer sources a listed or registered product from a particular overseas manufacturer, the sponsor must inform the relevant product regulator of the TGA of this change in accordance with any relevant guidelines appropriate to the product. MAS does not need to be notified in this circumstance.

If the sponsor fails to take action as required above, a Section 31 letter will be generated from MAS database identifying a sponsor to be contacted to participate in an onsite audit. To ensure that a Section 31 letter is not issued, sponsors are reminded to take appropriate action as outlined above.

- If a sponsor wishes to cancel a product from the ARTG, the sponsor must notify the relevant product regulator of the TGA in writing. MAS does not need to be notified in this circumstance.
- If a sponsor wishes to use GMP evidence that has previously been submitted by the sponsor and has not expired, the sponsor should indicate the previous clearance number in the application form.

How can I track the progress of a GMP clearance application?

Contact MAS by email at gmpclearance@health.gov.au.

General requirements for GMP evidence

1. Original certificates and other relevant documents should be submitted.
2. Where an original document cannot be obtained, a copy may be submitted. All information on the copy must be clearly legible, as illegible copies will not be accepted. Copies must be notarised as true copies of the original document by an independent authority such as a Justice of the Peace, Public Notary or an official of a recognised regulatory agency or an Australian embassy or consulate office. As an example, wording for such a declaration could be:

Declaration of Authenticity

As a registered notary public for the state of (xxxx), (country xxx), I declare that the attached copy of the certificate/licence issued by (xxxx) (certificate or licence number xxxx) is a true and accurate copy of the certificate/licence presented to me for review.

Signed (xxxxx) Date (xxxxx)

3. Copies of documents originally issued by TGA need not be notarised.
4. Faxed copies of documents will not be accepted, except for documents referred to in point 3 above
5. All certificates and other supporting documents must be in English. If the document has been translated to English a statement by the translator is required. An example is as follows:

Acceptable authentication

This is an accurate translation of the original document presented to me xxxxx, on xxxx

Signed (xxxxx) Date (xxxxx)

Position

TGA may require verification of the accuracy of translated documents.

6. Documentation which has passed its date of validity will not be accepted.
 7. Document requirements:
 - a) The name of the manufacturer of the goods
 - b) The street address of the manufacturing site (PO Box is not acceptable).
 - c) The date of issue and/or expiry of the document
 - d) The product or type(s) of product as specified in the Corporate Codes and steps of manufacture at the site
 - e) Date of the last inspection
 - f) The standard of manufacture with which the manufacturer of the product complies
- Note:
- The above requirements may be satisfied by providing more than one document.
 - Unless all the above requirements have been met, the application will be rejected.
8. Sponsors should note that TGA may refuse to issue GMP approval and revoke any previous Good Manufacturing Practice (GMP) approval where evidence exists that a manufacturer does not meet an acceptable standard.

What can I do if I cannot get acceptable evidence from the manufacturer or from an overseas regulator?

Where acceptable evidence of the standard of manufacture is not available, the sponsor may request MAS to obtain evidence from a PIC/S member or an MRA partner (see page 6) if applicable. Failing these two options, the sponsor must submit an application form requesting an audit of the overseas manufacturer.⁶ The manufacturer must agree to the audit and the sponsor is required to pay the costs of the audit, including the relevant audit fee, travel and accommodation costs, before the audit takes place.

⁶ Therapeutic Goods Act 1989 Subsections 25(2) (a,b) and, 26(2)(a,b)

A guidance document and an application form for arranging audits of overseas manufacturers and a current schedule of fees are available separately from TGA website at www.tga.gov.au/docs/html/gmphone.htm#os and www.tga.gov.au/docs/html/feesach.htm respectively

Initial enquiries from sponsors wishing to arrange audits of overseas manufacturers should be directed to MAS email address gmp@health.gov.au. If necessary the telephone contact is 02 6232 8629 or fax 02 6232 8426.

What is acceptable evidence of the standard of manufacture?

Medicinal Products

Manufacturers of medicinal products must comply with the requirements of current pharmaceutical GMP equivalent to that expected of licensed Australian manufacturers of medicinal products.

Inspection by overseas regulatory authorities

The TGA will accept GMP certification only from countries that have acceptable standard of GMP. Australia is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Australia has also entered into Mutual Recognition Agreements (MRAs)⁷, which deal with conformity assessment of medicinal products, with several countries. The TGA will accept a Certificate of GMP Compliance of a Manufacturer issued by PIC/S countries or under the MRA by the Official Inspection Service (OIS) of the countries listed below.

Under the MRA arrangement, certificates can be requested from the OIS in the country of manufacture by the manufacturer or by the sponsor or by the TGA. Certificates to be used as GMP evidence should comply with the general requirements for evidence outlined above.

The TGA will consider the certification to remain current until the date of expiry of the certificate. Where no expiry date is stated, the certification will be considered to remain current for a period of three years from date of issue.

The standard of GMP inspections of the relevant regulatory agencies in the following countries are considered by the TGA to be acceptable:

MRA Countries

Austria
Belgium
Denmark
Finland
France
Germany
Greece
Iceland
Ireland
Italy
Liechtenstein
Luxembourg
Netherlands
New Zealand
Norway
Portugal
Singapore
Spain
Sweden
United Kingdom

PIC/S Members

All MRA countries on the left except Luxembourg and New Zealand
Canada
Czech Republic
Hungary
Malaysia
Romania
Slovak Republic
Switzerland

Others

Japan
USA – see *Inspection by the US FDA* below

⁷ Agreement on Mutual Recognition in relation to Conformity Assessment, Certificates and Markings between Australia and the European Community. A copy of this document is available on the internet at <http://www.ecdel.org.au/agreements/mra.htm>

For lists of addresses:

- MRA members - www.tga.gov.au/docs/html/gmphome.htm; and
- Pharmaceutical Inspection Corporation Scheme (PIC/S) members - www.picscheme.org

Inspection by the US FDA

For companies inspected by the FDA, an acceptable rating for an inspection of the appropriate profile class (manufacturing process) by the FDA within the last three years is considered satisfactory evidence of GMP. If no such FDA inspection has been undertaken in the past three years then the sponsor will need to make other arrangements to provide GMP evidence.

The TGA has access to the FDA GMP computer database FACTS. This allows the TGA to determine the GMP status of manufacturers inspected by the FDA.

The TGA does NOT regard the following as evidence of an acceptable GMP standard:

- A copy of an annual product registration certificate, eg a 510{k} or copy of an Annual Registration of Drug Establishment Certificate;
- An FDA Form 482 and 483; and
- A letter stating that no Form 483 was issued.

The TGA is aware that the FDA does not issue any document that complies with the TGA requirements. If a sponsor wishes to use GMP evidence from the FDA, the sponsor may request MAS to search the FDA database (fee applies)

Active Pharmaceutical Ingredients (APIs)

At the present time, evidence of compliance with GMP for API manufacture is only required for registrable drugs evaluated by the Drug Safety and Evaluation Branch of the TGA.

If all steps are not carried out at a single site, the company that carries out the final steps of manufacture, purification, milling and sterilisation (if applicable) of the bulk active ingredient is responsible to ensure that key intermediates are also manufactured in accordance with GMP. Separate GMP certification need not routinely be supplied for the manufacturers of these intermediates. However, the TGA reserves the right to request evidence of GMP compliance for the manufacturers of critical intermediates if deemed necessary.

The TGA will accept GMP certification from the countries listed on page 6, which include a reference to active pharmaceutical ingredients, active raw materials or bulk drug material. In addition, an acceptable rating for the relevant profile class on the FDA FACTS database for manufacturing of bulk drugs is acceptable evidence of GMP compliance. In the case of FDA inspections outside the USA, the sponsor must provide objective evidence that the scope of the inspection included the relevant API(s). For example, a copy of the Establishment Inspection Report may be provided.

Some European countries have not yet commenced applying GMP to manufacturers of APIs, thus creating difficulty for Australian sponsors wishing to obtain GMP evidence. If certification is not readily available, sponsors may request the TGA to obtain certification directly from the relevant regulatory agency. However, sponsors should note that a fee is payable for this service (refer Attachment 1) and it may take up to 8 weeks to obtain certificates from those regulatory agencies, bringing the target timeframe for application processing to around 10 weeks.

Other therapeutic goods that are not medicines or medical devices

1. Therapeutic Devices

For existing therapeutic device manufacturers, of which Quality System (QS) has been assessed by MAS prior to 4 October 2002 and the sponsor wishes to update the QS status of the overseas manufacturer, the following documents will be accepted. This evidence can only be used in relation to therapeutic devices that were supplied on the ARTG prior to 4 October 2002 or otherwise are to be dealt with under Chapter 3 in accordance with the transitional arrangements.⁸ Any other product would be considered a new product and must meet the requirements of the new medical device legislation. Sponsors of such products would need to apply through the Device Electronic Application Lodgement (DEAL).

A. Products that are CE marked

For products certified (CE marked) as complying with the requirements of the European Medical Devices Directive (93/42/EEC), or the European Active Implantable Medical Devices Directive (90/385/EEC), current certificates issued by the European Notified Body and that indicate the manufacturer complies with the requirements of Annex II (2) Section 3 or with the requirements of Annex V (5) Section 3 will be accepted.

As the above certification includes specific controls over sub-contractors (including contract sterilisers), certification of the manufacturer will usually also cover these sub-manufacturers. However, TGA reserves the right to request further information on any sub-contractor if deemed necessary.

Sponsors should note:

- The scope of the certification must be relevant to the product.
- The certificate must be issued by a designated Notified Body in accordance with the European Medical Devices Directives. The Notified Body's number must appear on the certificate.
- An EC Type-Examination Certificate (Annex III) or Design Examination Certificate (Annex II Section 4) is not acceptable as evidence of an acceptable quality system.
- EC certification will be considered current until the expiry date of the certificate, or if no expiry is stated, 5 years after the issue date of the certificate.

For a current list of Designated Notified Bodies under the European Medical Devices Directives – see website www.europa.eu.int/comm/enterprise/newapproach/legislation/nb/en93-42-eec.pdf

B. Products not CE marked

FDA database profile classes will be considered and must be accompanied by a copy of the Establishment Inspection Report or other inspection reports that indicate the scope of the inspection. Other evidence such as EN46001/2 will also be considered, if a product is not CE marked.

An acceptable rating for an inspection of the appropriate profile class (manufacturing process) by the FDA within the last three years is considered satisfactory evidence of QS. If no FDA inspection has been undertaken in the past three years then the sponsor will need to make other arrangements to provide GMP evidence.

The TGA does NOT regard the following as evidence of an acceptable GMP standard although they may be useful as supporting documentation:

- A copy of an annual product registration certificate, eg a 510{k} or a copy of an Annual Registration of Device Establishment Certificate;
- An FDA Form 482 and 483; and
- A letter stating that no Form 483 was issued.

⁸ Therapeutic Goods Act 1989 Subsections 15A

2. In-vitro Diagnostics (IVDs)

For IVDs that are CE marked by a Notified Body according to the In-Vitro Diagnostic Medical Devices Directive (98/79/EC), certificates that indicate that the manufacturer complies with the requirements of Annex IV Section 3 or Annex VII of the Directive, will be accepted. In addition, EN46001 (or ISO 13485) certificates issued by recognised notified bodies will also be acceptable. See web site for the current list of designated Notified Bodies under the European Medical Devices Directives at www.europa.eu.int/comm/enterprise/newapproach/legislation/nb/notified-bodies.htm

3. Devices of human origin and or devices containing viable animal tissues

For sponsors of manufacturers who manufacture devices of human origin and/or devices containing viable animal tissues a TGA audit is required.

General Information

Sponsors of new medical devices to be “included” on the ARTG or medical devices to be transferred from registered/listed product(s) to “included” medical devices on the ARTG, please note:

- New medical devices cannot be entered on the ARTG until sponsors have lodged QS evidence (evidence of conformity) through DEAL.
- Products being transferred from registration/listing to inclusion cannot be entered on the ARTG until sponsors lodged QS evidence (evidence of conformity) through DEAL.
- Continuation of QS evidence for a registration/listing of a therapeutic device entry is only valid if it is in relation to a good that was registered or listed prior to 4 October 2002 (or otherwise within the transitional arrangements under s15A).
- See guideline documents for new regulations for medical devices at www.tga.gov.au/devices/devices.htm.

Acronyms

API	Active Pharmaceutical Ingredients
ARTG	Australian Register of Therapeutic Goods
DEAL	Device Electronic Application Lodgement System
ELF	Electronic Lodgement Facility
FACTS	Field Accomplishment and Compliance Tracking System
GMP	Good Manufacturing Practice
IVD	In-vitro Diagnostics
MAS	Manufacturer Assessment Section
MRA	Mutual Recognition Agreement
PIC/S	Pharmaceutical Inspection Cooperation Scheme
QS	Quality System
US FDA	United States Food and Drug Administration

Fees applicable to GMP clearance of overseas manufacturers

- **Fee for assessment of GMP evidence** – applicable to each application for GMP clearance of overseas manufacturers. This fee covers the period of approval given for the evidence provided.
- **Fee for obtaining GMP evidence** - this fee is in addition to the assessment fee and applicable only if the TGA is requested to obtain evidence of GMP compliance of an overseas manufacturer from a TGA Mutual Recognition Agreement partner or the US FDA. The fee applies to every application with such a request.
- **Fee for reinstatement of GMP approval** – applicable to approval of an overseas manufacturer that has been allowed to expire and a subsequent application for assessment is made. The TGA will notify sponsors at least 3 months before expiry to allow time for the sponsor to provide the TGA with current GMP evidence to support a new application.

Note:

1. If a GMP clearance approval has been granted prior to or during a registration process and the approval expires before the registration is finalised, no additional fees will be charged for an assessment or obtaining of further GMP evidence to support the ongoing approval.
2. Changes to any aspects of the GMP approval already given are considered a new application for assessment. Changes include:
 - Manufacturer name change.
 - New site.
 - Alternative manufacturer(s) for registered or listed products on the ARTG.
 - New steps in manufacture for an existing product that is listed/registered on the ARTG where the overseas manufacturer has current GMP clearance approval that does not include the new steps.
 - New products to be included on the ARTG if different to the clearance already obtained, eg current GMP clearance is for the manufacturing of effervescent tablet but the sponsor now wishes to include a soft gel capsule on the ARTG.
3. The above fees are effective from 1 July 2003. The current fees appear on the Summary of Fees And Charges on the TGA website at www.tga.gov.au/docs/html/feesach.htm.