Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

AUSTRALIAN REGULATORY GUIDELINES

MANUFACTURING QUALITY

Good Manufacturing Practice (GMP) Clearance for Overseas Manufacturers

September 2010

Draft for consultation

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GMP Clearance for Overseas Manufacturers

1. Introduction

These guidelines have been developed to provide information about the process of obtaining and maintaining Good Manufacturing Practice (GMP) clearances for the manufacturing steps of medicinal products including Active Pharmaceutical Ingredients (APIs) that are carried out overseas. They describe the approach of the Therapeutic Goods Administration (TGA) to granting approvals in relation to these manufacturing steps and the documentation required for the assessment of applications for those approvals.

The main objective of the *Therapeutic Goods Act 1989* (the Act) is to ensure the safety, quality, efficacy and timely supply of therapeutic goods for Australian consumers. With the increasing number of overseas suppliers and the growing complexity in supply chains, Australian consumers are entitled to be confident that manufacturers located outside Australia are subject to equivalent standards of oversight to those applying to Australian manufacturers.

Therapeutic goods that are medicines (medicinal products) supplied in Australia are required to be included on the Australian Register of Therapeutic Goods (ARTG) by a process of registration or listing[1]. The Office of Medicines Authorisation in the TGA issues a marketing authorisation for a medicinal product when it is included in the ARTG.

Under sections 25(1)(g) and 26A(3) of the Act a sponsor seeking registration or listing of a medicinal product must supply evidence that each overseas manufacturer involved in the manufacture of the product has satisfactory manufacturing and quality control procedures in place[2]. It is also a condition of ongoing registration and listing that such evidence is maintained[3]. These rules apply if, had the goods been wholly manufactured in Australia, the Australian manufacturer would be required to hold a manufacturing licence under the Act.

The TGA makes a decision about whether the overseas manufacturer complies with the *Manufacturing Principles* (or equivalent international standards for overseas

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[1] Note: Under the *Therapeutic Goods Act 1989* some therapeutic goods are not required to be included on the ARTG.

[2] The requirements in the Act vary, based on whether the final products are required to be registered or listed in the Register. For registered goods, section 25(1)(g) states:

> 25 Evaluation and registration of therapeutic goods
>
> (1) … the Secretary must evaluate the goods for registration having regard to:
>
> ...
>
> (g) if a step in the manufacture of the goods has been carried out outside Australia - whether the manufacturing and quality control procedures used in the manufacture of the goods are acceptable;
>
> ...

For listed goods, section 26A(3) states:

> 26A Listing of certain medicines
>
> (3) Subject to subsection (7), if a step in the manufacture of the medicine has been carried out outside Australia, the Secretary must have certified, prior to the application being made, that the manufacturing and quality control procedures used in each such step are acceptable.

[3] Under section 28 of the Therapeutic Goods Act sponsors are required to maintain evidence of GMP Compliance of an overseas manufacturer as a standard condition of registration or listing of a therapeutic good. Paragraph 23 of the Standard and Specific Conditions applying to Registered or Listed Therapeutic Goods determined under section 28(2) states:

> 23 Goods Manufactured Overseas
>
> Where the registered/listed goods are imported goods which if manufactured in Australia would be required under the provisions of the Act to be manufactured in licensed premises, the sponsor of the goods shall, upon request at any time by the Secretary or the Secretary's delegate appointed for the purposes of section 31 of the Act, provide to the National Manager, Therapeutic Goods Administration, an acceptable form of evidence which establishes the standard of manufacture of the goods. If this is not available, the sponsor shall pay the costs of an inspection of the principal Manufacturer of the goods by Australian inspectors where this is considered necessary by the Secretary or the Secretary's delegate referred to in this paragraph.

Manufacturers).[4] This approval process and the issuing of a document that confirms that approval is known as **GMP Clearance**. For the purposes of undertaking GMP Clearance, the TGA considers an application by the sponsor and evidence from a number of sources.

The TGA has established a range of international agreements to facilitate the efficient and effective management of its regulatory compliance programs and reduce the regulatory burden on industry. They include:

- **Mutual Recognition Agreements** (MRA) that are treaties between Australia and other countries and are enforceable under international law, and
- **Memoranda of Understanding** (MOU) that are agreements between the TGA and regulatory agencies of other countries that facilitate the exchange of information.

The parties to an MRA recognise and accept the certification issued by the relevant regulatory agency in each country in relation to manufacturers located within that country.[5]

An overseas GMP Clearance can be granted by the TGA to a sponsor on the basis of GMP Compliance evidenced by any one of the following:

- A GMP Certificate issued by a country with which Australia has an MRA in relation to the relevant overseas manufacturing site.
- A Compliance Verification assessment of a recent GMP inspection report of the relevant overseas manufacturing site prepared by a competent overseas regulatory agency acceptable to the TGA, together with supporting manufacturing documentation supplied by the sponsor or manufacturer.
- A GMP Certificate issued by the TGA following an on-site audit of the relevant overseas manufacturing site.

The TGA reserves the right to undertake an audit of an overseas manufacturing site, irrespective of any other evidence supplied. An audit may take place prior to granting an initial GMP Clearance for supply of the relevant product in Australia or at any time following the issue of a GMP Clearance.

Overseas GMP Clearances are granted for a specified time period. Sponsors must monitor the expiry date of GMP Clearances for all overseas manufacturers used and submit further applications with either supporting GMP evidence or a request for a TGA on-site audit of relevant overseas manufacturing sites **before** the current GMP Clearance expires.

As the TGA is required to recover the full cost of its regulatory activities, sponsors are required to pay to have an application for GMP Clearance assessed. Audit fees apply if the TGA carries out an overseas audit.

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[4] On 1 July 2010, the TGA adopted the PIC/S Guide to GMP for Medicinal Products, January 2009 – PE 009-8, for both Medicinal Products and APIs. This standard replaces the Australian Code of Good Manufacturing Practice for Medicinal Products 16 August 2002, the ICH Q7 Guideline and the Code of Good Manufacturing Practice for Sunscreen Products.

[5] The countries with which Australia has Mutual Recognition Agreements and the scope of the products covered by these agreements can be viewed at: www.tga.gov.au/international/index.htm#intagree. The mutual recognition of certificates is limited to manufacturers within the country of the issuing authority. MRA Certificates for manufacturers outside the regulator's country can be used as supporting evidence in conjunction with other documentary evidence as outlined in tables 1a and 1b.

The relevant fees and charges, including the basis of calculating fees, are located on the TGA website at www.tga.gov.au/docs/html/feesach.htm

TGA Contact Details

For further assistance, contact the TGA GMP Clearance Unit:
Tel - 1800 446 443
Fax - (02) 6232 8426Email - gmpclearance@tga.gov.au

GMP Clearance Unit
Office of Manufacturing Quality
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2600

To arrange for an audit of an overseas manufacturer, contact the TGA Licensing and Certification Unit

Tel - 1800 446 443
Fax - (02) 6232 8426
Email - gmp@tga.gov.au

Regulatory information

Information can be obtained from the Office of Medicines Authorisation about the circumstances in which a GMP Clearance is required for a particular activity involved in manufacturing a finished product or an API.

Sponsors can seek information or advice from an agent or regulatory consultant concerning the requirements for submitting an application for a clearance and/or the suitability and compliance of an overseas manufacturing site.

The TGA does not endorse agents or regulatory consultants. Further details concerning agents or consultants can be obtained from various industry associations or the Association of Therapeutic Goods Consultants Inc.

2. Responsibilities of Australian sponsors of medicines manufactured overseas

The key responsibilities of Australian sponsors of medicines that use overseas manufacturers in relation to GMP Clearances are listed below. Please note this list is not exhaustive and sponsors should satisfy themselves that they have done all that the relevant legislation and guidelines require.

A sponsor who proposes to seek market authorisation for supply in Australia through the registration or listing of the product on the ARTG or who has a product registered or listed on the ARTG is responsible for:

- Providing to the TGA relevant evidence of GMP compliance for the purposes of obtaining the marketing authorisation to supply medicinal products in Australia;
- Maintaining evidence of GMP compliance of all overseas manufacturing sites used in the manufacture of the registered or listed medicine, and notifying the TGA immediately of any changes in circumstances or regulatory compliance of the overseas manufacturer.[6]
    - Sponsors are responsible for all overseas manufacturing sites nominated in their Clearance applications at all times.
    - Sponsors are required to advise the TGA of any "significant changes" to the manufacturing site, QMS, products or product range (these are changes that could potentially affect GMP compliance) – changes may also require a variation application for the sponsor's listing or registration on the ARTG.
    - Sponsors should monitor regulatory actions by any competent overseas regulatory agency (i.e. recalls, unacceptable inspection findings, warning letters) that involves any overseas manufacturer used by the sponsor.
    - Sponsors must notify the TGA as soon as the overseas manufacturing site is no longer used and is not intended to be maintained as an alternative manufacturer.
- Establishing and maintaining GMP contracts with manufacturers with which the sponsor has a direct relationship. Sponsors are not expected to have a GMP contract with a manufacturer's sub-contractors[7].
- Ensuring that all required documents are submitted electronically with applications for GMP Clearance.
    - Incomplete applications may be rejected.

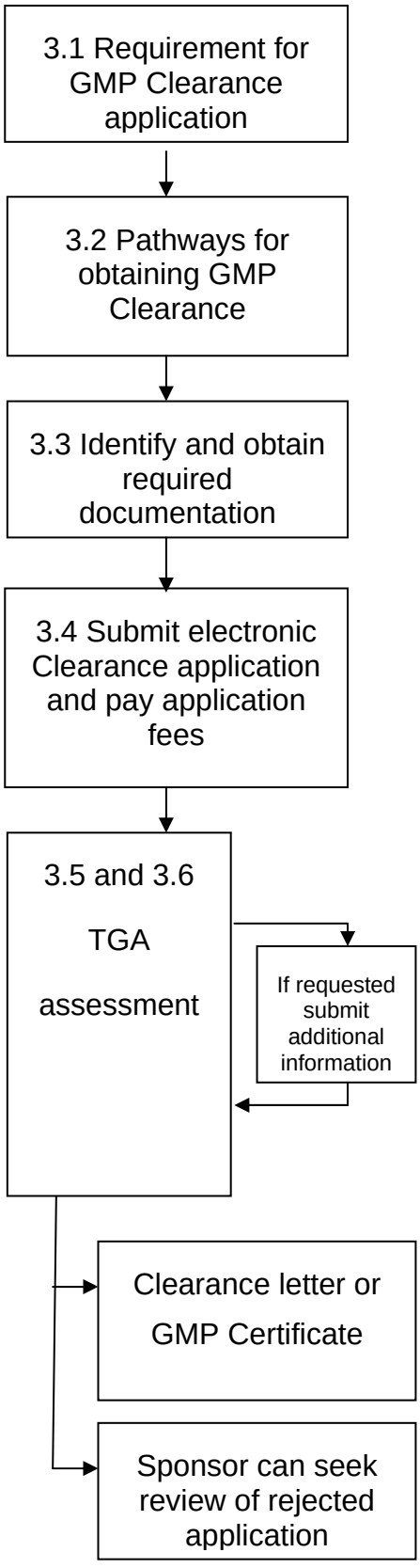
[6] The TGA is introducing a Periodic Manufacturer Update form to assist sponsors in meeting this responsibility.

[7] GMP contracts between principal manufacturers and sub-contractors are required by the code of GMP

- Remitting all application fees at the time of lodging an application for GMP Clearance (refer to Schedule of fees at www.tga.gov.au/docs/html/feesach.htm).
    - Initial processing of an application will not commence until payment of the application fee has been received.
    - Any applicable assessment fee invoiced to the sponsor must also be paid before assessment of an application can commence.
- Promptly submitting any additional information requested by the TGA during an assessment.
    - Failure to provide required documents in the time requested by the TGA may result in the application being rejected without a refund of fees paid.
- Submitting applications for renewal of a GMP Clearance at least three months prior to the expiry of the current Clearance.
    - This allows time for scheduling an overseas audit should it appear during the assessment that such an audit is required.
    - A separate application is required for each overseas manufacturing site used in relation to each registered or listed medicine of the sponsor.

3. GMP Clearance process

Figure 1 - Overview of the GMP clearance process



A separate application is required for each sponsor and for each overseas manufacturing site. Applications are required for renewals, changes to scope, changes to steps of manufacture and major facility changes.

Assessment of an application is based on the following evidence:

- Mutual Recognition Agreements (MRA)
- Compliance Verification (CV)
- a TGA on-site audit

(Applications for a TGA audit will not be accepted while an MRA or CV assessment is in progress.)

The extent of the review process increases with product risk and the complexity of manufacture.

Refer to Tables 1(a) and 1(b).

Incomplete applications can be rejected.

Refer to the current 'schedule of fees' at www.tga.gov.au/docs/html/feesach.htm. Additional fees may be payable if the TGA is requested to obtain evidence from an overseas regulator or if the application is subject to a CV.

TGA target timeframes:

MRA: 15 working days.

CV: 30 days (non-sterile, most API); 90 days (sterile, Biological API's).

TGA on-site audit: conducted within 6 months.

TGA may request additional information.

Application may be rejected if information is not supplied within due dates.

Sponsor is issued a GMP Clearance letter following a successful MRA or CV assessment or a TGA on-site audit. A Certificate of GMP Compliance may be issued to the manufacturer following a successful TGA on-site audit.

A request for an internal review by the Minister's delegate of a TGA clearance must be received within 60 days of notification of the TGA decision.

3.1. GMP Clearance application requirements

GMP Clearance

GMP Clearances are required for all the steps of manufacture of registered and listed medicinal products (including APIs used for the manufacture of registered products) before the products can be supplied in Australia.

Although the TGA does not currently require sponsors to submit Clearance applications for APIs used in listed medicines or registered over-the-counter (OTC) medicines, sponsors must ensure that any step of manufacture undertaken outside of Australia are manufactured in GMP compliant facilities.

Renewing a GMP Clearance

GMP Clearances relating to overseas manufacturers are provided for a specified period and have an expiry date. Sponsors must therefore apply periodically to renew their clearances for overseas manufacturing sites for as long as they continue to use that manufacturer. This permits the TGA to review the manufacturing and quality controls and provide continuous confidence to the public of the manufacturer's compliance with relevant international GMP standards.

Changes to a GMP Clearance

The TGA expects sponsors to remain vigilant in ensuring the regulatory compliance of the overseas manufacturing sites they use. When a sponsor becomes aware of a need to change or renew a GMP Clearance, a new application with all required documentation must be submitted, and applicable fees paid.

Examples of circumstances where a sponsor may need to amend or cancel a GMP Clearance include:

- If products are transferred between sponsors; an amendment of the Clearance must be requested within 3 months from the date of transfer.
    - Where products on the Register have been transferred to another sponsor, the new sponsor must provide the details of all affected clearances (products, MIS clearance numbers etc.) and enclose a letter from the transferring sponsor indicating assent to the clearance transfers. A copy of any sale/transfer agreement may also be acceptable.
    - Each sponsor must have a GMP contract with each manufacturer with whom they have a direct relationship.
    - There is no need to submit a new clearance application as long as the clearances in question are current.

      Note: There is currently no fee attached to this change.
- A change in the trading name of an overseas manufacturer following a change in ownership.

- Sponsors should provide a copy of the certificate of registration or a letter from the registrar in the manufacturer's country confirming the change of name[8].

  Note: There is currently no fee attached to this change.

- Changes in the scope of manufacture of the existing GMP Clearance, for instance where the Current GMP Clearance is for the manufacture of hard capsules and the sponsor now wishes to include soft gel capsules.
  - A new GMP Clearance application must be submitted. Fees are payable.
- New manufacturing site or a new manufacturing facility at the existing site.
  - A new GMP Clearance application must be submitted if manufacture for supply to Australia is to occur at the new site/facility. Fees are payable.
- Supply of products from the manufacturing site ceases.
  - The sponsor should notify the TGA GMP Clearance Unit in writing and the clearance will be cancelled.

    Note*:* There is currently no fee attached to this change.
- Significant new steps, or significantly different technology, in the manufacture of an existing product on the ARTG where the overseas manufacturer has current GMP Clearance approval that does not include the new steps or technology. (e.g. fermentation in addition to chemical synthesis for an API Manufacturer).
  - A new GMP Clearance application must be submitted. Fees are payable.
- A reduction in the scope of a GMP Clearance may be required where the manufacturing site decommissions facilities, or has ceased manufacture as a result of regulatory actions by an overseas agency. Sponsors should monitor their manufacturers and communicate these changes to the TGA promptly.
  - The sponsor should notify the TGA GMP Clearance Unit in writing and the clearance will be amended.

    Note*:* There is currently no fee attached to this change.

Extension of a GMP Clearance

A short term extension (generally 3 to 6 months) to a GMP Clearance may be granted under certain circumstances at the request of a sponsor. The circumstances might include for instance when an inspection has taken place (or is scheduled to take place) and there is a delay in the issuing of the GMP Certificate and/or inspection report. Documentation indicating the scope of the proposed inspection is relevant and should be supplied to the TGA when the application for extension is made.

The reasons for the extension must be clearly set out and relevant supporting documentation provided. Sponsors should not expect that the TGA will grant an extension where the application is made after the Clearance has expired.

[8] If either of these is are not available, a declaration from the manufacturer on its letterhead stating the change in the manufacturer's name may be accepted

Where an inspection report or other documentation received after an extension has been granted is found by the TGA to be unacceptable, any extension to a GMP Clearance previously granted may be cancelled.

3.2. Pathways for obtaining GMP Clearance

A GMP Clearance of an overseas manufacturer will always be based on the assessment of evidence of GMP Compliance that includes a recent inspection of the manufacturer by a competent regulatory agency.

There are three procedures used to grant a GMP Clearance:

- under a Mutual Recognition Agreement (MRA);
- through Compliance Verification (CV); or
- after a TGA on-site audit.

The available procedure for assessment will depend on:

- whether the TGA has agreements with the regulatory agency that has inspected a manufacturing site;
- where the site is located;
- the TGA's level of confidence of compliance with an equivalent Code of GMP demonstrated by the evidence submitted by the sponsor;
- the type of product or manufacturing steps undertaken at the site; and
- the timing of the inspection.

GMP Clearances issued under a Mutual Recognition Agreements (MRA)

In accordance with international agreements with certain countries, the TGA accepts compliance of an overseas site with the local GMP requirements based on a current GMP Certificate issued by the regulatory agency of the other party to the MRA.

Clearance may be granted by the TGA on the basis of a current GMP Certificate issued within the scope of a MRA agreement.

MRA-based assessments are limited to GMP Certificates issued for manufacturing sites located within the borders of the other party to the MRA.

The scope of the manufacturing activities for which approval is sought in the Clearance application should be within the scope of the activities covered by the GMP Certificate.

A list of countries with which Australia has an MRA is at **Appendix B**

Copies of relevant MRA's are available on the TGA's internet site at www.tga.gov.au/international/index.htm#intagree.

GMP Clearances issued through GMP Compliance Verification (CV)

Compliance Verification involves a detailed assessment by the TGA of specified documentary evidence supplied by the manufacturer/sponsor. The assessment will include a review of recent inspection reports of the relevant manufacturing site undertaken by a competent overseas regulatory agency together with other available regulatory information.

The documentation required for these assessments is listed in Tables 1(a) and 1(b) below.

More detailed assessments are undertaken for higher risk products or if the inspection reports from overseas regulatory agencies identify marginal GMP compliance.

TGA on-site audit

If a sponsor is unable to provide current documentary evidence of the GMP Compliance for an overseas manufacturer or the TGA's assessment of evidence does not support a GMP Clearance, the TGA will conduct an on-site audit. Clearance will be granted by the TGA if the audit concludes that the facility operates at an acceptable level of GMP compliance.

3.3. Identify and obtain the required documentation

The following tables set out the assessment methods available and documentation required for the assessment of GMP Compliance for medicines and APIs where a step in the manufacturing process is carried on outside Australia.

Table 1(a) identifies the method of assessment and applicable list of evidence required (Evidence List) where a Compliance Verification is required. Note that GMP Clearances are required where contracted laboratory and sterilisation services are engaged to support the release of a product or API.

Table 1 (a) – Required assessment type

Current Certification Product/ Activity	MRA Regulator (own country)	US FDA (all locations) or PIC/S Regulator (own country) or MRA Regulator (outside own country)	PIC/S Regulator (outside own country) or other Regulator or no certification
Listed medicines **(see note below)**	MRA Clearance Evidence List A	Compliance Verification Evidence List B	TGA on-site audit
Registered medicines (non-sterile) **API (non sterile)**	MRA Clearance Evidence List A	Compliance Verification Evidence List B	TGA on-site audit
Registered medicines (sterile) **API (sterile and biotech)**	MRA Clearance Evidence List A	Compliance Verification Evidence Lists B and C	TGA on-site audit
Contract testing laboratories **Contract sterilisers**	MRA Clearance Evidence List A	Compliance Verification Evidence List D	TGA on-site audit

***Note**:* A TGA on-site audit will always be required where the sponsor's listed or registered medicine is not regulated by the regulatory agency of the country in which the manufacturing site is located. **Complementary Medicines and Traditional Chinese Medicines** are commonly not regulated as medicines in other countries.

Table 1(b) lists the specific documents required for the Compliance Verification assessment. Explanatory notes for some of these documents are set out in **Appendix C**.

Table 1(b) – Documentary evidence requirements

	Required Evidence	Comments/Exclusions
Evidence List A	Current GMP Certificate. (GLP for testing laboratory, certification to relevant ISO Standards for sterilisation facility).	Certificates must be sufficient to cover the scope of the Clearance application.
Evidence List B **Compliance Verification** **for:** **APIs (other than sterile and biotech)** **Non-sterile medicines**	Current GMP Certificate.	GMP contracts may be requested if the overseas manufacturer performs the release for supply function.
	A list of all regulatory inspections conducted within the past 3 years and a copy of the most recent inspection report. (Processing can be expedited if reports for two or more of the above inspections are provided).	Inspection reports must be applicable to the scope of the application. These may be sent to the TGA directly from the manufacturer.
	Details of any regulatory actions in past 3 years.	For example, product alerts, warning letters, import alerts, recalls due to defects.
	Site Master File, Quality Manual or equivalent.	Not required if the scope of the application is only for the step of release for supply.
	GMP contract between the sponsor and the manufacturer.	Only applicable to products and related steps of manufacture in the Clearance application. Not required for APIs unless requested.
	List of products intended for supply in Australia.	
	Copy of the procedures for release for supply of products included in the Clearance application).	Not required for APIs unless requested. An applicant may also be requested to provide a Validation Master Plan or Product Quality Review (applicable to Finished Product medicines included in the Clearance application).
Evidence List C **Compliance Verification** **for** **Finished sterile medicines** **and** **Sterile and biotech APIs**	Validation Master Plan.	Not required if the scope of the application is only for the step of release for supply.
	Latest Product Quality Review.	Applicable to products and API's listed in the Clearance application only.

	Required Evidence	Comments / Exclusions
Evidence List D **Contract testing laboratories** **Contract sterilisers**	Current GMP Certificate.	For contract testing laboratories a Good Laboratory Practice (GLP) certificate issued by a recognised Regulatory Authority or a current ISO 17025 accreditation certificate may be used in lieu of a GMP Certificate. For contract sterilisation facilities certification to applicable ISO sterilisation standards (eg ISO 11137, ISO 11135) may be used in lieu of a GMP Certificate.
	A list of all regulatory inspections conducted within the past 3 years, and a copy of the most recent inspection report. (Processing can be expedited if reports for two or more of the above inspections are provided.)	Inspection reports must be applicable to the scope of the application. These may be sent to the TGA directly from the manufacturer.
	Details of any regulatory actions in past 3 years.	For example, product alerts, warning letters, import alerts, recalls due to defects.
	Quality Manual/Laboratory Manual or equivalent.	
	GMP contract between the sponsor and the contract test laboratory or steriliser.	For contract test laboratories and 3rd party sterilisation companies sub-contracted by an overseas manufacturer, a contract/ agreement may not exist with the Australian sponsor. A copy of the agreement between the manufacturer and contract test laboratory should be submitted in such a case.
	A list of tests a laboratory is authorised to perform. For botanical ingredients, evidence that authenticated standard reference materials are used.	For contract testing laboratories only.

***Note**:* Adequate supervisory control of contract testing laboratories or contract sterilisers by a principal manufacturer through a validated supplier qualification process may be accepted on a case-by-case basis. In such cases, the same expiry period will be assigned as for the "principal manufacturer". If a TGA on-site audit is required of the principal manufacturer then this may also include an audit of the contract test laboratories under its supervisory control.

General documentary requirements

Documentary evidence must adhere to the following requirements:

- all certificates and other supporting documents must be in English;
- translated documents must be accompanied by a signed and dated statement, by the certified translator, stating that it is a true and accurate translation of the original document;

- documents must be the most recent and reflect current manufacturing conditions and practices and dated (expired/superseded documentation cannot be used);
- documents must provide sufficient information to cover the scope of products for which clearance is sought; and
- documented evidence must be unambiguous, clearly demonstrating that the overseas manufacturer operates with an adequate level of GMP Compliance (ambiguous material will be disregarded).

All documents may be submitted electronically.

The TGA can request certified copies of original documents at any time. Certified copies must be legible and authenticated as true copies by any one of the following:

- an official of the regulatory agency of a country that is a party to an MRA or is a Memorandum of Understanding (MOU) partner;
- an Australian embassy or consulate office; or
- a Justice of the Peace, Public Notary or a lawyer, solicitor or accountant in the country of the manufacturer (include details of the relevant practice certificate or licence number).

The following is an example of a declaration that should appear on the front page of the document being certified:

Declaration of Authenticity *As a ……. for the state of (xxxxx), (country xxxxx), I declare that the attached copy of the document issued by (xxxxx) (certificate) is a true and accurate copy of an original certificate presented to me for review.* *Signed (xxxxx) Date (xxxxx)*

GMP Certificates

GMP Certificates provided with an application must be:

- current, and whenever possible, it must be not more than 2 years since the date of the last inspection in order to avoid a short expiry date on a GMP Clearance;
- for the products, APIs, steps of manufacture and/or dosage forms requested in the GMP Clearance application; and
- clear in identifying the expiry date and the name of the person authorised to issue the certificate and be duly signed and dated.

For MRA-based applications, GMP Certificates must also be:

- issued by a regulator of an overseas country that is a party to the MRA; and
- relate to a manufacturing site located within the borders of that country.

Where the sponsor has been unable to obtain the GMP certification issued by the MRA country, the sponsor may request that the TGA attempt to obtain evidence from the relevant MRA regulator. An additional fee is payable for this service.

Manufacturer's declarations for Active Pharmaceutical Ingredients

Sometimes various types of APIs are produced using similar manufacturing processes and the same quality system. A GMP Certificate for a site issued by another overseas regulatory agency may only list one or some of the APIs which are of interest to the country inspecting the site.

The TGA therefore permits a sponsor to submit a declaration consisting of a dated and signed letter from the manufacturer that the API for which a clearance is sought is manufactured by the same process, in the same plant and under the same quality system as those specified on a GMP Certificate. The form for a manufacturer's declaration is in **Appendix D** (Manufacturers Declaration for APIs).

If such a declaration cannot be submitted in these circumstances, a TGA on-site audit may be required.

Documents for a TGA on-site audit

A TGA on-site audit of an overseas manufacturer will be required where:

- the evidence supplied is inadequate to support clearance for supply to the Australian market, or
- where there has not been a recent inspection by a recognised competent regulatory agency covering the scope of the GMP Clearance application, or
- where GMP compliance was rated as unacceptable by another regulatory agency.

After receiving an application, but prior to confirming an audit, the TGA will require the Site Master File (SMF).

The SMF provides an overview of the manufacturer, its manufacturing activities and its quality system. The SMF is necessary to allow effective planning of the audit.

Guidance for preparing a SMF can be found in PIC/S document PE 008, *Explanatory Notes for Industry on the preparation of a Site Master File* that is available at: www.tga.gov.au/docs/html/siteinfo.htm.

Sponsors may submit other documents from the manufacturer, such as a Plant/Equipment File or a Quality Manual, which individually or collectively provides the same details.

Where the TGA will be undertaking an initial audit in a non-English speaking country, translated copies of the following will be required:

- Validation Master Plan.
- Deviation/Out of Specification Procedures.
- Release for Supply Procedures.
- Product Quality Reviews (as requested).

For any subsequent TGA audit, a list of products (with batch numbers) manufactured over the last 2 years for Australia will also be required.

The TGA lead auditor may request other documents prior to commencing an audit overseas.

Sharing of documentary evidence between sponsors and manufacturers

To reduce the regulatory burden on industry and avoid unnecessary re-assessments of clearance applications, the TGA has established Manufacturer Master Files and procedures for manufacturers and sponsors to authorise "access" to a site in relation to which a GMP Clearance has been granted previously for another sponsor. In such cases the sponsor must include in its clearance application a letter stating it is proposing to "access" another sponsor's clearance. A letter from the sponsor that obtained the clearance must also be included stating it consents to its clearance being "accessed". A copy of the clearance should be included.

The new clearance will only be granted for the same products and steps of manufacture covered in the "accessed" clearance.

A manufacturer may seek to submit all necessary documentation for GMP Compliance Verification on behalf of several sponsors. Once a clearance has been granted for one sponsor in relation to the manufacturer's site, the manufacturer may provide a **letter of access** for any Australian sponsor seeking clearance for products within the scope of the GMP Clearance at the relevant site. The letter of access must identify the GMP Clearance number.

Note: Each Sponsor must obtain their own separate GMP Clearance and pay the relevant fees.

3.4. Submit application and pay fees

Lodging an application for clearance by MRA and Compliance Verification

Sponsors applying for a GMP Clearance must complete the Overseas Manufacturer Clearance application found on the TGA online business system – eBusiness (eBS) – see www.ebs.tga.gov.au/).

Note: New users will need to establish an eBS account – refer to **Appendix E**.

The online system allows the progress of an application to be tracked by the Sponsor and the TGA. For assistance contact the TGA - GMP Clearance Unit by email at gmpclearance@tga.gov.au.

To complete a GMP Clearance application the following requirements are essential:

- the full legal name of the manufacturer;
- the street address of the manufacturing site (a P.O. Box is not acceptable);
- the standard to which the manufacturer complies in relation to the required dosage form (product) or API;
- a description of the products or types of products (dosage forms) in sufficient detail to be able to verify the relevance of the clearance request;
- the steps of manufacture undertaken at the site;
- the date of last inspection of the electronically attached GMP Certificate (if this date is unknown, enter a date earlier than the application date);
- a visible and legible signature and date for signed documents; and

- Dosage Form Codes in the drop down menus within eBS.

Copies of GMP Certificates and any other documents required to support the application should be submitted electronically. (A hard-copy is acceptable if the sponsor is unable to submit these electronically.)

An electronic application checklist is provided in **Appendix F**.

Failure to provide adequate GMP evidence

Applications that are lodged with incomplete or missing documentation or where the sponsor has not been able to provide the required or requested documents within the period allowed by the TGA or, if no period has been nominated, a reasonable time after being requested to do so by the TGA may be rejected. In such a case a letter of rejection will be sent to the sponsor (or its agent).

***Note**:* Application fees will be forfeited where an application is rejected.

Payment of application fees (for MRA and CV)

A TGA invoice will be generated as part of the online application process. This invoice can be printed off and payment should be made as per the instructions provided on the invoice.

Once the application fees are paid, the application can be assessed and processed.

Lodging an application for a TGA on-site audit

Simultaneous applications for a GMP Clearance by Compliance Verification and a TGA audit are not permitted. Where an application has been made for both, the application for the on-site TGA audit will not be considered.

Sponsors applying for a TGA on-site audit must complete the Application for On-site Audit for Certification which can be found on the TGA online business system – eBusiness (eBS) – see www.ebs.tga.gov.au/.

The online system allows the progress of an application to be tracked by the sponsor and the TGA. For assistance contact the TGA Office of Manufacturing Quality by email at gmp@tga.gov.au.

Fees for TGA on-site audit

There is no application fee for a TGA on-site audit. When the audit is scheduled, the sponsor will be advised of the audit fees that will be payable. The basis of calculation of the fees can be found at www.tga.gov.au/docs/html/feesach.htm.

The audit will commence only after payment of the applicable fees.

Schedule of fees

The current 'schedule of fees' available at www.tga.gov.au/docs/html/feesach.htm includes details of the following charges:

- overseas Manufacturers GMP Audit Fee (this covers the issuing of a GMP Clearance to the sponsor and GMP Certification to the manufacturer);

- assessment of GMP evidence in support of a GMP Clearance application (fees for an assessment using evidence from MRA will be different from those for a Compliance Verification);
- fee for obtaining evidence from an overseas regulatory agency (also referred to as a 'liaison fee') which is applicable if the sponsor requests the TGA to obtain evidence of GMP Compliance from the regulator in an MRA country;

  Please note this service is only available if the manufacturer is located within the boundaries of the relevant MRA country.
- reinstatement of an expired GMP Clearance approval.

The TGA is fully cost-recovered and collects its revenue primarily through fees and charges for the application, evaluation, audit and assessment.

The TGA is conscious of the costs associated with its regulatory responsibilities and is continually seeking to contain these costs through improvements in both efficiency and effectiveness.

3.5. TGA assessment

Target timeframes

The following targets for dealing with GMP Clearance applications enable orderly processing and assessment. The TGA is usually able to meet these targets unless the level of compliance demonstrated in the evidence supplied is low or there are delays in receiving any additional documentation requested. The relevant period starts when the TGA has received the application, supporting data and fees.

Assessment procedure	Target timeframe
Mutual Recognition Agreement (MRA)	15 working days
Compliance Verification for manufacture of non-sterile APIs and finished products	30 calendar days
Compliance Verification for manufacture of sterile or biotechnology APIs and finished products	90 calendar days
TGA on-site audit	Auditors are on-site within 6 months

Any application for a GMP Clearance that is not accompanied by correctly completed documentation will be considered ineffective and the sponsor will be notified within 20 working days (with forfeiture of the fees paid).

Where a GMP Clearance is based on a GMP Certificate issued under the terms of a MRA, the processing time will normally be within 15 working days.

- The TGA's processing time excludes any delay where a sponsor has requested the TGA to obtain the GMP Certificate.
- MRA agreements provide each party with 30 calendar days to supply a GMP Certificate, or 60 days if an inspection is required.

Where a GMP Clearance involves Compliance Verification of documentary evidence, the processing and assessment time will vary, depending on the risk of the products or substances manufactured, the manufacturing steps and the level of compliance identified in the most recent GMP Inspection Report supplied.

Where a **TGA on-site audit** is required, the TGA will initiate an application for a separate GMP Clearance for each of the sponsors paying for the TGA audit. GMP Clearances will be issued to each relevant sponsor after the audit has been completed and acceptable compliance has been found.

Overseas TGA on-site audits involve considerable lead-time in planning to ensure efficient audit visits. The usual lead time for an initial overseas on-site audit or a renewal of a GMP Certification for a site that was previously audited by the TGA is 6 months from the date of an effective GMP Certification application.

3.6. Outcomes of TGA assessment

Clearance approval

Once a GMP Clearance application has been assessed and a decision made that it is acceptable, the TGA will update the status of the application to “Approved”. Sponsors are able to view this status through eBS.

A notification letter of the clearance approval will be mailed to the applicant.

GMP Certification

Where a TGA on-site audit has found acceptable compliance, a GMP Certificate will be issued and mailed to the manufacturer.

Conditional Clearance

Where marginal compliance has been demonstrated through the Compliance Verification process or other issues have been identified, the TGA may grant a conditional GMP Clearance. The conditions may relate to the scope of the GMP Clearance or the expiry date, and/or may stipulate that the next GMP Clearance will only be granted following a successful outcome of an on-site TGA audit.

Rejection of an application

If the TGA determines that the evidence available does not demonstrate that the manufacturer complies with relevant GMP standards the sponsor will be notified.

If the GMP Clearance was assessed through a Compliance Verification, an on-site TGA audit may be required. If so, the sponsor will have to lodge an application on eBS.

Where a TGA on-site audit has taken place and the TGA has not found acceptable compliance, the GMP Clearance application will be rejected and any current GMP Clearances will be revoked.

Reviews of decisions (appeals)

The TGA follows the good decision making principles of lawfulness, fairness, evidence and facts, and transparency.

A sponsor may request a review when a GMP Clearance application has been deemed rejected after the assessment of a MRA certificate or Compliance Verification.

If dissatisfied with a GMP clearance decision, a sponsor may also seek an internal review and/or the reasons for the TGA's decision to:

- refuse to issue a GMP Certificate for a manufacturing site following an on-site audit, or
- suspend, cancel, or reduce the scope of a GMP clearance.

A request for a statement of reasons or internal review of a decision must be made within 28 days of the date of notification of the decision. If a request is not received within this period the clearance application is taken to have been finalised.

A request for internal review must be made in writing to:

Request for GMP Clearance Review
Head of Office
Office of Manufacturing Quality
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2600

4. Maintenance of a Clearance

In order to maintain a clearance, sponsors are required to:

- Advise the TGA of any significant changes to the manufacturing site, QMS, products, product range. Significant changes are changes that could potentially affect GMP compliance[9].
- Maintain evidence of GMP compliance of all overseas manufacturing sites used, and notify the TGA immediately of any changes in circumstances or regulatory compliance of the overseas manufacturer.

Please refer to the Responsibilities of Australian Sponsors of Overseas Manufacturers on pages 6-7.

Clearance expiry

The expiry of GMP Clearances will depend on the type of product(s) manufactured and the outcome of the assessment (MRA or Compliance Verification).

The period of GMP Clearance given to a manufacturing site is normally a maximum of the certification expiry plus 6 months; or three years plus 6 months from the date of inspection. (The additional 6 month period facilitates the completion and assessment of re-inspections/audits.) The expiry period may be reduced based on a risk assessment or other justification.

Where a GMP Clearance has expired, or is about to expire, a new GMP Clearance application **must** be submitted for assessment.

The TGA sends reminder letters to sponsors 90 days prior to the date of expiry of a GMP Clearance. The TGA may also seek information from a sponsor under Section 31 of the Act to obtain evidence of GMP compliance for a manufacturing site outside of Australia.

[9] The TGA is introducing a Periodic Manufacturer Update form to assist sponsors in meeting this requirement

5. Revocation or reduction in scope of a clearance

The TGA may revoke or reduce the scope of a GMP Clearance where:

- GMP Certification is withdrawn by an MRA partner or other regulatory agency.
- Evidence submitted to the TGA is subsequently found to be incorrect.
- The manufacturer or sponsor declines a scheduled re-inspection/audit.
- The outcome of a TGA on-site audit determines that GMP compliance is unsatisfactory.

The sponsor will be notified of the revocation by mail.

The sponsor may request a review of a decision to revoke or reduce the scope of a clearance. (Refer to Reviews of decisions (appeals) on page 23.)

Appendix A - Glossary of terms

This appendix contains interpretations of terms used in this document.

Terms that appear in the *Therapeutic Goods Administration Act 1989* or the *Therapeutic Goods Administration Regulations 1990* may be described slightly differently (for example, to expand or narrow a definition) in Orders made under the Act.

Glossary	
the Act	The *Therapeutic Goods Act 1989*
Active Pharmaceutical Ingredient (API):	Therapeutically active component in the final formulation of therapeutic goods.
ARTG	Australian Register of Therapeutic Goods
Audit	"Audit" and "inspection" are used interchangeably, meaning when the GMP Compliance of a facility is assessed at the overseas site either by TGA auditors or by inspectors of another competent authority recognised by the TGA as meeting an equivalent standard.
Authorised person	A person recognised by the TGA as having the necessary background and experience to undertake particular functions.
Batch (or lot)	A defined quantity of starting material, packaging material or product processed in one process or series of processes such that it could be expected to be homogeneous. Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. For the control of the finished product, a batch of a medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.
Batch number (or lot number)	A distinctive combination of numbers and/or letters which identifies a specific batch.
Bulk product	Any product which has completed all processing stages up to, but not including, final packaging.
Codes of GMP (GMP)	Principles and practices to be followed in the manufacture of therapeutic goods to provide assurance of product quality and compliance with product registration or listing in the Register.
Compliance Verification	An assessment based on the evaluation of prior evidence by a competent authority recognised by the TGA [???]. This assessment is performed by considering documents provided by other regulators, the sponsor and the manufacturer to verify the manufacturer's compliance with GMP.
Contract manufacture	Any part of the manufacturing process of therapeutic goods that is carried out by a person other than the sponsor on a contract basis (including principal manufacturers and other (sub) manufacturers).
Dosage form	The pharmaceutical form in which a product is presented for therapeutic administration, for example, tablet, cream. A list of dosage forms and their definitions for the purpose of recording information in the ARTG database is included in the TGA Approved Terminology for Medicines.
eBS	TGA's online business system – eBusiness System.
Finished Product	A medicinal product which has undergone all stages of production, including packaging in its final container.
GMP Certificate	A document issued by an authorised regulatory body certifying compliance of the

	manufacturer to the applicable GMP standard.
GMP Clearance	The approval of GMP documentary evidence as demonstrating that a manufacturer is of an acceptable GMP standard.
GMP contract or agreement	A GMP contract is a written contract covering the manufacture and any technical arrangements made in connection with it.
Inspection	See "Audit" above.
Listed medicines	See definition in section 3(1) of the Act. Listed goods are entered on the ARTG based on approved ingredients, low level claims and certification by the sponsor of the evidence to support their application. Listed goods are not evaluated by the TGA prior to inclusion on the ARTG.
Manufacture	All steps in the manufacture of therapeutic goods, including production, labelling, packaging, sterilisation, quality control, release, storage and distribution of medicinal products and the related controls.
Manufacturer	The person which manufactures medicinal products ie produces the product, or engages in any part of the process of producing the product or of bringing the product to its final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the product or of any component of ingredient of the product as part of that process.
Manufacturing premises	A building, a part of a building or a part of a group of buildings on one or more sites: (a) that is for use in the manufacture of a particular kind of therapeutic goods; and (b) in relation to which the same person/s have control of the management of the production of those goods and the procedures for quality control.
Marketing authorisation	Compliance with regulatory requirements specified on the ARTG and any other requirements imposed by a relevant delegate of the Secretary of the Department of Health and Ageing upon the listing or registration of the product. Examples of regulatory requirements include the following: compliance with registered formulations, special storage and transportation conditions, shelf life, labelling, batch release testing requirements, etc.
Medicine	Therapeutic goods that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human or animal (previously referred to as a drug).
Medicinal products	Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing country.
MRA	Mutual Recognition Agreement
MRA regulator	A regulator who is recognized by other partners to a Mutual Recognition Agreement.
Overseas manufacturer	Manufacturer with manufacturing premises or testing laboratory located outside Australia.
Packaging	All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.
Procedures	Description of the processes to be carried out, including the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of medicinal products.
Production	All processes involved in the preparation of medicinal products, from receipt of materials, through processing and packaging, to completion as a finished product.
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word "validation" is sometimes used to incorporate the concept of qualification.
Release for Supply	That step of manufacture in which an authorised person certifies that a production batch has been produced and controlled in accordance with the requirements of the marketing authorisation and any other regulations relevant to the production, control and release of

	medicinal products following review of all pertinent information to allow supply to the market.
Site Master File	The Site Master File is prepared by the manufacturer and contains specific information about the quality assurance, the production and/or quality control of pharmaceutical manufacturing processes carried out at the named site and any closely integrated processes at adjacent and nearby buildings. If only part of a pharmaceutical process is carried out on the site, a Site Master File need only describe those processes, e.g. analysis, packaging, etc.
Sponsor	Defined in section 3(1) of the Act as A person who exports, or arranges the exportation of, the goods from Australia or a person who imports, or arranges the importation of, the goods into Australia or a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere) but does not include a person who: exports, imports or manufactures the goods or arranges the exportation, importation or manufacture of the goods on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.
TGA on-site audit	An audit carried out by the TGA at the facility of the manufacturer.
Validation	Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Appendix B – International agreements

Countries which are recognised participants in an MRA (or equivalent) with Australia

Austria	France	Liechtenstein	Spain
Belgium	Germany	Luxembourg	Sweden
Canada	Greece	Malta	Switzerland
Cyprus	Hungary	Netherlands	United Kingdom
Czech Republic	Iceland	Norway	
Denmark	Ireland	Portugal	
Finland	Italy	Singapore	

***Note**:* A TGA on-site audit will always be required where the listed or registered medicines are not regulated by the regulatory agency in their own country. **Complementary Medicines and Traditional Chinese Medicines** are commonly not regulated as medicines in other countries.

GMP agreements and arrangements with Competent Regulatory Authorities

The TGA is a member of the **Pharmaceutical Inspection Cooperation Scheme (PIC/S)**. The PIC/S aims to develop harmonised regulatory guidelines and facilitate the training and development of inspectors. PIC/S membership is subject to initial and periodic assessment of the participating authority to ensure that it has equivalent legislation, regulatory and enforcement procedures and inspection capacity.

PIC/S membership also provides for the confidential exchange of regulatory information including the planning of inspections, compliance status of a manufacturer and the results of inspections.

The TGA does not automatically accept GMP Certification from PIC/S member countries unless also covered by an MRA with Australia. Certificates and inspection reports from an overseas regulator for inspections that predate its official membership to PIC/S will not be accepted.

A list of PIC/S member countries is available at www.picscheme.org/members.php.

The TGA has entered into various **other international agreements** to support information sharing and other desirable objectives for international regulatory collaboration. These agreements do not permit legally enforceable acceptance of the decisions of the other party, but may be used to enhance regulatory oversight and significantly reduce regulatory burden without diminution of compliance.

Organisation	Agreement	Scope
USA Food and Drug Administration	Cooperation agreement/ confidentiality undertakings	Exchange of information in relation to manufacturers for regulatory purposes.
European Directorate for the Quality of Medicines (EDQM)	Co-operative arrangement between the TGA and the European Directorate for the Quality of Medicines and	Exchange of information in relation to the manufacture of APIs and excipients used in the manufacture of

	Healthcare Council of Europe	therapeutic goods.
New Zealand: Department of Health Housing Local Government and Community Services	Memorandum of Understanding	Exchange of information in relation to manufacturers for regulatory purposes
Switzerland Swiss Confederation regarding Therapeutic Products	Memorandum of Understanding (arrangements generally equivalent to an MRA)	Exchange of information relating to the regulation of medicines GMP inspections and post market monitoring of therapeutic products.

The TGA also participates in other agreements with agencies with a view to increase international cooperation and capacity building. Generally they do not support the exchange of GMP certifications and inspection reports.

Note: The above information is current as at 31 July 2010.

For further details of international arrangements, please refer to: www.tga.gov.au/international/index.htm#intagree.

Appendix C - Explanatory notes for documentary evidence

GMP Contracts with manufacturers

Matters required to be contained in the GMP contract are outlined in Chapter 7 of the PIC/S Guide to GMP for Medicinal Products, January 2009.

Particular consideration in the assessment will be given to the responsibilities for validation, stability, complaints, recall, release for supply, testing methodology and change control.

Where the Australian sponsor is a subsidiary of the overseas manufacturer who conducts the step of Release for Supply (and other manufacturing steps) then the TGA accepts that a formal GMP contract may not exist. In this circumstance, the sponsor must provide the TGA with a written explanation of the arrangements.

Procedure(s) for Release for Supply of Finished Products/APIs

Release for Supply procedures detail the arrangements used to ensure that each batch has been manufactured and checked for compliance with the requirements of the marketing authorisation or in the case of APIs, with relevant specifications.

Note that a GMP Clearance for the manufacturing step, Release for Supply (only) to another manufacturer for further manufacturing will not be granted for intermediate or bulk products.

Product Quality Reviews

Product Quality Reviews are mandatory for APIs, and for medicine finished product dosage forms.

Product Quality Reviews are used to assess the effectiveness of controls and processes on the quality of manufactured products

As outlined in clause 1.4 of the PIC/S Guide to GMP for Medicinal Products (PE 009-8, January 2009), Product Quality Reviews should normally be conducted annually, and the results of the review evaluated by the manufacturer and the sponsor. Some of the items to be reviewed are:

- Starting materials including packaging materials used in the product.
- Critical in process controls and finished product results.
- Significant deviations, non-conformities, their related investigations, and the effectiveness of resultant corrective and preventative actions.
- Changes carried out to processes or analytical methods.
- Stability monitoring program and adverse trends.
- Quality related returns, complaints, recalls and the investigations performed at the time.

- Contractual agreements.

Site Master File (SMF)

A Site Master File or equivalent document will detail the facilities, operating structure, quality management system, manufacturing equipment and activities of the manufacturing site(s). This is used to understand the nature and operations of the manufacturer.

Guidance for preparing a SMF can be found in The PIC/S document PE 008, *Explanatory Notes for Industry on the preparation of a Site Master File* available on the TGA website www.tga.gov.au/docs/html/siteinfo.htm.

Manufacturers may supply other documents, such as a Plant/Equipment File or a Quality Manual, which individually or collectively provide the same details.

Validation Master Plan (VMP)

As outlined in Annex 15, clause 4 of the PIC/S Guide to GMP for Medicinal Products, January 2009, a Validation Master Plan should contain data on at least the following:

- Validation policy.
- Organisational structure of validation activities.
- Summary of facilities, systems, equipment and processes to be validated.
- Documentation format: the format to be used for protocols and reports.
- Planning and scheduling.
- Change control.
- References to existing documents.

The Validation Master Plan is used to assess the company's identification of the scope and extent of validation and qualification requirements for its operations, the status of validation activities so identified, and the level of assurance that the company has addressed the control of critical aspects of its operations.

A Validation Master Plan is not required for GMP Clearances involving QC testing or Release for Supply steps only.

Appendix D - Manufacturer's declaration for APIs

There is no set format for the "manufacturer declaration". The document must:

- carry the company letterhead (or other identifier of the manufacturer); and
- be authorised by an officer of that company at the senior management level.

The letter should also provide the tracking numbers of the relevant Clearance application(s) submitted by the sponsor.

A manufacturer's declaration must include the following:

1. Confirmation that the API(s) included in the application (include names of APIs) are manufactured at the nominated facility under the same quality system and in the same facility (buildings) as the APIs stated in the audit report provided to the TGA.
2. Details of starting material APIs (include names) for the API(s) included in the application, and confirmation that all steps of manufacture (for each API) are carried out at the nominated site. If any steps of manufacture are carried out at another site or company, please provide details.
3. Details of whether any previous audits by any other regulatory agencies have covered the API(s) included in the application. If so, a copy of the audit report should be provided.

Appendix E - Electronic application on eBusiness

Registration

This section outlines the process for initial registration on the TGA eBusiness system. To complete an electronic application on the TGA's eBusiness system a new applicant must first establish an eBusiness account.

NEW USERS
You will NOT be able to access any of the TGA eBusiness Services (eBS) systems without an account.

To establish an e-business account with the TGA visit the website at http://www.tga.gov.au/manuf/mis.htm and enter the eBusiness Access Forms area at https://www.ebs.tga.gov.au/:

- download the UserForms.zip file and download or copy the e-business and client details forms from the file (to view the page click on this link Document - Access Application Forms); and
- complete and fax both forms to the TGA on +61 (0) 2 6232 8581 (there is no requirement to send in the original forms, a fax copy is sufficient).

usually within three workng days of faxing these documents, you will receive 2 emails; one with your master e-business account the other with instructions about how to set up the e-business account. Using the master account you can log onto the user management area in eBS and establish the appropriate number of user accounts for your organisation.

If you have difficulties setting up your accounts please call the TGA eBusiness Services help desk on 1800 010 624.

A user support help line has been established to provide user support for the Manufacturers Information System (MIS) on 1800 446 443. A user manual can also be downloaded once MIS is accessed using your password.

The TGA will keep clients informed and up to date with news bulletins published in the '*What's New?'* area of the TGA online services home page.

Appendix F - Electronic application checklist

For GMP Clearances based on a Mutual Recognition Agreement

☐ A copy of a current GMP Certificate for the site and the relevant dosage form or substance; or

☐ A request to the TGA for it to obtain evidence of compliance from an MRA regulator (a fee applies).

For GMP Clearances to be assessed by Compliance Verification

☐ Documents from Evidence List B of Table 1b or

☐ Documents from Evidence Lists B and C of Table 1b or

☐ Documents from Evidence List D of Table 1b

☐ Details of any regulatory actions in the past 3 years relating to the manufacturing site.

Application and Fees:

☐ An electronic application has been lodged. Documents have been attached or copies have been forwarded to the TGA.

☐ All required fees have been remitted.

Declaration:

I, being a person authorised to make this application, hereby declare that in electronically submitting this application to the TGA, all of the information given is current and correct.

Note A false declaration will result in the cancellation of any previous current GMP Clearances for this manufacturer at this site and the rejection of the GMP Clearance application.

Signatory name of the person submitting the application:

……

Please scan the signed application checklist and submit electronically with the eBS application.