Australian Government
Department of Health
Therapeutic Goods Administration

Guidance on the management of GMP compliance signals

for domestic and overseas manufacturers of medicines and biologicals

Version 1.0, May 2021

TGA Health Safety Regulation

Contents

About this guidance

The guidance outlines the Good Manufacturing Practice (GMP) compliance requirements (according to the Manufacturing Principles) for manufacturing **biologicals** and **medicines** intended for supply in Australia and our framework for managing GMP compliance signals.

GMP is used internationally to describe a set of principles and procedures which, when followed by manufacturers of therapeutic goods, helps ensure that each batch of a therapeutic good is safe, reliable and of consistent high quality.

This guidance applies to:

- licensed manufacturers in Australia
- sponsors responsible for any overseas site in the manufacture of a medicine or active pharmaceutical ingredient (API) supplied to Australia.

This guidance is not intended for manufacturers and sponsors of medical devices.

GMP for medicines and biologicals

For medicinal products supplied in Australia, all steps of manufacture must be compliant with GMP unless they are exempt.

Manufacturers of medicines or biologicals must comply with either the:

- Good Manufacturing Practice for Medicines
- Good Manufacturing Practice for Human Blood and Tissues

Evidence of acceptable GMP Compliance is required to be supplied for registration and listing (including Registered Over the counter and Complementary Medicines) of products to be supplied in Australia on the Australian Register of Therapeutic Goods (ARTG) and must be maintained for ongoing supply of such products.

More information is available at Responsibilities of manufacturers of medicines and biologicals.

Sponsors of Registered Over the Counter (OTC), Listed and Complementary Medicines are expected to advise the TGA when they become aware of potential or actual GMP issues at a manufacturing site. The sponsor oversight of the GMP compliance status of the manufacturing site should be stipulated in the GMP Agreement between the sponsor and manufacturer.

Licensing, GMP certification and clearance requirements

The *Therapeutic Goods Act 1989* requires all sites that manufacture therapeutic goods in Australia to hold a GMP licence unless either the therapeutic goods, or the person manufacturing the therapeutic goods are exempt. Under Section 35 of the Act it is an offence to manufacture therapeutic goods at a site in Australia unless either (1) the goods are exempt, (2) the person is exempt or (3) the person holds a manufacturing licence.

For more information on licensing, certification and GMP clearances see:

- GMP-an overview
- Australian licensing and overseas GMP certification process
- GMP clearance guidance
- Sponsor responsibilities related to GMP clearance and certification

GMP compliance signals

GMP compliance signals (that, is non-compliance alerts) include but are not limited to, intelligence, data and information that we receive from various internal and external intelligence sources, as well as our inspections and routine compliance monitoring process which indicate a departure from the manufacturing principles (or equivalent overseas standards) by a manufacturer.

In addition, for overseas manufacturing sites we perform routine monitoring of overseas compliance systems and databases published by other overseas regulatory authorities.

GMP compliance signals and sponsor / manufacturer responsibilities

Sponsors and manufacturers **are expected to** report potential or known GMP compliance signals at their manufacturing sites and provide this information to the TGA when they become aware of such information.

These potential compliance signals include, though are not limited to:

- concerns raised by the manufacturers where it is identified there is a potential or actual breach of the Good Manufacturing Practices for medicines, blood or biologicals, particularly where this may lead to a risk to products.
- any regulatory actions by any competent authority for the manufacturing sites.

We may request further information from you after we have reviewed/investigated potential or known GMP signals reported to us.

Additional information related to your regulatory reporting requirements is available at Pharmacovigilance responsibilities of medicines sponsors.

Anyone can report suspected GMP compliance signals.

You can contact GMP compliance to report a potential compliance issue or concern related to GMP manufacturing of medicines and/or biologicals.

Management of GMP compliance signals

The TGA manages GMP compliance signals related to the manufacturing of medicines and biologicals from licensed domestic manufacturing sites and overseas manufacturing sites for products intended for supply in Australia. We also manage signals relating to licence, certification and clearance applications.

Information on the criteria we use to triage and manage GMP compliance signals is available at Regulatory compliance frame work – prioritisation.

When triaging and managing GMP compliance signals relating to **overseas** manufacturers, we also take into account:

- the impacts on products supplied and/or intended to be supplied in Australia
- the outcome of the risk assessment provided by applicable sponsors
- any other relevant information such as:
  - site master files
  - GMP agreements
  - corrective and preventative actions (CAPAs).

Review and investigation of GMP Compliance signals

Once we receive and triage a GMP compliance signal, it undergoes a review and investigation process to determine if compliance action is required to address the signal.

Risk assessments

We may ask sponsors to provide risk assessments to support the **continued and/or intended** supply of products on the Australian Register of Therapeutic Goods (ARTG) from manufacturing sites that are identified to have GMP compliance signals.

Where the risk assessment does not support ongoing or intended supply, or does not provide information relevant to support the quality and safety of products supplied to the Australian market, we will investigate further regulatory actions as outlined in this guidance.

Your risk assessment should provide enough detail for us to make an unbiased decision regarding supply from the site in question, and should be prepared in accordance with ICH Q9 Quality Risk Management / PICS GMP Guide: Annex 20.

Request for additional information

We may also ask sponsors to provide additional information that may be relevant to the GMP compliance signal investigation and risk assessment process. For example, we may request the:

- inspection report
- post-inspection letter (PIL)
- manufacturer's responses to the regulatory authority
- evidence of corrective and preventative actions (CAPAs)
- Site Master Files (SMF)
- GMP or Quality agreements (or equivalent), where appropriate
- TGA manufacturer questionnaire

Your CAPA report or inspection response **should** indicate the specifics of how it relates to the compliance signal under investigation.

Compliance and risk framework for licensed manufacturers

Our approach to managing compliance issues according to risk and the approach of manufacturers to compliance obligations is detailed in the table below.

In using our powers, we deal with compliance signals in a manner proportionate to the risk posed to public health.

How licensed manufacturers comply with licensing obligations and how the TGA manages compliance risks

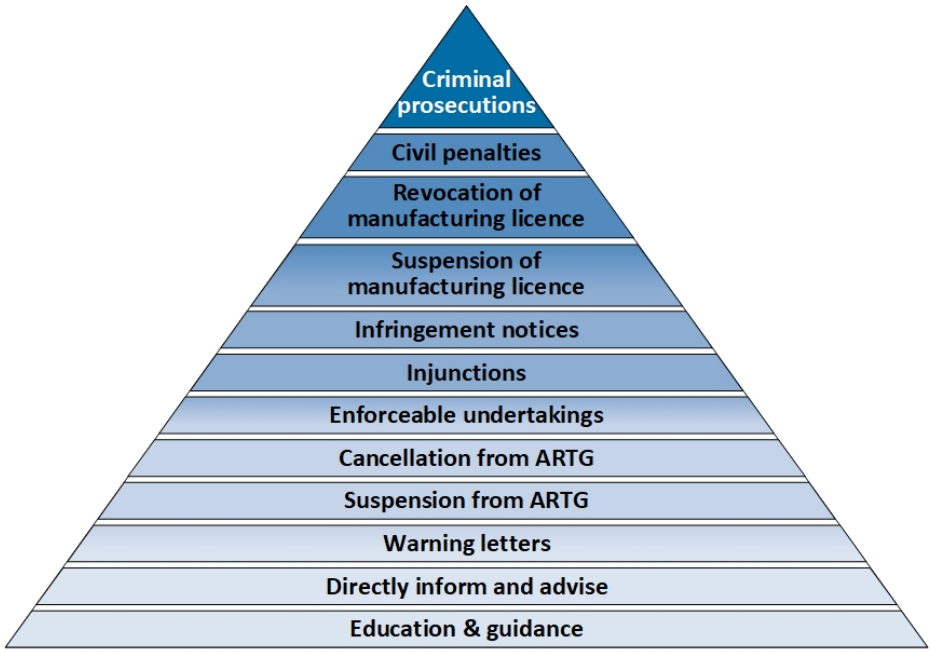
Compliance risk	Manufacturers' approach to compliance with licensing obligations	TGA approach to managing compliance risk
Low	**Voluntary compliance** • Committed to doing the right thing • Effective quality management systems in place • Management is compliance oriented	**Help and support** • Make on-going compliance easy through clear education and guidance material

Compliance risk	Manufacturers' approach to compliance with licensing obligations	TGA approach to managing compliance risk
Medium	**Accidental non-compliance** • Trying to do the right thing but don't always succeed • Ineffective compliance and/or developing compliance systems • Management compliance orientation but lacks capability	**Inform and advise** • Direct education and guidance in a legal obligations letter to help the manufacturer become and stay compliant
High	**Opportunistic non-compliance** • Don't want to comply but will if made to • Resistant to compliance • Limited or poor compliance systems • Management not compliance orientated	**Correct non-compliant behaviour** • Send a formal warning letter and schedule a follow up inspection • Giving notice of available compliance and enforcement options available to the TGA • Impose licence conditions to ensure compliance • Enforceable undertakings • Infringement notices
Critical	**Intentional non-compliance** • Decision to be non-compliant • No or ineffective compliance systems • Reckless attitude to manufacturing licence obligations	**Enforce penalties** • Criminal offences • Civil penalties • Infringement notice

Regulatory actions for domestic licensed manufacturers

A range of compliance and enforcement tools are employed by us to address alleged non-compliance, either individually or in combination, and to encourage compliance with the *Therapeutic Goods Act 1989*. These tools are illustrated in the diagram below.

GMP compliance and enforcement tools



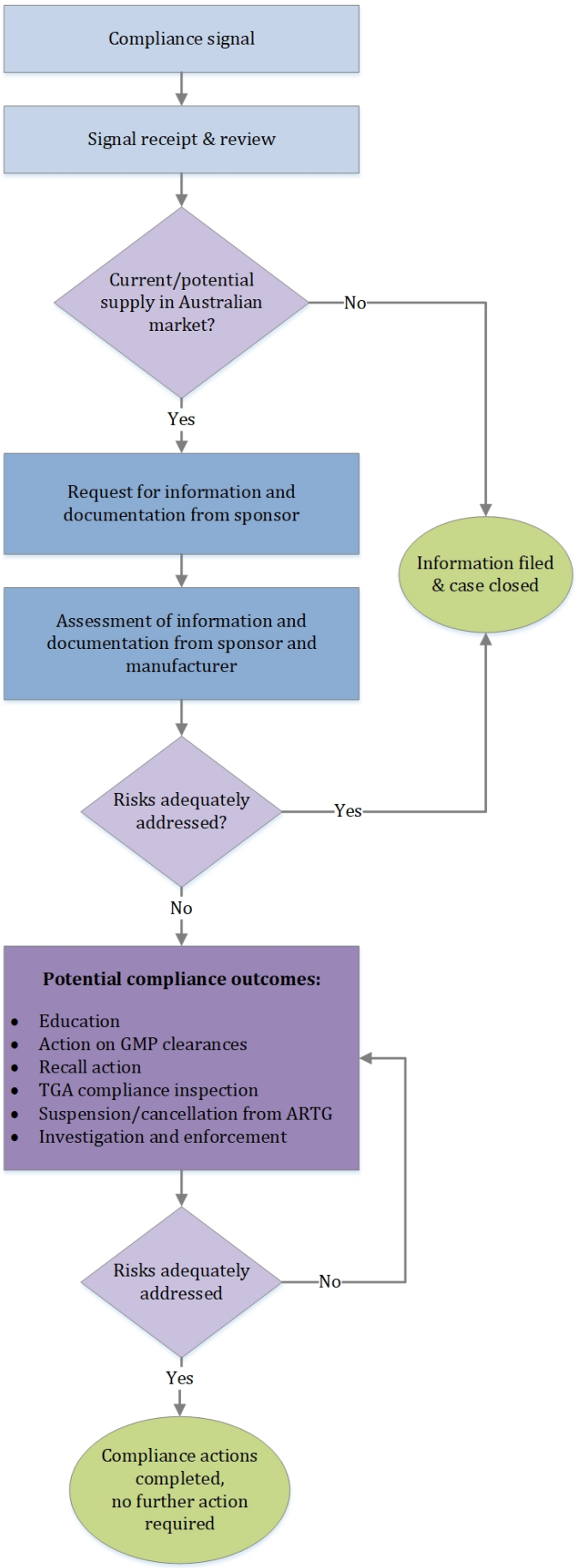
For further information on the regulatory actions and enforcements, see Compliance actions and outcomes.

Regulatory actions for overseas manufacturers

Overseas manufacturers of medicines supplied to Australia are also required to meet an acceptable standard of GMP (the Manufacturing Principles or equivalent standards).

The process for managing GMP compliance signals relating to overseas manufacturing sites is illustrated in the flow chart below.

Compliance signal process flow chart for overseas manufacturing sites



GMP Compliance signal review and investigation

During the GMP Compliance signal review and investigation phase, all GMP clearance applications related to the site are placed on hold pending the outcome of the assessment. No further assessment is conducted until requested documentation to support supply is provided from the site in question.

Sponsors will be requested to provide risk assessments for products supplied (or intended to be supplied) in Australia. Additional further information may also be requested where warranted.

If you require an extension for the provision of the risk assessment and information, please notify GMP Compliance as soon as practicable and provide an estimated timeframe and justification for the extension. Extensions will delay any determinations made by us for the GMP Compliance signal. If the requested information is not provided by the specified due date, the assessment will progress and we may take further regulatory action.

Sponsors will be notified of the outcome of the compliance review and investigation including any further compliance regulatory action that is required to be taken to address the signal.

The outcome of a compliance signal investigation may determine that action is required against a GMP clearance. The action taken may be one or a combination of the following:

- reduction of clearance validity
- reduction of the clearance scope
- addition of a condition or restriction to the clearance
- suspension of clearance
- cancellation of clearance
- TGA compliance inspection (on site, remote or hybrid inspection)
- product recalls
- action against the ARTGs

Where an issued GMP clearance includes dosage forms that are **not supplied** or **not included** in the requested risk assessment, we may take action including, but not limited to, removing these dosage forms/manufacturing steps from an issued GMP clearance.

Any product submissions related to the non-compliant manufacturing site may also be impacted. Please ensure the requested risk assessments take into consideration the products under pre-market submissions in order for us to make a determination on the related clearance.

It is a sponsor responsibility to confirm with the manufacturing site prior to submitting a clearance application whether there are any potential or ongoing regulatory actions and/or compliance issues.

Compliance and enforcement tools available to the TGA

Information or documents

To assist in our decision making we may write to you seeking information or documents as detailed in Section 41AB of the *Therapeutic Goods Act 1989*.

The Act provides for criminal offences and civil penalties if you fail to respond, provide an incomplete response or knowingly provide information that is false or misleading in response to a notice given under Section 41AB.

Recall and public notification powers

We may recall products from the marketplace to protect public health, as allowed by our powers under the *Therapeutic Goods Act 1989*.

Recalls and associated actions are carried out in accordance with the Uniform Recall Provisions for Therapeutic Goods (URPTG)).

More information is available at:

- Recall procedure
- Roles in recalling therapeutic goods

Powers to suspend or cancel goods from the ARTG

Our powers to suspend or cancel the entry of a therapeutic good from the Australian Register of Therapeutic Goods (ARTG) is not affected by:

- imposing requirements relating to matters such as:
  - conditions on a manufacturing licence
  - suspension or cancellation of a manufacturing licence
- other compliance and enforcement actions relating to non-compliance under Part 3-3 of the *Therapeutic Goods Act 1989*.

Enforceable undertaking

If you believe you have, or are likely to have breached an offence or civil penalty provision in our legislation, you can offer to enter into an enforceable undertaking as an alternative to court action being commenced by us.

An example may include where a licensed manufacturer undertakes to establish, review or improve their quality management systems and certain manufacturing equipment that is not up to the standards required by the code of GMP. The licence holder may set a timeline for the implementation of these processes and the installation of the equipment to be compliant with the requirements in the *Therapeutic Goods Act 1989* and to make regular reports to the TGA for the period of the undertaking.

Injunction

We may seek an injunction in the Federal Court or Federal Circuit Court (a Federal Court).

An example of when the TGA would seek an injunction is where a manufacturer refuses to comply with a suspension of their licence to cease manufacture of particular therapeutic goods. This would be appropriate when, because of failure to meet manufacturing principles there is an **actual** or **potential** risk to public health and safety from the use of the therapeutic goods.

Seeking an injunction does **not** prevent us from taking other forms of compliance or enforcement actions at the same time.

Infringement notice

We may issue you an infringement notice (fine) where you have, within **12 months**, breached a strict liability offence or civil penalty provision of the *Therapeutic Goods Act 1989* that relates to manufacturing licences and the statutory obligations on licence holders under Part 3-3 of the Act. You can choose to pay the infringement notice amount as an alternative to having court proceedings brought against you.

An example of when an infringement notice may be issued is where a licence holder has continued to rate a number of major deficiencies in two or three consecutive inspections despite being fully aware of the issues and has failed to address them adequately.

Revocation or suspension of manufacturing licence

We may advise you of our proposal to either revoke or suspend your licence for a specified period of time, in certain circumstances, as allowed by the *Therapeutic Goods Act 1989*.

Further information is available at Revoking and suspending Australian manufacturing licences.

Civil penalty provisions

If within **six years** you have breached a civil penalty provision in the *Therapeutic Goods Act 1989*, we may apply to the Federal Court for an order against you to pay a penalty (fine).

The maximum penalty that can be imposed on conviction of a body corporate (company) is five times higher than the penalty that can be imposed on an individual. For more information see subsection 4B(3) of the *Crimes Act 1914*.

The Act also provides for **continuing contraventions** (breaches) of civil penalty provisions. If you have an obligation to do something within or before a particular time, and you have not met that obligation, a separate civil penalty contravention can continue each day until that obligation has been met.

Criminal offences

The *Therapeutic Goods Act 1989* provides for a number of criminal offence provisions relating to manufacturing licences and statutory obligations on licence holders.

For more information on criminal offence provisions, see Part 3.3 of the Act.

Publication of compliance or enforcement outcomes

If you fail to comply with your legal obligations relating to the manufacture of therapeutic goods, the *Therapeutic Goods Act 1989* allows us to publish your details and any actions we undertake.

Information we may publish includes, but is not limited to:

- Information on our website about infringement notices if they are paid. Details of the payment of the notice may be referred to in media or social media releases.
- The Act requires us to publish details of enforceable undertakings entered into between a promisor and the TGA on our website. If we pursue a person in the Federal Court and the court imposes civil penalties, those matters will be published on our website and may be referred to in media or social media releases when the case is finalised.
- If we pursue a person in the criminal courts through the Commonwealth Director of Public Prosecutions (CDPP), details of convictions will be published on our website and may be referred to in media or social media releases when the case is finalised.

GMP Compliance case studies

The following GMP Compliance case studies are generic case examples and are **for information only**.

Suspension of EDQM Certificate of Suitability (CEP)

Following a European Medicines Agency (EMA)/European Directorate for the Quality of Medicines & Healthcare (EDQM) joint inspection of an active pharmaceutical ingredient (API) manufacturer, a non-compliance report was issued. The EDQM subsequently suspended Certificates of Suitability (CEPs) for several APIs manufactured at this site.

In response to a TGA request, relevant sponsors provided further information, including details of products that they have registered on the Australian Register of Therapeutic Goods (ARTG), product supply details and risk assessments. Critical medicines and current/potential medicine shortages were identified and confirmed.

TGA GMP Compliance Team were subsequently notified that the manufacturer had suspended their manufacturing activities until all of the activities impacted by the EDQM findings had been addressed and compliant activities can be assured. The CEPs remained suspended.

Following assessment of the information available including sponsor specific information and risk assessments, the following compliance actions were taken:

- Suspension of existing clearances where there were no ARTGs or no products being supplied in Australia.
- Suspension of existing clearances that were not related to medicines shortages or critical medicines.
- Relevant sponsors were notified of the compliance actions to be taken, including advice regarding on-going or future supply and potential recall actions.
- Continued monitoring of further compliance intelligence including the reinstatement of the CEPs.

Anonymous Tip-off

The TGA received an anonymous tip-off related to *Company A*, an Australian TGA licensed manufacturer. The tip-off was in relation to falsification of test results and the use of toxic raw materials in the manufacture of products at this site.

Assessment of the available information, determined that the TGA conduct a compliance inspection of this site to review this signal. The site was due to have a reinspection within 12-months, but the inspection date for this manufacturer was brought forward following assessment of this GMP compliance signal.

USFDA Warning Letter

Company B is a large manufacturing facility for sterile injectable products. The USFDA conducted an inspection of this site and issued a warning letter.

Sponsors were requested to provide information including products that they have registered and/or listed on the Australian Register of Therapeutic Goods (ARTG), product supply detail and risk assessment. There were no critical medicines or medicine shortage associated with this manufacturing site.

Following assessment of the information available including sponsor specific information and risk assessments, there was insufficient evidence to demonstrate that the risks are adequately managed. The following compliance actions were taken:

- Information was requested on the progress of the CAPAs relevant to products to be supplied to Australia. However, the information was insufficient to demonstrate that there is no ongoing problem that would impact the supply for Australia for this manufacturing site. Therefore, a TGA inspection was scheduled.
- All clearance applications in progress were progressed based on the proviso of satisfactory TGA inspection only.
- All existing clearances were suspended.
- Relevant sponsors were notified of the compliance actions to be taken, including advice regarding on-going or future supply and potential recall actions.

Hazard alerts for missing donor related medical history

Company C is a medium scale human tissue processing facility that provides human tissue for implantation to surgeons operating within Australian hospitals. The TGA received five consecutive hazard alerts for missing donor related medical history data.

Following assessment of the information the following compliance actions were taken:

- The GMP compliance signal was referred to the Lead Inspector for review at the next scheduled reinspection as the site was scheduled to undergo a TGA inspection within the following month.
- The manufacturer's donor assessment processes and procedures were a focus of the inspection plan.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch	April 2021

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication # D20-3505403