The Good Manufacturing Practice (GMP) Clearance Framework – an overview

Rheannon McNeil
Assistant Director, GMP Clearance Section
Manufacturing Quality Branch
Therapeutic Goods Administration

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Welcome: The GMP Clearance Framework – an overview

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Legislative basis for manufacturing requirements

- The Therapeutic Goods Act 1989 sets out the legal requirements for the import, export, manufacture and supply of therapeutic goods in Australia. It details the requirements for listing, registering or including medicines, medical devices and biological products on the Australian Register of Therapeutic Goods (ARTG), as well as many other aspects of the law including advertising, labelling, and product appearance.
- The Act aims to ensure the safety, quality, efficacy and timely supply of therapeutic goods for Australians.
- Chapter 3, Part 3 outlines the requirements for domestic manufacturing facilities.
- Paragraphs 25(1)(g) and (h), 26(1)(g) and (h) and subsection 26A(3) of the Act specify that the manufacturing and quality control procedures used in the manufacture of therapeutic goods must be acceptable.
- The Manufacturing Quality Branch operates several programs designed to ensure these aims are met.
Manufacturing Quality Branch (MQB)

- Assessing compliance of manufacturers of:
  - Prescription medicines*
  - Over the counter medicines*
  - Complementary medicines (herbal, traditional, vitamins)*
  - Blood, tissues and cellular therapies^

  against *Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP Guide or ^Australian Manufacturing Standards through licensing, certification and clearance.

- Monitoring and investigation of non-compliant manufacturers

- Coordinate and manage product recall of therapeutic goods
Manufacturing Quality Branch

- **GMP Clearance**
  Application management and desk top assessments of overseas manufacturing sites in lieu of an onsite inspection through the Mutual Recognition Agreement (MRA) and Compliance Verification (CV) pathways, maintaining GMP Clearances through ownership transfers, administrative amendments to names and minor address changes, extensions and issue clearances following TGA inspections.

- **Inspectorate**
  Undertaking inspections of Australian manufacturing facilities, undertaking inspections of overseas manufacturing facilities where required and undertaking investigations into GMP Compliance Signals

- **Licensing and Certification**
  Responsible for licensing of Australian Manufacturers, receiving and reviewing requests for inspections, scheduling inspections, issuing GMP certificates for TGA inspected overseas sites, travel support and management of the GMP compliance program

- **Recalls**
  Management and co-ordination of recall activity of both medicines and medical devices

- **Manufacturing Quality Branch Manufacturers Assessment Support Section**
  Providing coordination and system support to the branch, overseeing business improvements
Manufacturer Approval

- All medicine manufacturers must receive approval from the TGA prior to manufacture and supply of products in Australia, unless exemptions or other provisions apply.
- An approval demonstrates that the manufacturing site complies with the principles of GMP
  - Australian manufacturers – GMP licence
  - Overseas manufacturers – GMP clearance* to product sponsor of a medicine or Active Pharmaceutical Ingredients (API) if there is acceptable evidence demonstrating that the overseas manufacturer complies with the principles of GMP. Sponsors are required to obtain GMP clearance for overseas manufacturers of their registered or listed products to satisfy the legislative requirements.
- Clearances are issued for specified time periods unlike domestic licences which are perpetual
- Applications are lodged through the TGA business portal

*May be based on GMP certification following a TGA inspection
History

- GMP Clearance was introduced in the early 2000’s to reduce regulatory burden on industry, while also maintaining assurance that the suitability of the manufacturing processes and quality control procedures are appropriate.
- GMP Clearance is a non-statutory mechanism used to verify that overseas manufacturing sites comply with the principles of GMP for the products being supplied to Australia.
- Prior to the introduction of the GMP Clearance process, many sites were required to undergo an on-site inspection of the overseas manufacturing facility. This was an expensive option.
- The introduction of the GMP Clearance process has assisted in reducing the costs associated with compliance.
- The process continues to evolve in order to keep pace with changes in the global regulatory environment and industry trends, including advances in technology.
- We work with other international regulatory authorities to promote harmonisation and have entered into several Mutual Recognition Agreements (MRA) and cooperative arrangements.
GMP Clearance – 2 pathways

- **Pathway 1** - Desk top based assessment (MRA or CV)
  - Assessment of documentation from overseas regulatory authorities.
  - Regulatory documents like certificates and inspection reports
  - Manufacturer documents like Site Master files and Validation Master Plans

- **Pathway 2** - TGA on-site inspection
  - GMP Compliance signal received
  - Different regulatory framework
  - Poor compliance identified during desk top assessment
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High level TGA overseas manufacturer assessment process

1. **GMP Clearance application submitted**
2. **Identify if GMP Signal exists**
3. **Is evidence from a recognised regulator with a similar regulatory framework available?**
   - **Seek evidence from recognised regulator**
   - **TGA inspection may be required**
4. **Confirm required fees paid, documents provided, evidence is for the correct site and covers application scope**
5. **Assess documentation and determine whether evidence is sufficient to support a GMP Clearance being issued.**
   - **GMP Clearance application not issued**
   - **Issue GMP Clearance**
      - **Issue with conditions**
      - **Issue with amended scope**
Leading the way

- We are one of a few regulators who have adapted a desk top assessment process in lieu of an on-site inspection.
- Health Canada and Medicines and Healthcare products Regulatory Agency (MHRA) also use a desktop process for overseas manufacturers, to varying extents, however they also inspect and licence their importers and distributors/wholesalers (sponsors).
- PIC/S have adopted a new guidance on GMP inspections reliance based on the draft by the International Coalition of Medicines Regulatory Authorities of which Australia is the vice-chair.
- This guidance remains voluntary for PIC/S participating authorities but reflects the increasing international trend on utilising Desk Top Assessment processes where appropriate.
Agreements

• **Mutual Recognition Agreement:**
  – MRAs - treaties between Australia and other countries and are enforceable under international law
  – Department of Foreign Affairs and Trade is involved in process of entering into an MRA. Decision made at a Government not a Departmental level.
  – The parties to a MRA recognise and accept the certification issued by the relevant regulatory agency in each country in relation to manufacturers located within that country.

• **Other arrangements:**
  – Cooperation agreements
  – Memorandums of Understanding (MOUs)
  – PIC/S membership –non-binding, informal, cooperative arrangement between the authorities that regulate GMP for medicinal products. Joint membership of PIC/S enables us in some circumstances, to assess evidence from regulators in member nations using the CV pathway where the inspection is undertaken in their own country and has occurred after the authority has ascended.
Recognised authorities

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

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

Other arrangements with:
- United States Food and Drug Administration (US FDA)
- European Directorate for the Quality of Medicines (EDQM)
- Members of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)

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. For example, Complementary Medicines and Traditional Chinese Medicines are commonly not regulated as medicines in other countries.
MRA pathway

Mutual Recognition Agreement (MRA) assessment:

• The TGA accepts compliance of an overseas site with the local GMP requirements based on an assessment of a current GMP Certificate issued by the regulatory agency of the other party to the MRA provided that:
  – The manufacturer is located within the border of the MRA partner
  – The manufacturer was assessed against an equivalent GMP standard
  – The GMP certificate is current and covers the scope of the application

• Liaison undertaken with overseas regulators to obtain GMP Certificates where requested by sponsors.

• 1912 MRA applications completed to Q3 2018/19 (1810 approved, 102 not issued)

• 2511 MRA applications completed 2017/18 (2347 approved, 163 not issued)
Compliance Verification (CV) pathway

• Compliance verification applications can be submitted for:
  – MRA regulators who have performed an inspection outside their own country
  – US FDA inspections performed either within or outside of their own country
  – PIC/S participating authorities who have inspected within their own country

• Compliance Verification involves a detailed assessment of specified documentary evidence supplied by the manufacturer/sponsor. For example:
  – GMP certificate & inspection report from a recent inspection
  – Other supporting manufacturing documentation supplied by the sponsor or manufacturer such as Site Master File (SMF) and quality agreement.

• Evidence required for assessment bridges gaps between regulatory frameworks (ie release for supply requirements)

• 1327 CV applications completed to Q3 2018/19 (1093 approved, 232 not issued)
• 1913 CV applications completed 2017/18 (1649 approved, 264 not issued)
Evidence requirements

• The evidence requirements for GMP Clearance are considered carefully. They are based on risk and vary depending on
  - manufacturer location
  - inspecting authority and agreement in place
  - risk/complexity of the product/process

• The evidence requirements for each application type are outlined within the GMP Clearance Guidance document

• The evidence requirements continue to evolve with each update of the GMP Clearance Guidance and are based around changes within the international regulatory environment and updates to GMP requirements.

• Most recent update was published in March 2019.
What we do

• We review applications made by sponsors to determine whether the site complies with GMP
• We assess certificates, inspection reports, Site Master Files, Inspection History and other relevant documents to determine whether the site complies with the Manufacturing Principles.
• We assess whether the evidence supplied supports the application being made, ie the dosage forms and steps of manufacture selected within the application.
• We look at the overall systems and processes in place, not at individual products
What we don’t do

We don’t provide advice to sponsors about whether a specific product or steps of manufacture require a GMP Clearance. We refer these questions to the product regulation area as they are the experts when it comes to the product requirements, application systems and validation rules. They also know more about the products than we do as we only assess the manufacturing process not the specific product and its chemistry.
Changes in 2017

• Updated guidance (first update in 6 years)
• Applications progressed from receipt to assessment once all fees are paid
• Changed process to reduce number of times we communicated with sponsors about their application
• Increased communication with industry by providing regular updates via TGA website, TGA Business services portal, TWIGG, and other relevant channels

These changes have resulted in an overall reduction of the backlog, improved data analytics and more efficient processing of applications through a reduction in invoices raised and email correspondence.
Further changes 2018-2019

- Implemented and clarified Industry vs TGA time
- Further clarification in the GMP Clearance guidance document to further support industry in submitting complete clearance applications
- Assessment of Sterile CV applications in house rather than by inspectorate

**Future changes include:**

- Published timeframes for each application type. Significant backlog has previously prevented us from committing to timeframes, however the team have made significant progress to remove the backlog.
- Consideration of other overseas regulators and the equivalency of their manufacturing standards.

These changes will provide industry with consistent and predictable target processing times to assist them to plan their regulatory activities.
Timeframes

- MRA Applications – 30 working days
- CV – Non-sterile API – 60 working days
- CV – Sterile API – 75 working days
- CV – Non-sterile product – 90 working days
- CV – Sterile product – 120 working days

Processing timeframes commence when all fees have been paid and all documentation has been provided. Target processing times do not apply where we are required to liaise with an overseas authority or where the site is placed onto GMP Signal.

Target processing timeframes are also dependent on volume of applications received, available TGA resources and prioritisation of other applications.
Challenges

• Consistently high number of clearance applications received year on year

• Incomplete and poor quality applications

• Increase in competing priorities for applications (priority and provisional pathways, medicine shortages changes)
Future

- GMP Clearance will remain a key part of our regulatory framework
- We aim to monitor changes to the international regulatory environment and assess impact
- Work with industry to improve efficiency and clarity of the process
Website and link references

Information about the GMP Clearance process is available at:

Information about international agreements and arrangements for GMP clearance:

Regular updates about changes are provided through the Notices about GMP Clearance
  ▪ Increases to fees and charges
  ▪ Timeframes

Enquiries regarding desk top assessments using overseas regulator evidence
GMPClearance@health.gov.au

Enquiries regarding general GMP enquiries, Australian manufacturers, overseas sites seeking a TGA inspection of their facility
GMP@health.gov.au
Rheannon is currently reading over your submitted questions.

We would appreciate your participation in our live polling.
We’ll will be back shortly for Q&A

LIVE POLL
Question time
More on TGA visit………………

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