TGA – ARCS 2018
Good Manufacturing Practice and the TIWGG

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Inspections Section

21 August 2018
Today’s agenda

• Update on the 2018 GMP Forum
• GMP clearance processes including a review of improvements implemented in September 2017 and future improvements
• GMP clearance and inspection metrics
• Overview of TGA involvement in PIC/S
• Update on the TGA Industry Working Group on Good Manufacturing Practice (TIWGG)
Today’s agenda

• PIC/S update and process of industry input into guidance materials
• Common deficiencies
• Overseas inspections
History and overview

• All medicine manufacturers must receive an approval from the TGA before manufacture and supply of products to Australia, subject to exemption provisions and other requirements.

• Approvals – demonstrate compliance to the principles of Good Manufacturing practice
  – Australian manufacturers - GMP licence
  – Overseas manufacturers - GMP clearance to product sponsors

• An application must be lodged via the TGA business portal (licence, GMP clearance or GMP certification)
History and overview

• GMP Clearance process 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

• Clearances are required for the purpose of ARTG registration or listing and for continued supply once products have been registered or listed

• Clearances are granted to Australian sponsors for a specific time period only

• Two pathways to obtain a GMP clearance:
  – Desk top based assessment
  – TGA on-site inspection
GMP Clearance Process

• The GMP Clearance process was introduced as a way to reduce the regulatory burden on industry while maintaining assurance that the suitability of manufacturing processes and quality control procedures are appropriate.

• Prior to the introduction of the GMP Clearance process, the default requirement was to have an on-site inspection of the overseas manufacturing facility.

• As at 30 June 2017, there were 207 manufacturing sites that were subject to TGA inspection and approximately 2,700 overseas manufacturing sites that relied on evidence from recognised regulators.
GMP Clearance Process

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

• The evidence requirements have evolved through each iteration of the GMP clearance guidance

• Historically these requirements have been reduced as confidence in overseas regulatory authorities has increased
International comparison

• We are one of the few regulators that have adopted a Desk Top Assessment (DTA) process in lieu of an onsite inspection.
• Health Canada also use a desktop process for overseas manufacturers however they inspect and license their importers and distributors (sponsors).
• PIC/S recently adopted a new guidance on GMP inspection reliance based on the draft by the International Coalition of Medicines Regulatory Authorities (ICMRA) of which Australia is the vice-chair.
• The level of adoption by PIC/S participating authorities remains voluntary but reflects the increasing international trend on utilising DTA processes where appropriate.
Improvements made in 2017

There were 5 main areas identified during internal improvement reviews. These were:

• Guidance & Education
• IT system
• Application data management
• Process flows and functionality
• Communication

Complete revision of the GMP clearance guidance document and the first update in over 6 years
Clearance Application Assistance Tool (CAAT)

- CAAT was created as a way to assist sponsors in preparing better quality GMP clearance applications by:
  - determining the general evidence requirements for their GMP clearance applications
  - complementing the updated GMP Clearance Guidance and the redesigned e-forms
  - Allowing a “dry run” before submitting an incorrect application
- Sponsors can access the tool directly from the TGA website or via hyperlinks in the guidance and e-forms as they process
Re-designed tBS e-forms

• The online e-forms were updated to improve the user experience for applicants by:
  – reducing duplication and pre-populating data with information that already exists on other TGA databases
  – improving the help functionality on the form to assist applicants
  – improving invoicing functionality and visibility of cost
  – allowing extension requests to be submitted via tBs
  – Improving data capture of critical information (i.e. priority of application)
Process and communication

• Streamlined receipt and assessment process for CV applications consisting of:
  – Progression of applications from receipt to assessment once all fees have been paid
  – Reduction in several rounds of correspondence to applicants during assessment

• Improved communication by providing regular updates to industry via the TGA website, TIWGG, TGA Business Services (tBS) portal and email signature blocks
Benefits realised to date

- 30% reduction in the number of invoices TGA staff have to raise internally
- Improved quality of applications submitted, since Sept 2017, we estimate that approximately 70% of applications are submitted with the required evidence
- Reduction of approximately 250 emails per month received to the GMP clearance mailbox
- Reduction in time and effort by TGA staff to produce internal reports, by approximately 40%. This allows improved management of applications by TGA
Benefits yet to be realised

• Data analytical reporting potential cannot be fully realised until all applications in the system migrate to the new e-form

• The impact of the streamlined receipt and assessment has not yet been felt by industry due to the current backlog of applications

• Continued education will be required to:
  – Increase the number of applications that don’t require fees to be raised by TGA staff
  – Decrease the number of applications submitted with insufficient evidence
Applications received annually

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Data taken on 04 July 2018
Where we are now

GMP Clearances - Total

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<td>1-May-18</td>
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# CV's total

# MRAs total
Where we are now

Applications by type - Trend over time
Ongoing Challenges

- The number of GMP clearance applications continues to increase annually
- Incomplete CV applications and poor quality applications
- Increase of competing priorities for applications (i.e. priority and provisional pathways)
- Historical backlog of CV’s resulting in extended processing timelines
The future of GMP clearance - TGA perspective

• The GMP Clearance process will remain an integral part of our regulatory framework
• We aim to monitor changes to the international regulatory environment (such as the PIC/S adoption of GMP inspection reliance) and assess any impact
• We will continue to work with industry to improve the efficiency and clarity of the process through the appropriate forums (TIWGG and associated working groups)
• We aim to continue to communicate updates, issues and trends for GMP Clearance through the TGA website, the TBS portal and through email
Inspection metrics
Domestic Inspection Outcomes
(Medicines and Blood, Tissue and Cellular Therapies)

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<th>Category</th>
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<th>FY 11/12</th>
<th>FY 12/13</th>
<th>FY 13/14</th>
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<td>2%</td>
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Source: data extracted 01 May 2018
# Overseas Inspection Outcomes

*(Medicines and Blood, Tissue and Cellular Therapies)*

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*Source: data extracted 01 May 2018*
Overview of TGA involvement in PIC/S

• TGA involvement includes
  – PIC/S reassessments of existing PIC/S members
  – Assessments of proposed PIC/S members
  – Joint inspections with MHRA, USFDA, Health Canada, HPRA
  – Shared information under confidentiality agreements with PIC/S members
Overview of TGA involvement in PIC/S

• TGA has provided training to various regulatory agencies e.g. Medsafe, ThaiFDA, and USFDA.

• TGA successfully hosted the Expert Circle on APIs in 2017

• TGA has been involved in PIC/S drafting groups
PIC/S committee structure

OVERVIEW ON SUB-COMMITTEE STRUCTURE

Most competences of the PIC/S Committee are delegated to Sub-Committees, which report back to the Committee.

**PIC/S Committee**

- Election of office holders & SC Members;
- Treaty power
- Acceptance of new PA
- Adoption of budget
  - Etc.

**Plenary Meeting:** operates PIC Scheme and takes decisions

- Sub-Committee on Compliance
  - Plans & reviews both assessments & reassessments
- Sub-Committee on Strategic Development
  - Reviews PIC/S strategy & policies
- Sub-Committee on Harmonisation of GM(D)P
  - Harmonises GM(D)P & establishes Best Practice
- Sub-Committee on Communication
  - Defines communication strategy
- Sub-Committee on Budget, Risk & Audit
  - Assesses all risks, reviews audits; prepares budget
- Sub-Committee on Expert Circle
  - Reviews activities of Expert Circle
- Sub-Committee on Training
  - Plans & reviews GMP Training
TGA Industry Working Group on Good Manufacturing Practice (TIWGG)

• The TIWGG was established in 2014 to facilitate consultation between TGA and the industry on matters relating to good manufacturing practice (GMP).

• The TIWGG will also provide a mechanism for TGA to seek comments from the Australian industry on the revision, development and application of PIC/S guidelines.
TGA Industry Working Group on Good Manufacturing Practice (TIWGG)

- To prioritise and discuss issues of a regulatory and technical nature arising from current regulation and propose solutions
- To determine the need for establishing a Technical Working Groups (TWGs) to develop e.g. guidance
- Oversight the work of TWGs established by the TIWGG, including making decisions on when the work of a TWG has been completed.
TGA Industry Working Group on Good Manufacturing Practice (TIWGG)

• To provide a forum for members to raise regulatory or technical issues of concern, both current and emerging, faced by the TGA, the representative associations or members of the manufacturing community generally.

• To inform parties about TGA’s present and future activities relating to GMP.
TGA Industry Working Group on Good Manufacturing Practice (TIWGG)

The TIWGG is comprised of representatives from TGA and peak therapeutic goods industry bodies as follows:

- Head, TGA Office of Manufacturing Quality (Chair)
- Accord
- Australia New Zealand Industrial Gas Association (ANZIGA)
- Active Pharmaceutical Ingredient Manufacturer’s Association of Australia (APIMAA)
- Australian Self Medication Industry (ASMI)
- Complementary Medicines Australia (CMA)
- Generic and Biosimilar Medicines Association (GBMA)
- Medicines Australia (MA)
PIC/S update and process of industry input into guidance materials

- The TGA will develop a gap analysis of the proposed changes with the PIC/S version
- Changes are assessed as to impact
- The industry representatives in the TIWGG will review the changes and share the information with their members as part of the consultation
PIC/S update and process of industry input into guidance materials

• The feedback is reviewed from the consultation

• This feedback may include the update to guidance documents, development of guidance.
Common deficiencies
Common deficiencies for non sterile medicines manufacturers

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<th>2017 – Domestic and overseas manufacturers</th>
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<td><strong>Poor investigations</strong></td>
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<td><strong>Marketing authorisation</strong></td>
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<tr>
<td><strong>Potential for cross contamination</strong></td>
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<td><strong>Change control</strong></td>
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<td><strong>Procedures/documentation</strong></td>
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<tr>
<td>validation</td>
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Overseas inspections

• TGA has 22 Inspectors who perform GMP inspections

• 20 inspectors perform overseas inspections

• Inspectors could perform between 2 and 4 overseas inspections per year as well as domestic inspections
Overseas inspections

- The inspections have different durations based on risk and complexity
- Inspections can vary from 1 day to 6 days depending on the risk and complexity of process
- There could be team inspections or solo inspections
Overseas inspections

• We don’t publish an inspection agenda and manufacturers see this at the opening meeting of the inspection

• Inspections are typically closed out to timeframes unless there are issues. For example

• Poor or delayed responses
Questions?

Thank you