Latest trends in manufacturing quality
Enhancing the TGA inspection process

Harry Rothenfluh PhD
Assistant Secretary
Manufacturing Quality Branch
Monitoring and Compliance Division, TGA
ARCS Scientific Congress 2015

5 May 2015
Overview

• TGA manufacturer assessment process and workloads
• Challenges
  – What can sponsors do
  – What is TGA doing
  – Common deficiencies
Manufacturing Quality Branch

On-site inspections of manufacturers and compliance verifications (paper-based assessments)

Australian and overseas manufacturers are assessed prior to supply of goods and are then regularly reviewed

Inspections against the relevant Code of Good Manufacturing Practice (GMP) or Standard (devices) which describes the range conditions required for safe, sterile production of goods

Quality manufacturing
High level TGA manufacturer assessment process

- **Is evidence from recognised regulator available?**
  - Yes: If evidence is acceptable, GMP clearance issued.
  - No: Inspections scheduling
    - Arrange inspection dates with:
      - Manufacturer
      - Sponsor
    - Plan inspection
    - Conduct inspection
    - Close out inspection and assign A1, A2, A3 or U rating
    - Issue licence/certificate & clearance
    - Close out inspection and assign A1, A2, A3 or U rating
    - Issue licence/certificate & clearance

Latest trends in manufacturing quality
## TGA manufacturer assessment workloads

<table>
<thead>
<tr>
<th>Manufacturer assessment type</th>
<th>Annual volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of domestic inspections</td>
<td>200 – 250</td>
</tr>
<tr>
<td>Number of overseas inspections</td>
<td>100 – 150</td>
</tr>
<tr>
<td>Number of GMP clearance applications</td>
<td>2500 – 4200</td>
</tr>
</tbody>
</table>

Given the high volume of tasks involving complex information sponsors and TGA both play a role in identifying and addressing challenges.
Challenge: Drop in and drop out inspections

Challenge
‘Drop outs’ – inspections not needed due to change in circumstance but TGA finds out only when contacting sponsor before an inspection. Inspectors and scheduling staff will have already invested time in planning and preparation.

‘Drop ins’ – applications for new facility

Sponsor
‘Drop outs’ – please notify TGA asap if:
• you are no longer planning to use a manufacturer
• you intend to use evidence from another regulator

‘Drop ins’ – please tell TGA about planned new facility as early as possible in the building/fit out process.

TGA
Currently assessing business process improvements to reduce workloads associated with inspection scheduling

Latest trends in manufacturing quality
Challenge: Manufacturers with multiple sponsors – invoicing

Challenge
Some manufacturers are used by >12 sponsors. Any delays in process has significant impact on TGA inspections planning and invoicing.

Sponsor
Please respond to TGA requests for pre-inspection confirmation that manufacturer is still supplying product to sponsor asap.

TGA
No feasible alternatives identified to date.

Latest trends in manufacturing quality
Enhancing the inspection process

- Inspections scheduling
  - Arrange inspection dates with:
    - Manufacturer
    - Sponsor
  - Plan inspection
  - Conduct inspection
  - Close out inspection and assign A1, A2, A3 or U rating
  - Issue licence/certificate & clearance

TGA
Internationally harmonised practices.

Latest trends in manufacturing quality
Challenge: \( \uparrow \) deficiencies = \( \uparrow \) inspector work load

Challenge
Work associated with closing out inspections of manufacturers with identified deficiencies, especially A3, but also some A2 manufacturers

Sponsor
- Ensure manufacturer is aware of, and able to comply with Australian requirements

Manufacturer
- Effective QMS and quality risk management (QRM)
- Develop and implement effective corrective and preventative actions (CAPAs) to address identified deficiencies

TGA
- Currently looking at options for reducing work loads associated with close out process
- Assessing disincentives for repeat A3
- Assessing incentives for repeat A1
- Chairing PIC/S working group on Classification of Deficiencies
- Medical Device Single Audit Program (MDSAP)

Challenge Diagram:
- Inspections scheduling
  - Issue licence/certificate & clearance
  - Arrange inspection dates with:
    - Manufacturer
    - Sponsor
  - Plan inspection
  - Conduct inspection
  - Close out inspection and assign A1, A2, A3 or U rating

Latest trends in manufacturing quality
Major deficiencies commonly identified by TGA inspectors

- **Quality management system (QMS)**
  - Unsatisfactory deviation management, such as inadequate investigation and record keeping
  - Inadequate resourcing of quality management functions including product release
  - Product quality reviews not conducted or not all elements included

- **Personnel**
  - Inadequate training and skills assessment
  - Practices do not reflect documented procedures

- **Premises and equipment**
  - Absent or inadequate equipment qualification
  - Clean-rooms classification, qualification, cleanliness and maintenance – sterile manufacture
    - Aseptic processing not always performed under required conditions
  - HVAC systems inadequately designed/qualified/maintained

- **Documentation**
  - Inadequate manufacturing instructions
  - Inadequate records keeping – including batch records keeping
Major deficiencies commonly identified by TGA inspectors (cont’d)

- **Production**
  - Processes not validated or inadequately validated
    - Aseptic processes not simulated adequately
  - Revalidation not done routinely
  - Inadequate Change Control management
  - Inadequate design of facilities and equipment and procedural measures for the prevention of contamination and cross-contamination (often noted a combination of multiple factors)
  - Inadequate monitoring of manufacturing environment (sterile manufacturing)
  - Reprocessing/rework inadequately controlled

- **Quality Control**
  - Test methods not validated or validation incomplete
  - Testing inadequate and records of testing incomplete, often with ineffective review arrangements

- **Storage**
  - Storage containers not protected
  - Inadequate maintenance of storage areas
Challenge: ↑ deficiencies = ↑ inspector work load

**Challenge**
- Incomplete applications
- Insufficient information to connect information provided by manufacturer to sponsor
- Paper applications

**Sponsor**
- Please submit electronic data only
- Check that your application is complete and provides required information
- Do not submit information not required

**TGA**
- Business process reviews of:
  - GMP clearance process
  - Post-inspection close out processes
- Revision of guidelines

---

**Flowchart**
- **Challenge**
  - Issue licence/certificate & clearance
  - Close out inspection and assign A1, A2, A3 or U rating
  - Conduct inspection
  - Plan inspection
  - Arrange inspection dates with:
    - Manufacturer
    - Sponsor
  - Inspections scheduling

---

*Latest trends in manufacturing quality*
TGA – Industry Working Group on GMP

• Membership:
  – Accord
  – Active Pharmaceutical Ingredient Manufacturer’s Association of Australia
  – Australia New Zealand Industrial Gas Association
  – Australian Self Medication Industry
  – Complementary Medicines Australia
  – Generic Medicines Industry Australia
  – Medicines Australia

• To prioritise and discuss issues of a regulatory and technical nature arising from current regulation and propose solutions

• Establish and oversight Technical Working Groups to develop:
  – new, or review existing, guidelines
  – comments on draft PIC/S guidelines for tabling by TGA at PIC/S meetings
  – guidance documents