TGA’s GMP Audits:
Trends and observations

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Essentials

• The GMP Audit program in the context of OMQ’s manufacturer assessment programs

• Some statistics

• A typical TGA medicines audit

• Overseas GMP audits as opposed to domestic audits

• Issues found

• Provisional top 10 of categories of deficiencies found

• Crystal ball on GMP
Mission of OMQ

“Providing the community with confidence about the quality and safety of manufactured therapeutic goods available in Australia”

Therapeutic goods = Medicines/Medical Devices/Biologicals
GMP audit program

• Not a stand-alone program, but embedded in OMQ’s two manufacturer assessment programs:
  - Licensing and certification of domestic manufacturers
  - Clearance and certification of overseas manufacturers

• Based on either an application:
  - Licence application or variation (domestic only)
  - GMP Certification application or variation:
    • Domestic manufacturer (for export purposes)
    • Domestic veterinary manufacturer (for export under MRA)
    • Overseas manufacturer connected to a clearance
  - Clearance application (overseas only)

• Or a re-audit for a manufacturer already in the audit program
  - Risk based frequency (parameters: product type and compliance rating)
Medicines manufacturing statistics

Domestic

- Non-sterile: 70%
- Sterile: 30%

Overseas

- Non Sterile: 59%
- Sterile: 41%

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Medicines manufacturing statistics

- API
- Packaging
- Storage
- Full
- Testing

Domestic vs Overseas
Domestic medicines manufacturers

- Audit only
- Audit outcome also used by the TGA’s overseas regulatory partners
- Audit prior to issue of a licence
- Periodical re-audits
- All licensing arrangements and obligations outlined in the Therapeutic Goods Act (1989) and the Therapeutic Goods Regulations (1990)
Domestic Metrics per annum

- ~300 Licences
- ~500 Sites
- <350 audits
- ~75% Good/Avg
- ~23% Basic
- ~2% Unacceptable
- ~90% on time
Overseas medicines manufacturers

• Clearance: given to an Australian sponsor or manufacturer, to use a specified overseas manufacturer, based on Compliance Verification by the OMQ:
  – Audit by an MRA regulator (Mutual Recognition Agreement: EU, Canada, Singapore) in their own country
  – Audit by MRA regulator in third countries or by MoU or PIC/S regulator in their own or third countries
    • Examples are US-FDA; NZ. These are also formal arrangements, but with option not to accept
  – TGA Audit
    • If TGA audited, same principles and procedures applied as for domestic manufacturers
Overseas Metrics per annum

1,500 Manufacturers
>2,000 Sites
>3,000 clearances
~70% on time
150-200 audits
~80% Good/Avg
~17% Basic
~3% Unacceptable
~80% on time

Europe 54%
US/Canada 15%
India 13%
China 6%
New Zealand 5%
Other 7%
Typical medicines manufacturer audit

- 1-5 audit days, 1-2 auditors, sometimes with a specialist from other TGA Offices

- Cover all aspects of Code of GMP:
  - Quality system, deviations handling, change control, release for supply, complaints, recall, self inspection
  - Personnel, organisation description, training
  - Documentation system
  - Facilities, maintenance, calibration
  - Warehouse, quarantining, sampling, weighing
  - Production
  - Quality Control
  - Contracts
  - ARTG conformity
Typical medicines manufacturer audit

- If announced, usually 2-4 weeks prior to audit
- Preparation incl. review previous audits, ARTG entries
- Audit: leave manufacturer with written overview of issues identified by audit team
- Report: internal review, issued 4 weeks after audit
- Corrective action plan required, including for any majors/criticals:
  - Root cause identification
  - Objective evidence
- Reviewed and closed out if acceptable
- Review of implementation of corrective actions at next audit
- Re-audit scheduled, licence or certificate issued
Variety of overseas manufacturers (1)

• Dosage forms manufactured:
  – Vaccines
  – Steriles
  – Non-steriles
  – Generics
  – Active Pharmaceutical Ingredients (APIs)
  – Complementary medicines, including Traditional Chinese Medicines

• Situation of the manufacturer, e.g.:
  – Local affiliate of multinational
  – One site of a local multi-site manufacturer
  – Single site local manufacturer expanding business

• Typically the top 10% of manufacturers in each country apply for GMP certification to export products around the world and specifically Australia
Variety of overseas manufacturers (2)

- Variety in understanding of internationally harmonised cGMPs
  - Local GMPs may be more stringent than "our" PIC/S GMP, or less
  - Depending on the country, international standards being in English only may be an issue for the manufacturer’s lower / middle management and up

- Variety in aim for manufacturer to have TGA audit:
  - Primary purpose may be to use TGA certification to obtain entry into other markets (Europe, Asia), rather than export to Australia

- Variety in supply chain situations:
  - APIs typically (but not always!) include all GMP relevant steps of synthesis
  - For many finished products Asian manufacturers do only a few steps in manufacture (e.g. bulk only)
Overseas GMP audits:

• Local agency (national level) is advised about the audit being scheduled and invited to attend *as an observer*. The purposes are:
  – Developing cooperation
  – Confidence building
  – Opportunity to discuss on-going issues
  – In some cases, observers may assist with translation
  – We’d like to be informed too if they audit Australian manufacturers

• Some countries attend TGA audits whenever they can, some never do

• OMQ pursues options of work sharing with other regulators (US-FDA, Health Canada, EU, Singapore and WHO) in auditing Asian manufacturers
Some challenges when auditing overseas (1):

- Language issues / working with an interpreter
- May make a few introductory moves before getting to the point
- In some countries a tendency to say “yes” to build a good relationship with the questioner
- Background of local individuals may be of significance to their role within the manufacturer’s team
- Tendency to try and lead the auditor through the audit / facility in a pre-determined pathway
Some challenges when auditing overseas (2):

- Tendency for management to avoid the auditor directly interviewing lower level staff
  - May be embarrassing if management does not know details of process

- Tendency of manufacturer to assume individual failure while auditor looks for system failure
  - Potential consequences for individual involved

- Sometimes exuberant hospitality

- Each country has its very own specifics
Supply chain issues during audit:

- **Supply chain clarity:**
  - Supply chain often not clearly documented
  - Supply chain may change very quickly and frequently
  - Multiple suppliers used for each material

- Contracting out steps to local sites, e.g. QC test laboratories not audited by the TGA

- Issues with trade secrets between different steps in supply chain

- Issues with steps of manufacture taking place outside the audited facility

- Issues with the annual sales of a manufactured material exceeding the maximum factory capacity

- Issues related to falsification or addition of certain ingredients to change characteristics

**GMP Agreements**
Auditing computer systems at overseas manufacturers

• When part of a multinational or a multi-site local manufacturer:
  – Typically same computer systems as (overseas) owners
  – Typically managed, validated etc from corporate site
  – May be hard to obtain evidence during audit
  – Sometimes little on-site knowledge on computer systems

• When one-site local manufacturer:
  – Many avoid using computers in manufacture to avoid being audited on the topic
  – Often little understanding on computer management and validation
  – If they use computers, it’s typically:
    o In-house made systems from MS Office etc
    o Fully bespoke systems built by a local supplier
    o Older systems
Auditing computers at a site that is recently taken over by a multinational:

- Does the computer system fit the specific needs of the local site?
- Are SOPs relating to use of computer effectively implemented?
- Do relevant staff understand the specifics of the system?
- If all validation is done off-site (e.g. by regional HQ):
  - Does auditee have sufficient data to demonstrate validation status?
  - Does the auditee have sufficient understanding of the validation?
  - When was ‘corporate’ validation completed? If prior to take-over, what was done to validate local site after take-over?
- Who manages:
  - Updates, versions and their implementation
  - Audit trail
  - Backups, archives
  - Test environments
- GMP agreements also expected between sites of a multinational
Auditing computers at a one-site local manufacturer:

- If the manufacturer states not using computer systems for GMP relevant activities:
  - Look for any “hidden” systems used, like:
    - Calculations spreadsheets
    - Printing labels
    - Lab equipment like HPLCs

- If the manufacturer uses locally built system, e.g. MRP:
  - Often bespoke systems
  - Often older with longer revision / version history
  - Rarely software supplier audits done by the manufacturer
  - Rarely validated to current standards
Provisional top ten of categories of deficiencies (2010/11):

1. **Product Quality Reviews**
   - New requirement in Australia since 2009, not new internationally
   - Grouping, getting results in

2. **On-going stability testing program**
   - Not new in Australia, but new GMP provides much more detail
   - Outsourcing issues
   - Trade secrets

3. **Quality Risk Management**
   - New concept for many ‘lower end’ manufacturers
   - System issues

4. **Release for supply issues in relation to these**

5. **GMP agreements covering the entire supply chain**
Provisional top ten of categories of deficiencies (2010/11):

6. Contamination control
   – Including Environmental control / HVAC

7. Documentation and records

8. Starting material and packaging material receipt / testing

9. Sterility assurance

10. Handling of changes, deviations, out-of-specs
Crystal ball on GMP

- Australia intends to adopt next versions of PIC/S Guide to GMP, probably every 3-5 years, so in 2-3 years from now
- Exact timing depends on upcoming changes to PIC/S GMP:
  - Balance between significance of changes in PIC/S GMP, changes in the pipeline and time/efforts for OMQ
- Changes foreseen:
  - Annex 3: radiopharmaceuticals
  - Annex 2: biological products
  - Annex 6: medicinal gases
  - Annex 7: herbal medicines
  - Annex 13: investigational medicinal products
  - Chapters 1 + 2: implementation of ICH Q10
  - Chapter 3 + 5: dedicated facilities
  - Chapter 4 + Annex 11: e-documentation systems
  - Chapter 5: API supply chain; raw materials control
  - Chapter 6: general update and fixing gaps
  - Chapter 7: outsourcing
Thank you

Some additional challenges when auditing overseas:

- Facing the difference between rich and poor
- Selecting healthy food
- Having your laundry done