



Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

TGA's GMP Audits:

Trends and observations

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TGA Health Safety
Regulation



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



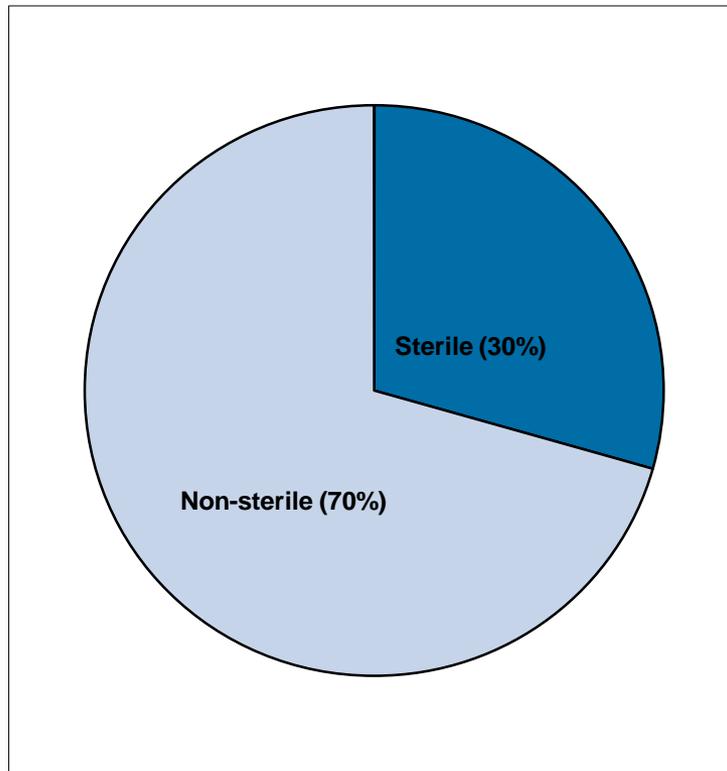
GMP audit program

- 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)

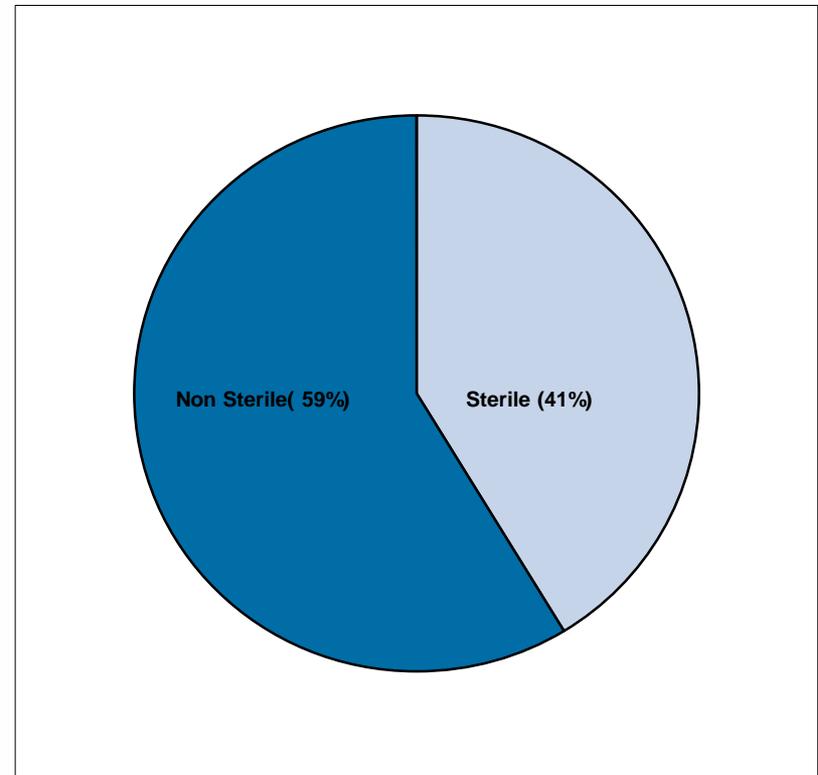


Medicines manufacturing statistics

Domestic

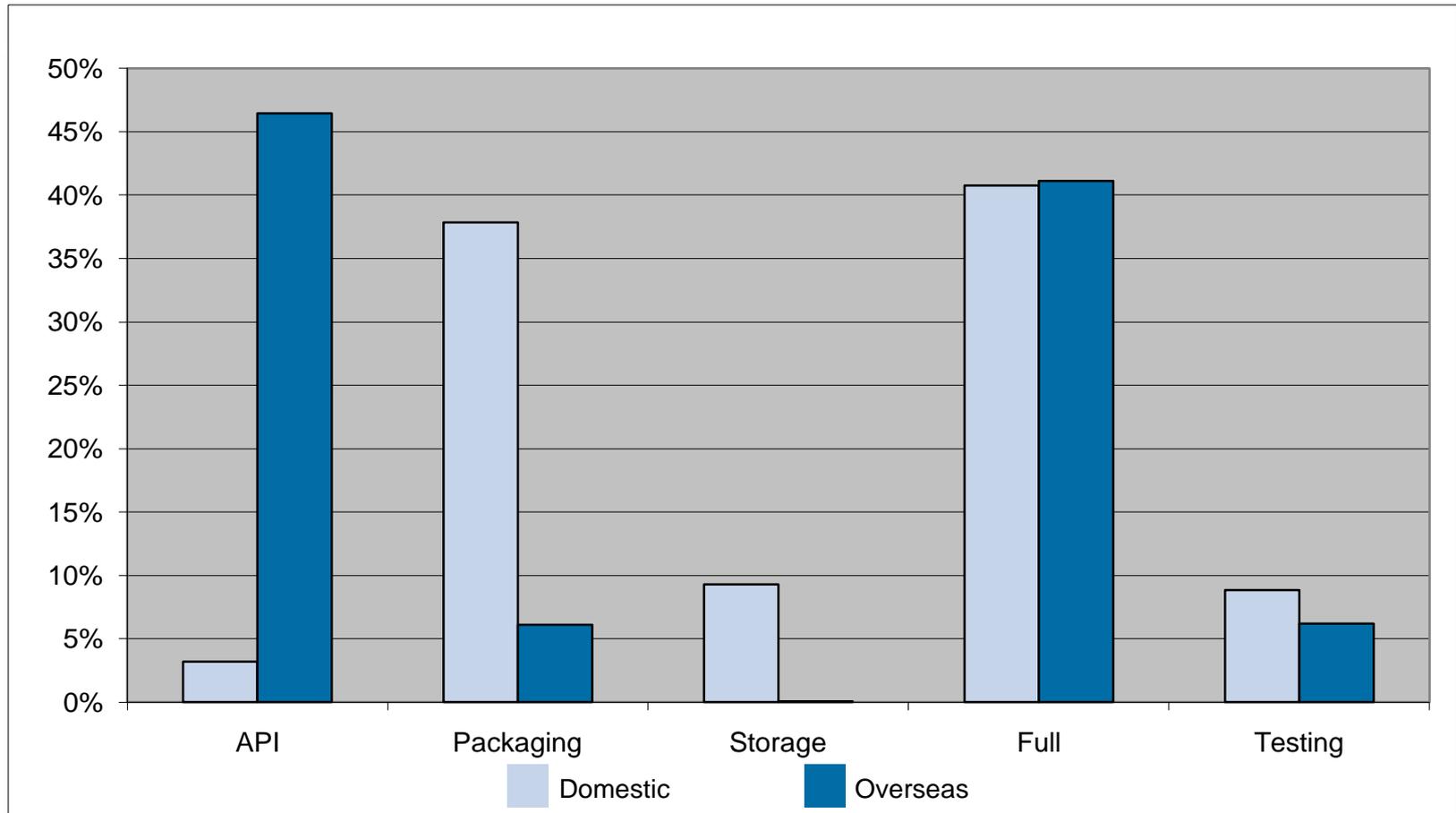


Overseas





Medicines manufacturing statistics





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

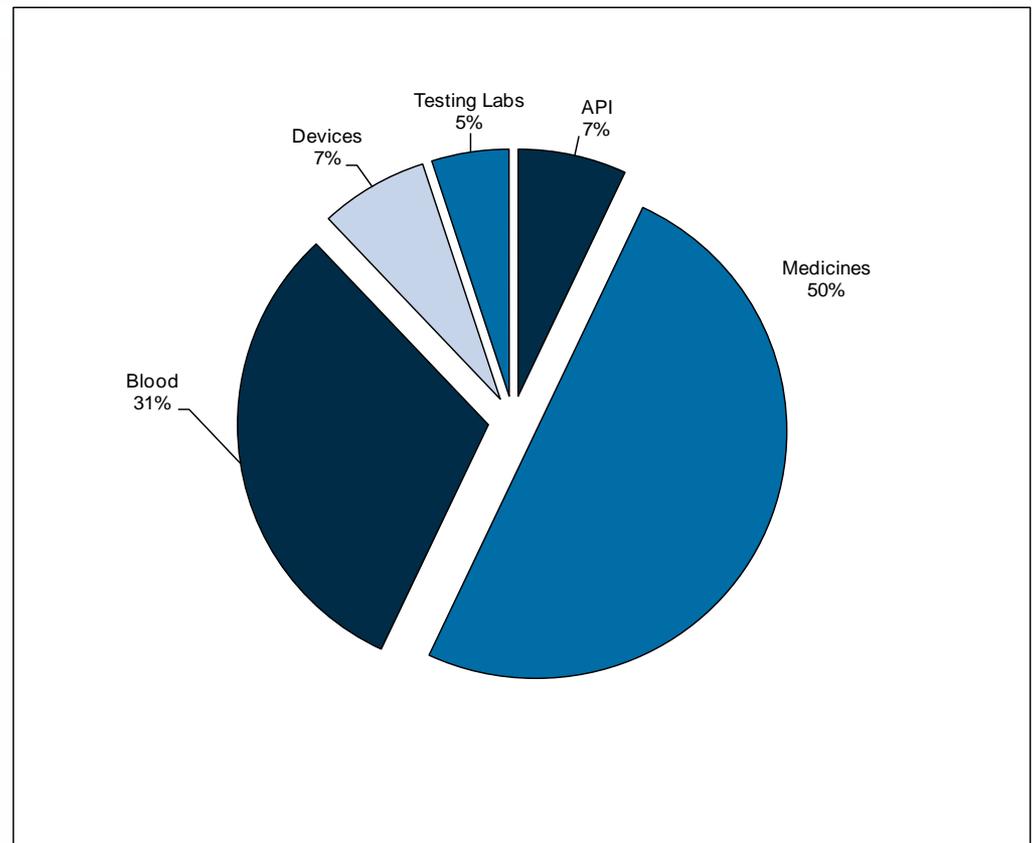
<350 audits

~75% Good/Avg

~23% Basic

~2% Unacceptable

~90% on time



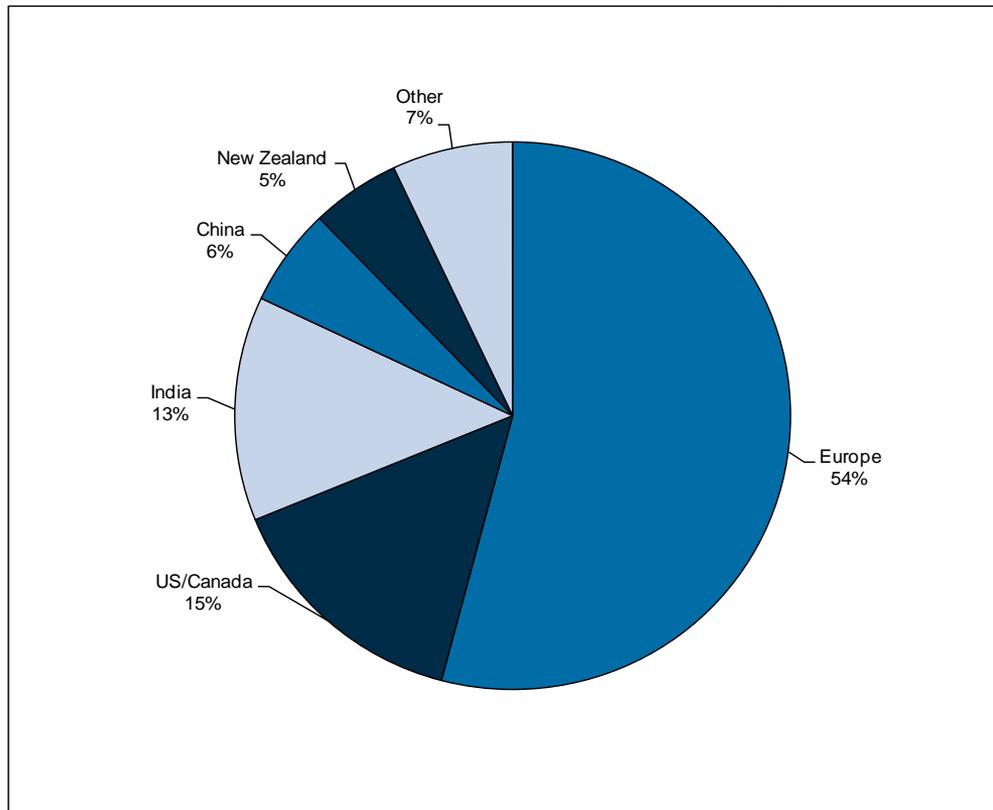


Overseas medicines manufacturers

- 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



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:
 - In-house made systems from MS Office etc
 - Fully bespoke systems built by a local supplier
 - 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

GMP Agreements



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:
 - q Annex 3: radiopharmaceuticals
 - q Annex 2: biological products
 - q Annex 6: medicinal gases
 - q Annex 7: herbal medicines
 - q Annex 13: investigational medicinal products
 - q Chapters 1 + 2: implementation of ICH Q10
 - q Chapter 3 + 5: dedicated facilities
 - q Chapter 4 + Annex 11: e-documentation systems
 - q Chapter 5: API supply chain; raw materials control
 - q Chapter 6: general update and fixing gaps
 - q Chapter 7: outsourcing



Thank you

Some additional challenges when auditing overseas:



Facing the difference
between rich
and poor
ISPE Conference



Selecting healthy food



Having your laundry
done