Successful Inspections - Before, During and After

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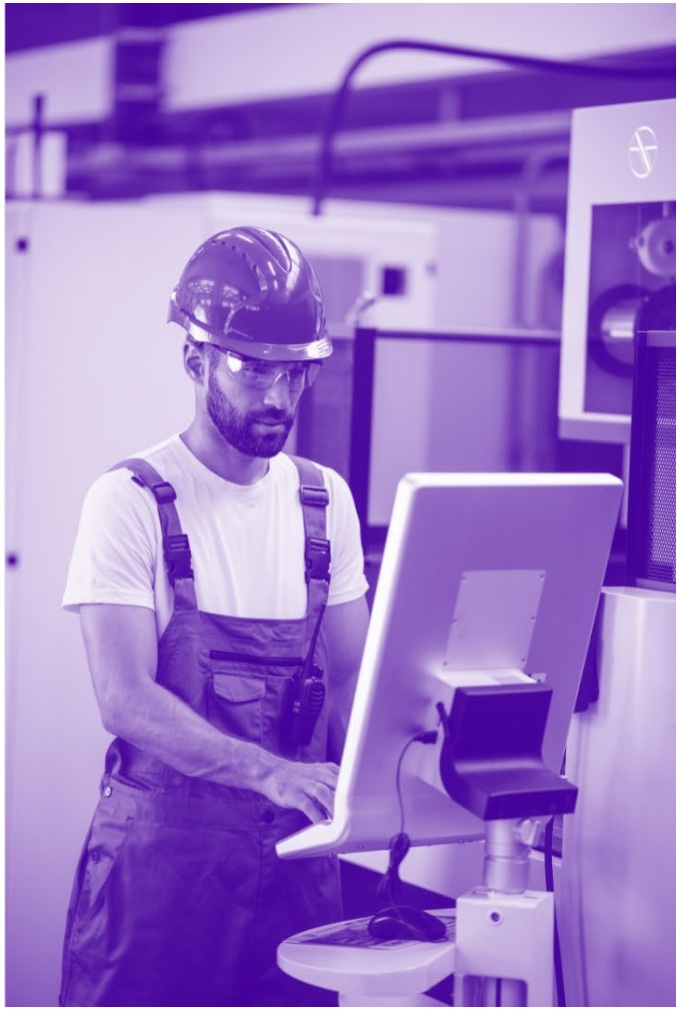
GMP FORUM 2024

Agenda

- Types of inspections
- Importance of GMP inspections
- GMP Code & Coverage
- Inspection preparation and process
- Expectation at Inspection
- Effective close out
- Cases
- Q&A

Inspection Types

- **Initial inspection**
- Variation inspections
- Routine re-inspections
- Compliance inspections



Both domestic and overseas manufacture for the Australian market

Initial inspection
A new manufacturing site in Australia or the first time TGA inspects an overseas manufacturing site

Purpose
To assess the GMP compliance of the facility, quality system and processes for issuing a licence or certificate

How to be successful
Engage early, understand application and inspection timeframes for effective planning.

Inspection Types

- Initial inspection
- **Variation inspections**
- Routine re-inspections
- Compliance inspections

Both domestic and overseas manufacture for the Australian market

Variation inspection
A variation inspection assesses the ability of a manufacturing site to undertake a new process

Purpose
To allow licensed sites in Australia to vary their manufacturing licences

How to be successful
Engage early, understand application and inspection timeframes for effective planning.

Inspection Types

- Initial inspection
- Variation inspections
- **Routine re-inspections**
- Compliance inspections

Both domestic and overseas manufacture for the Australian market

Routine re-inspection
A risk based inspection program of licensed sites and overseas sites supplying Australia.

Purpose
Ongoing assessment of the GMP compliance of manufacturing sites.

How to be successful
Be inspection ready. Maintain your QMS and corrective and preventative actions.

Inspection Types

- Initial inspection
- Variation inspections
- Routine re-inspections
- **Compliance inspections**

Both domestic and overseas manufacture for the Australian market

Compliance inspection
An inspection triggered by information received by the TGA to determine possible enforcement actions.

Purpose
To assess a compliance signal at either licensed sites or overseas sites supplying Australia

How to be successful
Be transparent, provide requested information and explain your processes to show how your systems are GMP compliant

Importance of GMP Inspections

Effective application of GMP Level of compliance
Marketing Authorisation verification

Additional reasons we may plan an inspection of a manufacturer:

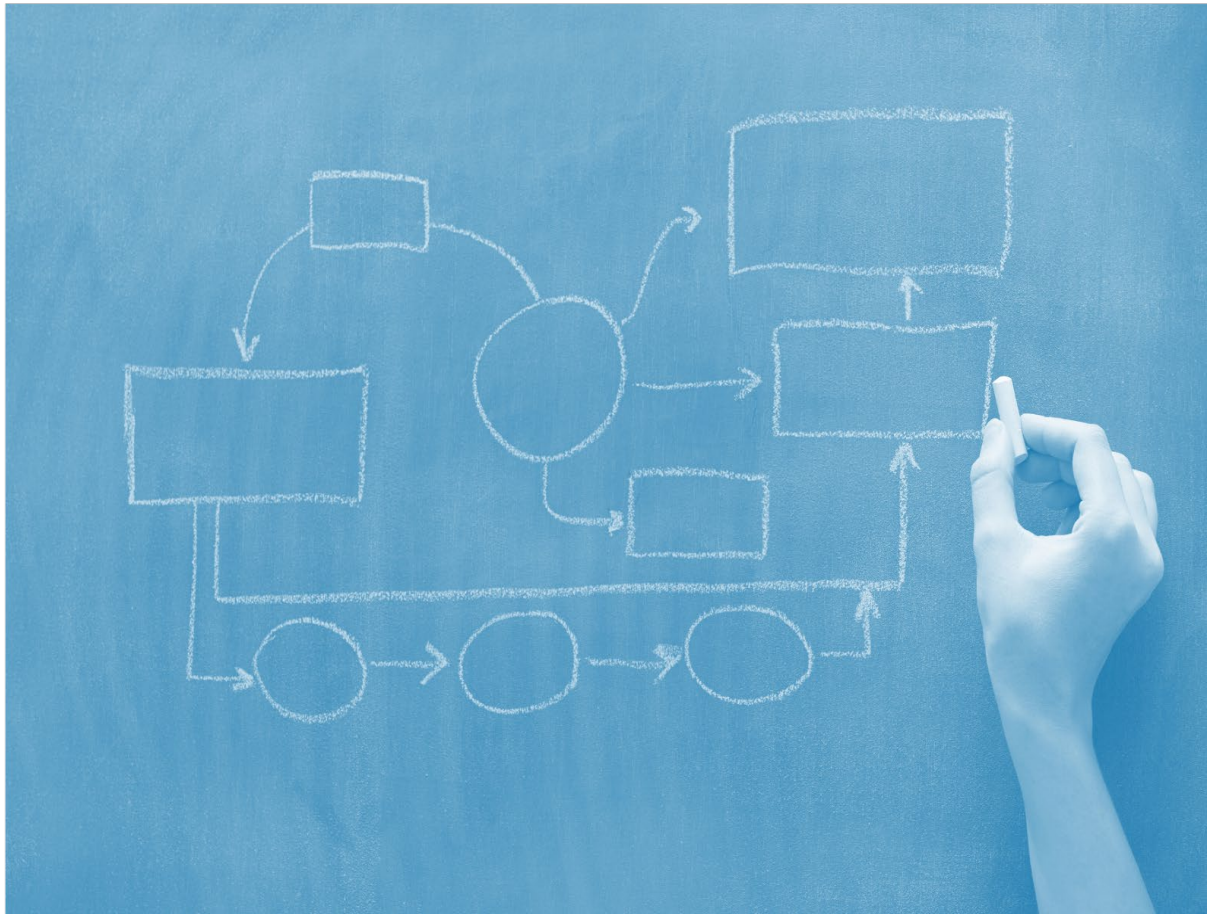
- Review the effective close out of CAPAs
- Follow-up after product recall
- Examine specific quality issues
- Collect evidence in an unannounced inspection

Importance of GMP Inspections

Verify effective application of GMP

Effective Pharmaceutical Quality System (PQS)

- Facility
- Systems
- Processes
- Equipment
- People
- Product quality control



Importance of GMP Inspections

Ability to investigate effectively & evaluate impacts

Ability to follow documented procedures

Ability to assess risks & control potential impacts

- New product introduction
- Equipment changes
- New technology or software introduction
- Deviation & non-conforming product or processes
- Validations & qualifications

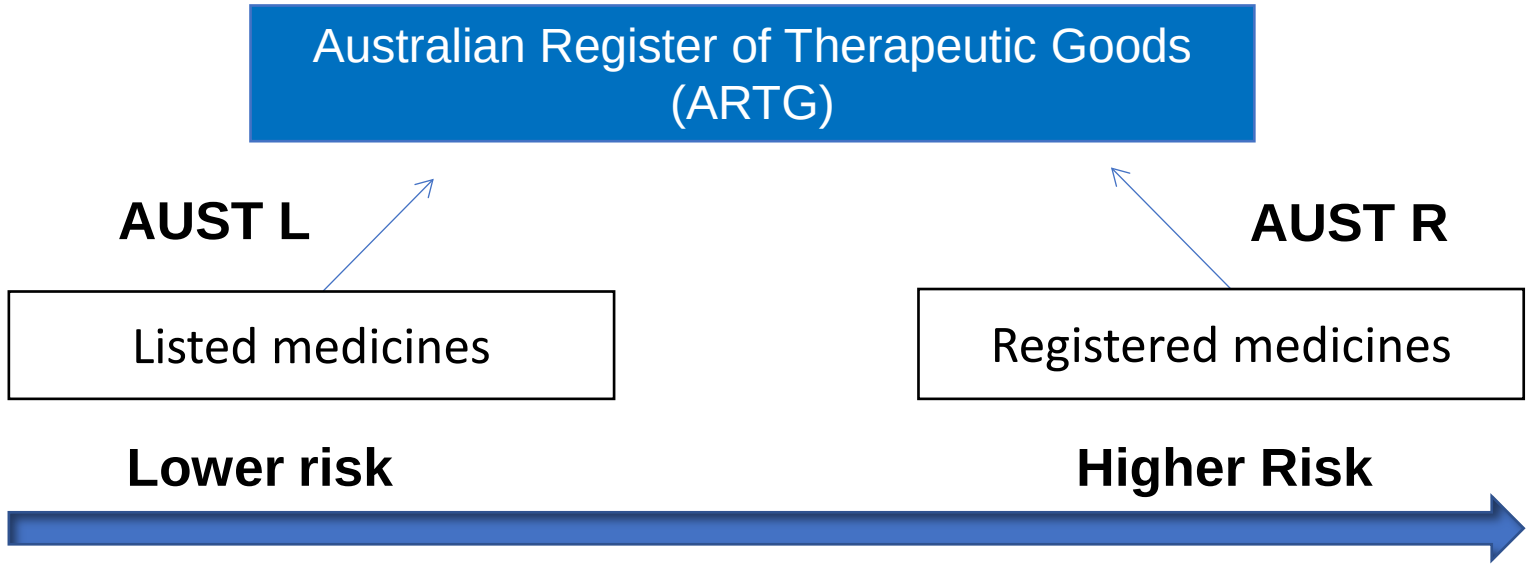
Importance of GMP Inspections

Marketing Authorisation

The approval given to supply a therapeutic good in Australia and, in most cases, involves entry on the Australian Register of Therapeutic Goods (ARTG).

Applies to:

- **Domestically manufactured** therapeutic goods approved, or unapproved, for supply in Australia
- Therapeutic goods **imported** into, or **exported** from, Australia



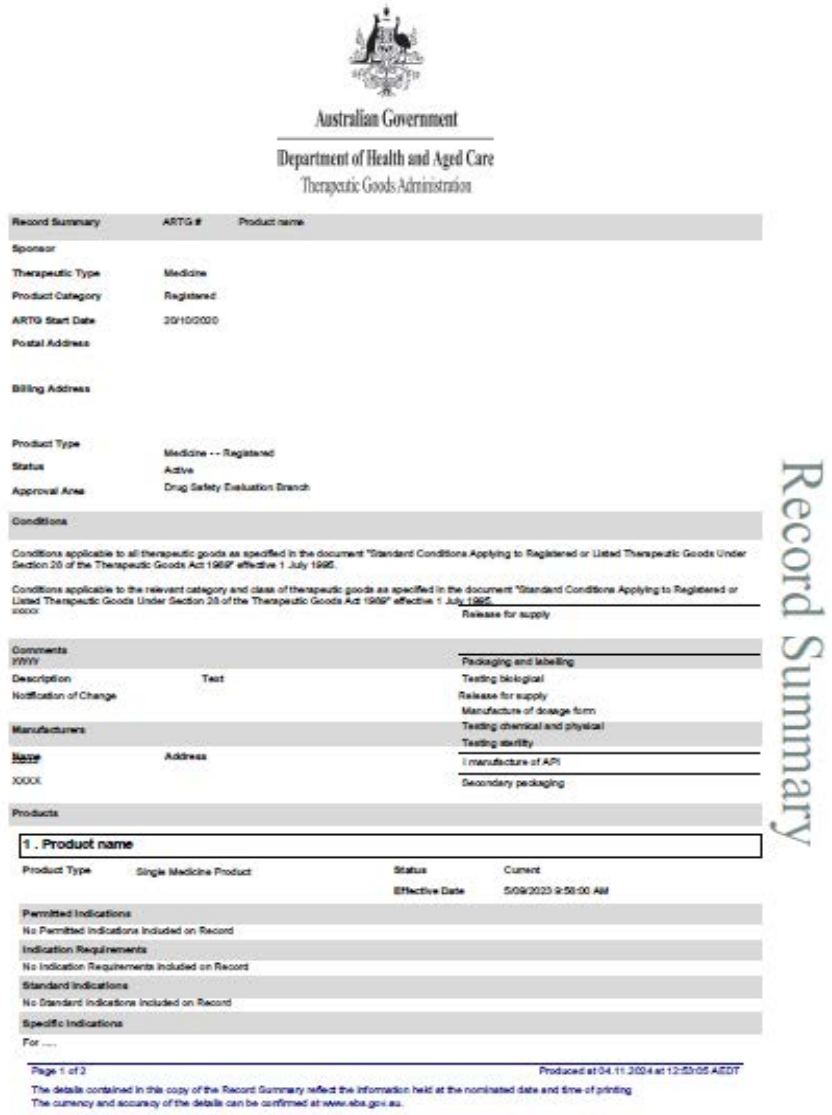
Marketing Authorisation

Australian Register of Therapeutic Goods (ARTG)

When market authorisation is granted, the product is added to an **electronic register** of therapeutic goods.

The ARTG details

- Information such as the product name, dosage form, therapeutic type, product category
- All sites of manufacturer involved in bringing the product to its finished state
- Formulation including actives and excipients
- Packaging presentation (AUSTR only)
- The ARTG entry is usually under the sponsor's name



Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Record Summary

Record Summary	ARTG #	Product name
Sponsor		
Therapeutic Type	Medicine	
Product Category	Registered	
ARTG Start Date	30/10/2020	
Postal Address		
Billing Address		
Product Type	Medicine - - Registered	
Status	Active	
Approval Area	Drug Safety Evaluation Branch	

Conditions

Conditions applicable to all therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 26 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 26 of the Therapeutic Goods Act 1989" effective 1 July 1995.
xxxx

Release for supply

Comments
wwww

Description Test

Notification of Change

Packaging and labelling
Testing biological
Release for supply
Manufacture of dosage form
Testing chemical and physical
Testing sterility
Manufacture of API
Secondary packaging

Manufacturers

Name	Address
XXXX	

Products

1 . Product name

Product Type: Single Medicine Product
Status: Current
Effective Date: 5/09/2023 9:56:00 AM

Permitted Indications
No Permitted Indications included on Record

Indication Requirements
No Indication Requirements included on Record

Standard Indications
No Standard Indications included on Record

Specific Indications
For ....

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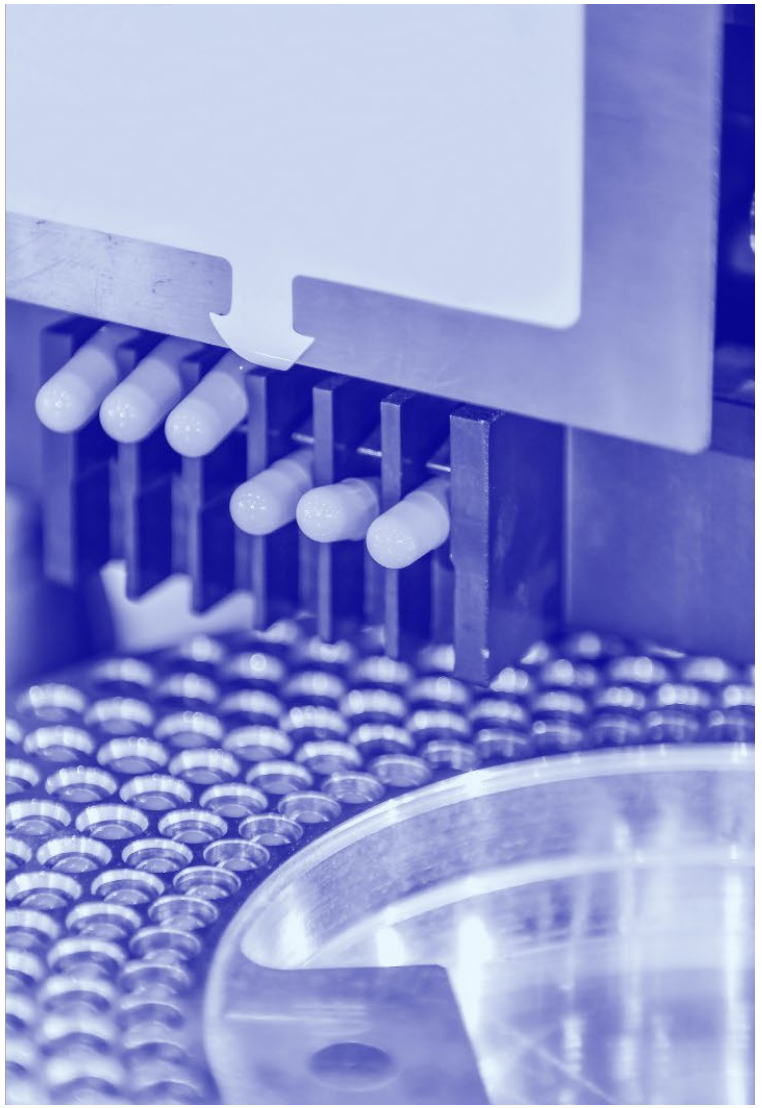
The details contained in this copy of the Record Summary reflect the information held at the nominated date and time of printing
The currency and accuracy of the details can be confirmed at www.ebs.gov.au.

GMP Code

Guide to Good Manufacturing Practice for Medicinal Products - version 16 (PE009-16)

- The design and elements of a Pharmaceutical Quality System
- Facility and equipment design and suitability
- Product manufacture, packaging, labelled, storage and release
- Quality control testing, including on-going stability
- Consistency of processes via validation& qualification
- Cleaning effectiveness and measure to minimise cross contamination risks
- Environmental monitoring
- Equipment maintenance & calibration
- Suitability of staff and effective training measures



Inspection process

- **Preparation**
- Conduct
- Post inspection and closure

Inspector preparation

- Scheduling of inspection – manufacturer contacted
- Announcement of the inspection via letter detailing agreed dates
- Document requests to assist in inspection preparation
- Review of TGA files - compliance issues to follow up, previous inspection issues, CAPA from previous inspections requiring verification
- Search for any recall events since last inspection
- Prepare the inspection plan in accordance with the information received

Preparing for a successful inspection

Manufacturer preparation

- Scheduling → ensure site contact information in eBS is correct
- Announcement → alert inspector if key personnel will be unavailable or no production is planned during the inspection
- Pre-inspection document requests → ensure documents accurately reflect the site & activities conducted e.g. Site Master File schematics
- Review close-out commitments from previous TGA inspection.
  Is CAPA complete and effective?
- Ensure documentation, quality incident reports, PQS, validation, qualification, BMR/BPR documentation, and related quality records will be available for review

Inspection process

- Preparation
- **Conduct**
- Post inspection and closure

During inspection we examine:

- **Personnel & training**
- **Documentation**
- **Quality System** deviations, change controls, complaints, risk assessments, annual product reviews, recalls, self-inspections, returned goods, hygiene and gowning, technical agreements, supplier approval, rework, reprocessing, stability program, technical agreements
- **Production processes**
- **Facility/Engineering** calibration and maintenance
- **Utilities** HVAC, water systems, compressed air, gases
- **Validation and Qualification**
- **Quality Control activities and records**
- **Batch records**

Manufacturer Preparation

- **Documentation**
- QA systems
- Production
- QC
- Validations/Qualifications

- Documentation revision & distribution
- Registers and logs available & in use
- System for document revisions and obsoletion
- Batch document design, issuance, control
- Clear procedures available in agreed format
- Good documentation practices adhered to

Manufacturer Preparation

- Documentation
- **QA systems**
- Production
- Quality Control
- Validations/Qualifications

- Product quality reviews & grouping strategies
- Product release
- Management reviews & resourcing
- Training & its effectiveness
- Control of quality incidents
- Risk management
- Change management
- Control of materials & supplier approval
- Outsourced activities

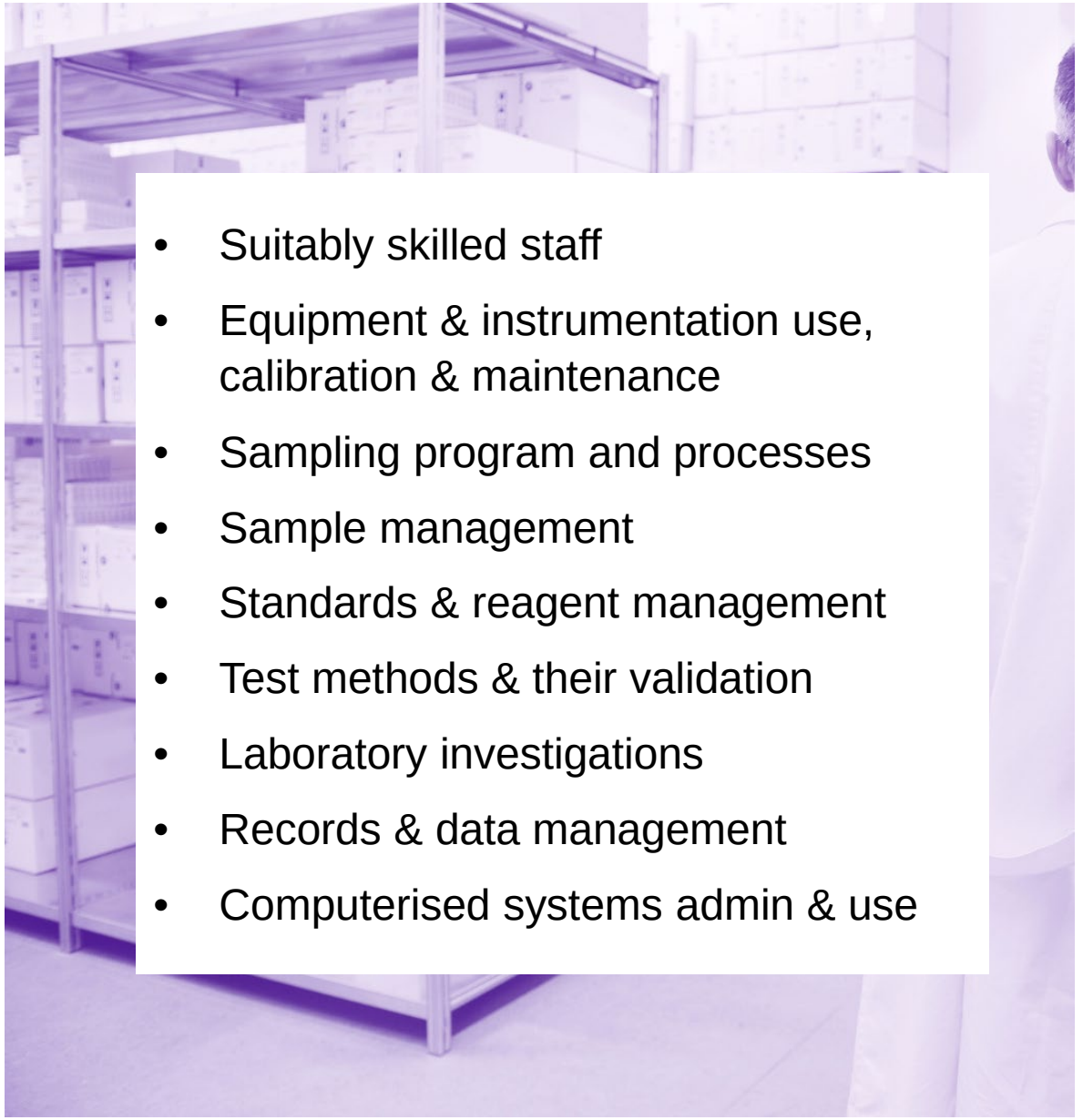
Manufacturer Preparation

- Documentation
- QA systems
- Production
- Quality Control
- Validations/Qualifications

- Warehousing processes & monitoring
- Control of materials
- Facilities and equipment
- Manufacturing & packaging instructions
- Manufacturing & packaging processes & cleaning
- Process monitoring & records
- Environmental controls & monitoring
- Calibration & maintenance of equipment
- Cross contamination control strategies
  - People/ Environment
  - Equipment
  - Process

Manufacturer Preparation

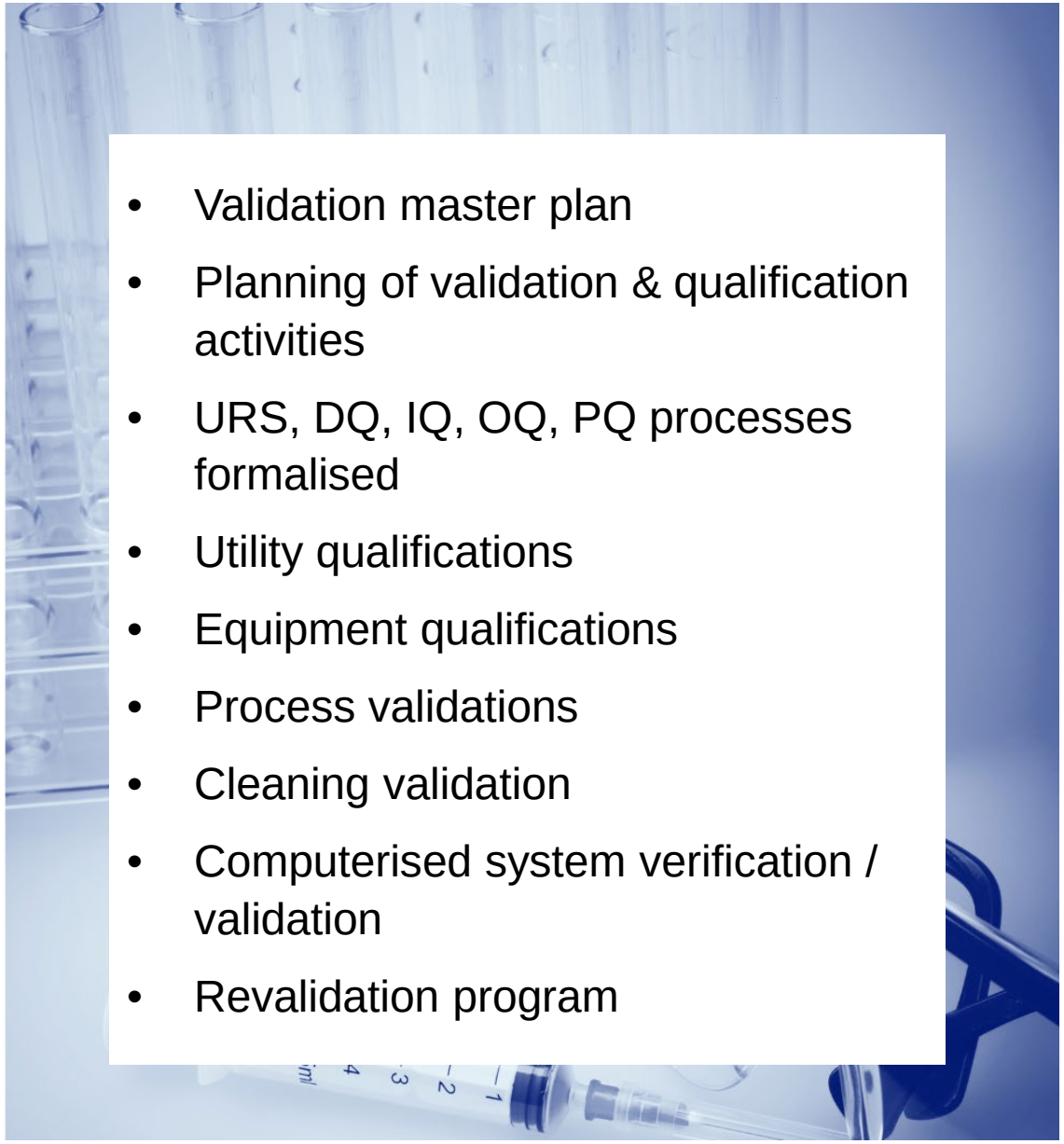
- Documentation
- Investigations/QA systems
- Production
- **Quality Control**
- Validations/Qualifications



- Suitably skilled staff
- Equipment & instrumentation use, calibration & maintenance
- Sampling program and processes
- Sample management
- Standards & reagent management
- Test methods & their validation
- Laboratory investigations
- Records & data management
- Computerised systems admin & use

Manufacturer Preparation

- Documentation
- QA systems
- Production
- Quality Control
- **Validations**



- Validation master plan
- Planning of validation & qualification activities
- URS, DQ, IQ, OQ, PQ processes formalised
- Utility qualifications
- Equipment qualifications
- Process validations
- Cleaning validation
- Computerised system verification / validation
- Revalidation program

Expectation during inspection

The inspector

- Honest, open and respectful
- Empathetic
- Encourage and allow staff time to respond
- Be patient and allow time to evaluate manufacturer’s responses
- Respectfully evaluate feedback to any issue raised and engage in reasoned discussion
- Provide a daily summary of points to avoid any surprises
- Leave site with a summary of all observations

Expectations during inspection

Manufacturer representatives

- Honest, open and respectful
- No delaying tactics
- Respond to questions and provide evidence
- Have your SMEs available,
- Have support staff ready to retrieve documents
- Have planned activities for the inspector to observe at the time of inspection (where possible)
- Help the inspector to execute the inspection plan while in each area
- Provide accurate site schematics as requested

Expectation at Inspection

Manufacturer representatives

- Use scientific expertise to justify points
- Be truthful
- Be aware of your body language (consistency with words said)
- **Words to avoid:** I think, I'm not sure, In my opinion,
  As I recall, Honestly, Usually, Typically, don't remember,…
- **Phrases to avoid :**
  - That's the way we've always done it.
  - Off the record,…….
  - I shouldn't say this but……

Post Inspection

Classification of Deficiencies

Deficiency	Few examples for illustration
CRITICAL	Lack of sterilisation validation Intentional falsification or misrepresentation of test results or records Inadequate segregation
MAJOR	Lack of appropriate validation Cleaning program not followed Grossly inadequate or no air filtration
OTHER	GMP issue, but not classified as a critical or major issue. A single hand amendment to a procedure A single missing signature on a document

Inspection process

- Preparation
- Conduct
- **Post inspection and closure**

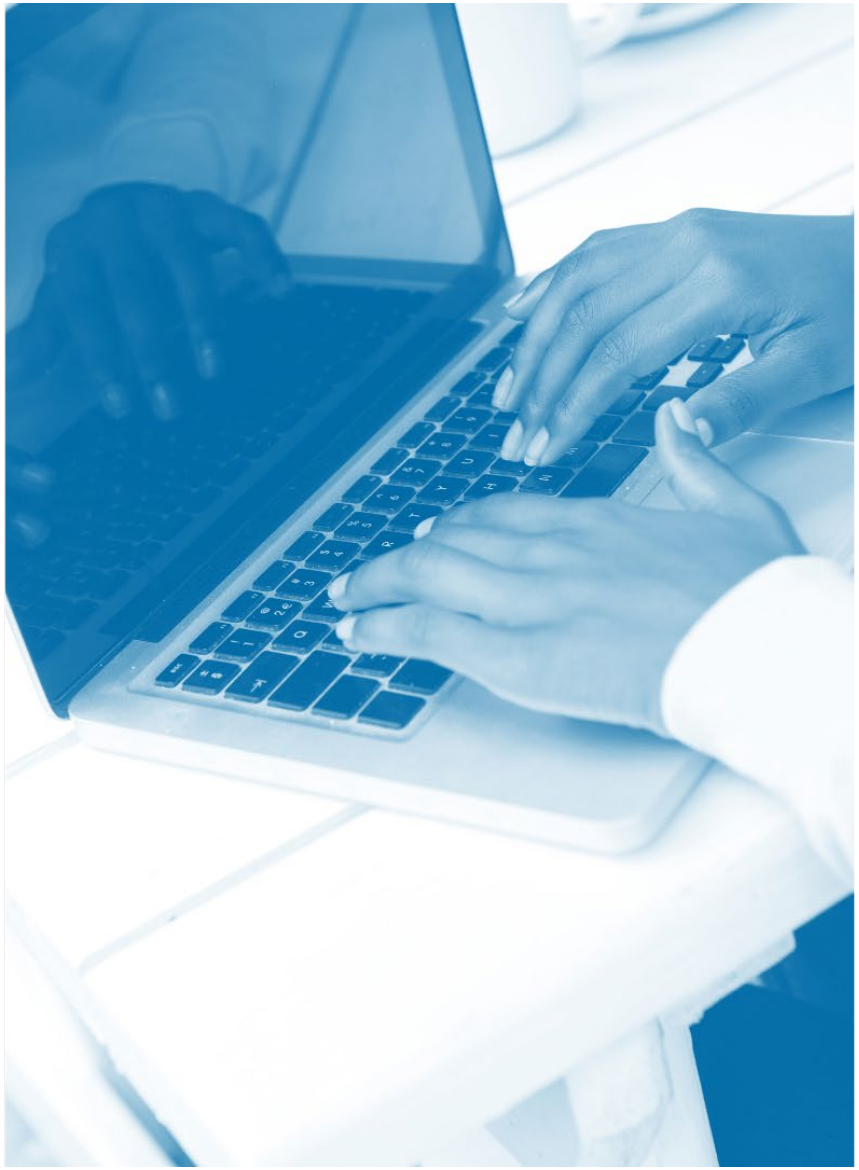
  - Post inspection letter (PIL) listing deficiencies is prepared, peer reviewed & issued
  - Manufacturer has 4 weeks for 1st response, 2 weeks for 2nd and 3rd response (if required) until satisfactory response received*
  - Once closed, the final inspection report is issued
    - compliance rating determined
    - indication of reinspection timing- based on product risk and compliance rating

*If the inspection cannot be closed in 3 responses it is escalated to a review panel with involvement of TGA compliance group

Post Inspection and Closure

Responding to deficiencies

- Manufacturer provides responses to the deficiencies. Details include how issues will be corrected + timeframes for completion
- Inspector reviews responses
    - Accepts or rejects proposed corrective actions
    - Can request additional information or clarification
- Three attempts to provide an acceptable response to all issues
- Following receipt of acceptable responses, an inspection report will be issued
- The report will contain both good practices and areas for
- improvement seen at inspection



Responding to the Post Inspection Letter (PIL)

Provide focused responses to reported deficiencies

- Focus on demonstrating compliance with the requirements as recorded in the close out record
- Conduct root cause analysis for critical & major issues
- Risk identifications & assess impacts
- Clearly document corrective actions
- Provide suitable & achievable CAPA completion date

If the response was not accepted

- Identify why and seek clarification if required
- Carefully respond to inspector’s comments
- Respond comprehensively to avoid further responses
- Provide focused response/s

Expectation of inspector during close out

REVIEW	• Allocate suitable time for review & prioritize provision of feedback • Assess manufacturer's response considering issues identified • Assess timing of completion of CAPA
PROVIDE FEEDBACK	• Identified gaps in information or request justifications as needed to ensure issues fully resolved • Provide guidance or clarification to the manufacturer to facilitate/target subsequent responses

After the Inspection Close-out

TGA risk based re-inspection frequency

Number of deficiencies	0 major & < 10 other			1-5 major & < 20 other	6-10 major & < 30 other		> 10 major & Any critical
Risk category	3rd consecutive A1	2nd consecutive A1	1st A1	A2	1st A3	Repeat A3	Unacceptable
HIGH	Sterile medicines, primary packaging of sterile medicines, non-sterile medicines containing potent actives (antibiotics, steroids, hormones antineoplastics), biotechnology APIs, sterile APIs for aseptic use & single step sterilisers						
Months to re-inspection	36 + possible reduced scope	36	24	18	12	Compliance management	Compliance management
MEDIUM	Registered non-sterile medicines (including registered herbal) & other APIs for use with sterile preparations that undergo a subsequent sterilisation step (filtration or terminal sterilisation) and not included in the high risk category						
Months to re-inspection	36 + possible reduced scope	36	30	20	15	Compliance management	Compliance management
LOW	Sunscreens, medicinal gases, non-sterile APIs for registered medicines & single manufacturing steps such as analysis & testing, labelling, secondary packaging, release for supply & storage						
Months to re-inspection	36 + possible reduced scope	36 + possible reduced scope	36	24	18	Compliance management	Compliance management
LOW - LISTED	Listed medicines						
Months to re-inspection	48 + possible reduced scope	48	42	30	18	12	Compliance management

Risk Based Approach to Inspection Frequency – TGA Forum June 2018

How to ensure GMP inspection success

- Maintain knowledge of current GMP requirements, TGOs & guidance documents
- Follow your own procedures confidently
- Make procedures clear, concise and easy to follow
- Consistently investigate quality incidents. Determine root cause using scientific principals. Implement meaningful CAPA
- Ensure core elements of the Code are applied consistently
- Confidently involve staff in the inspection process without reservations
- Ensure staff undergo regular training. Meaningful evaluate training effectiveness
- Always looking for ways to improve or upgrade over time

How to ensure GMP inspection success

- Trust staff in their areas of expertise to be involved in decision making
- Respond clearly to the inspector’s questions
    - Multiple different answers create doubts
    - Provide additional information in a timely manner
- Awareness of inspector’s next question or review topic
    - Being proactive and ready shows confidence
- Keep track of inspector’s requests & provide updates if delays
- Have a comprehensive self-inspection process

Case 1: Dispensing

A manufacturer has dispensing conducted for multiple products in one dispensing area.

Materials dispensed included an antibiotic that was allergenic, very low-density and high potency.

Dispensing performed in campaign.

Information provided at inspection:

- *Dedicated dispensing tools in use*
- *HVAC system last qualification 2017*
- *The HVAC system is shared with blending/mixing rooms*
- *One cleaning protocol applied to all*
- *Cleaning validation conducted for allergenic materials only (no justification recorded)*

Potential cross contamination issues

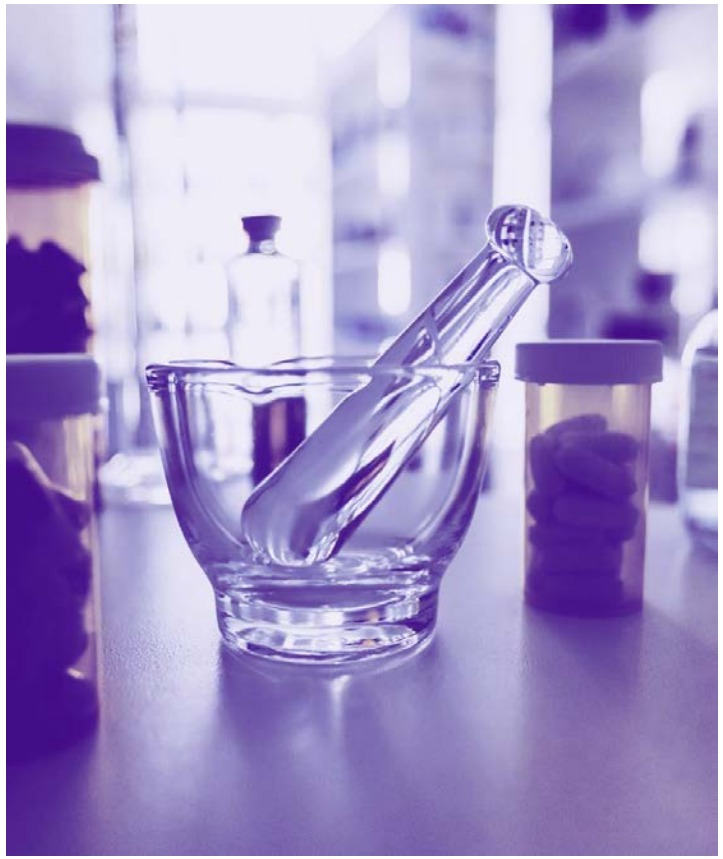
- One cleaning protocol not validated for all materials or scientifically assessed for effectiveness
- High risk materials, low density, allergenic and high potency dispensed in one area
- Effectiveness of the HVAC system operation not regularly confirmed

Case 1: Dispensing

If separate dispensing was not an option

- **Effective risk assessment showing mitigation and measures to minimise cross contamination**
    - Revalidation of the HVAC system more frequently
    - Pressure differential monitoring
    - HVAC system dedication, or use of LAF
    - Personnel gowning

- Specific cleaning protocols for high- risk materials including validation
- Periodic revalidation to confirm continuous control



Case 2: Non-conformance & OOS investigation

Laboratory analysis identified OOS in dual active tablet product

- Active A was 86% (spec. 95 -105%)
- Active B was 98% (spec. 95 -105%)

The same analytical method was used to analyse both actives.

The laboratory investigated and reported:

- No lab error and no root cause in the lab could be found
- The laboratory resampled and retested and results were A: 97.0% & 96.3%. No results recorded for Drug B
- The laboratory accepted the new result for Active A and released the batch

Issues

- Failure to risk assess and determine potential root cause/s to
  - Justify repeat testing
  - Facilitate corrective actions to eliminate repeat occurrence
- Failure to include active B in retest and include in the assessment
- Insufficient information obtained to justify invalidating original OOS result

Case 3: Change Control

New product introduction at a contract manufacturer.

Product active was highly viscous. The new active ingredient had NOT previously been used before in site operations.

A change control was raised. Product was accepted and contract approved based on:

- Similar product already manufactured at site, however, it did not include a viscous active material
- Supplier was approved for supply of other materials
- The risk assessment for new product evaluated it as low risk
- 2 trial batches to justify process validation

Issues /system failures

- Similar product contracted, does not mean new product with new material would be the same
- Supplier approval did not evaluate the new material
- The risk assessment for new product introduction failed to assess cleaning validation with new material, or cross contamination impact in manufacturing
- No scientific justification for 2 trial batches for process validation
- No evaluation of impact of material usage or handling

REMEMBER: Key points to ensure inspection success

Understanding of the GMP Code TGO's & guidance documents

Apply them effectively

Effective Design and application of the PQS system

Regular Quality Reviews

Understand Operation

Identify, mitigate, control or eliminate risks to product quality

Validation& Qualification

Revalidation reviews

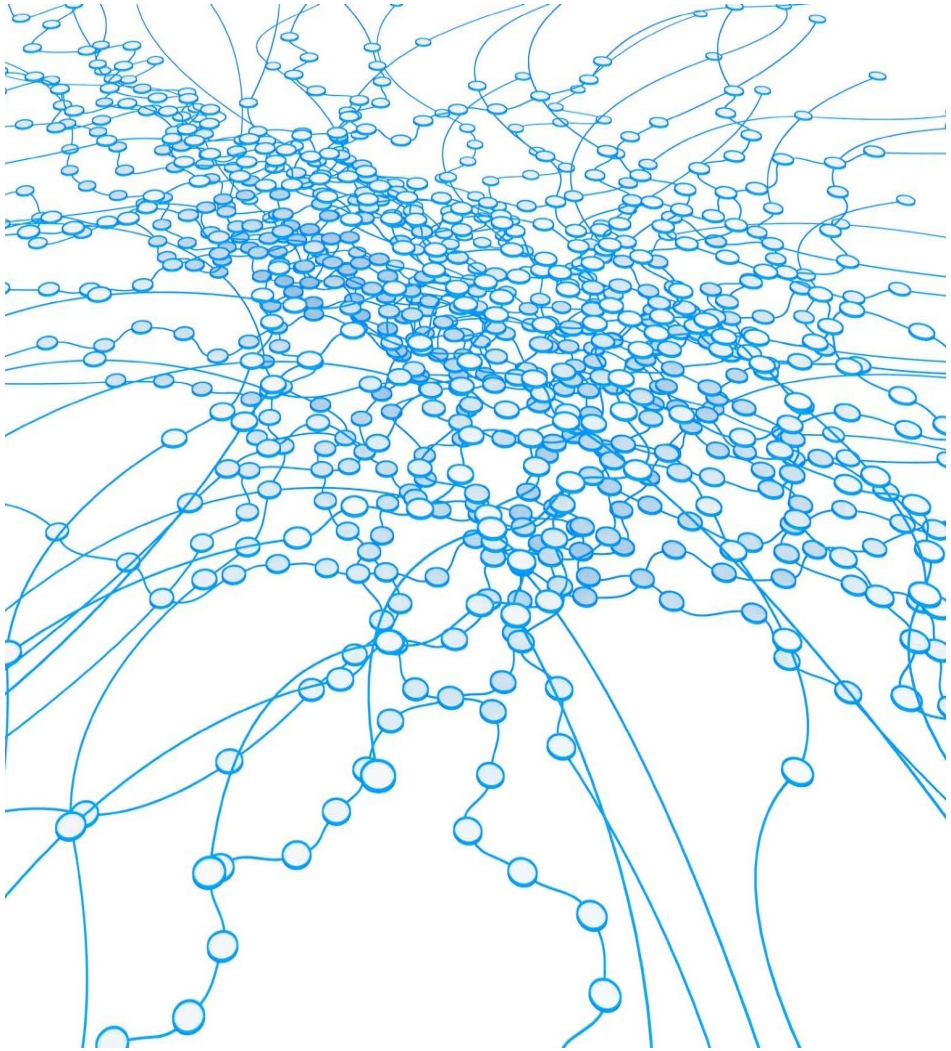
Quality Control /Quality Assurance expertise

Effective investigations to root cause/effective CAPAs

Effective self inspection program including for post release

Summary

- GMP inspections
- Inspection coverage
- Inspection preparation and process
- Expectation at Inspection
- Effective close out
- Case studies



Questions?

Scan this QR code with your device to submit a question

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Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration