GMP FORUM 2023

Common inspection deficiencies and trends

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GMP Inspections

Deficiency review

- Overseas & domestic inspections conducted from Jan - Dec 2022
- Critical, Major & Other deficiencies
- Manufacturers of API and finished dosage form
- Manufacturers of all categories excluding Biologicals
- PIC/S Guide to GMP PE009-15 (1 May 2021)

Previous Trends

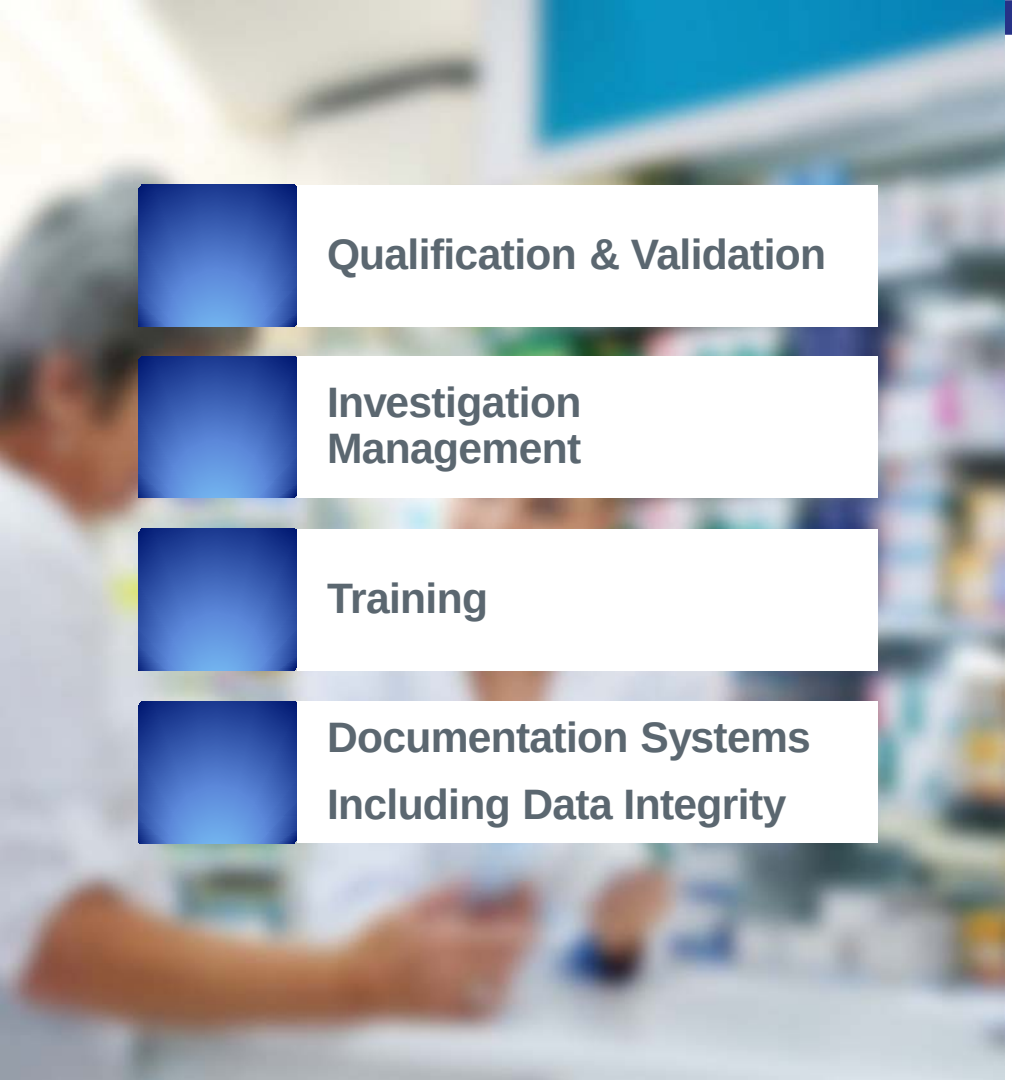
Deficiency Category

Deviation & Complaint Investigations (Part I Clause 1.4 xiv)

Quality Risk Management (Part I Clause 1.12 & 1.13)

Computerised Systems (Annex 11)

Qualification & Validation (Annex 15)



- **Qualification & Validation**
- **Investigation Management**
- **Training**
- **Documentation Systems Including Data Integrity**

2022

Most cited deficiencies

- Similar trend observed for Validation & Investigation deficiencies from previous years
- Re-emergence of Training and Documentation into most common deficiencies

Qualification & Validation

Annex 15 Principle

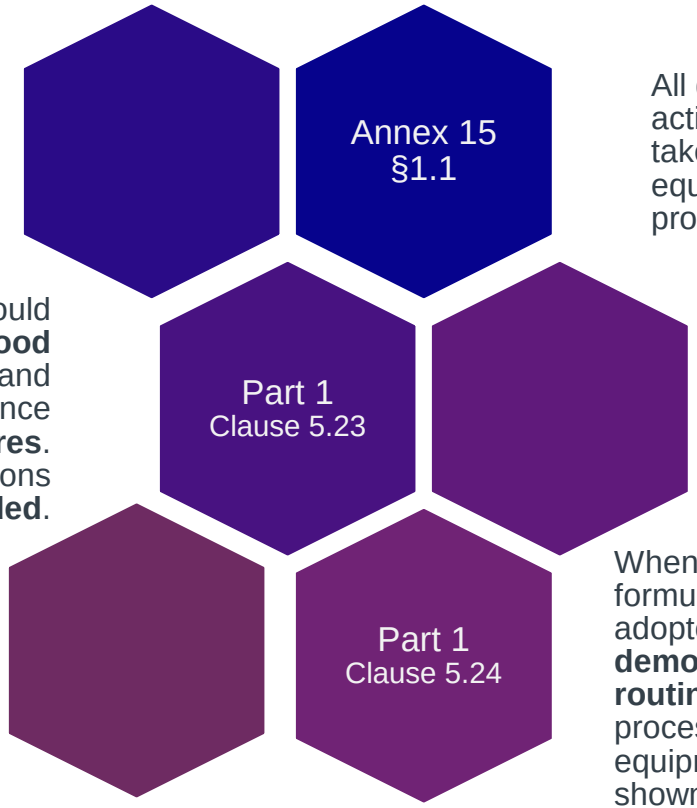
Applicable to the **facilities, equipment, utilities and processes** used for the manufacture of medicinal products

It is a GMP requirement that **manufacturers control the critical aspects….**over the **life cycle of the product and process**.

Any planned changes…..should be formally **documented and the impact on the validated status or control strategy assessed**.

Part II section 12

The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.



All qualification and validation activities should be **planned** and take the **life cycle** of facilities, equipment, utilities, process and product into consideration.

Validation studies should reinforce **Good Manufacturing Practice** and be conducted in accordance with **defined procedures**. Results and conclusions should be **recorded**.

When any new manufacturing formula or method of preparation is adopted, steps should be taken to **demonstrate its suitability for routine processing**. The defined process, using the materials and equipment specified, should be shown to yield a **product consistently of the required quality**.

Validation Deficiency Themes

Overview

- Poor risk assessment & determination of validation requirements
- Incomplete or inaccurate validation documentation
- Failed validation criteria not adequately addressed
- Insufficient periodic review of validation

Investigation of deviations, suspected product defects…

Part I Clause 1.4 (xiv)

An **appropriate level of root cause analysis** should be applied during the investigation of deviations, suspected product defects and other problems

This can be determined using **Quality Risk Management** principles.

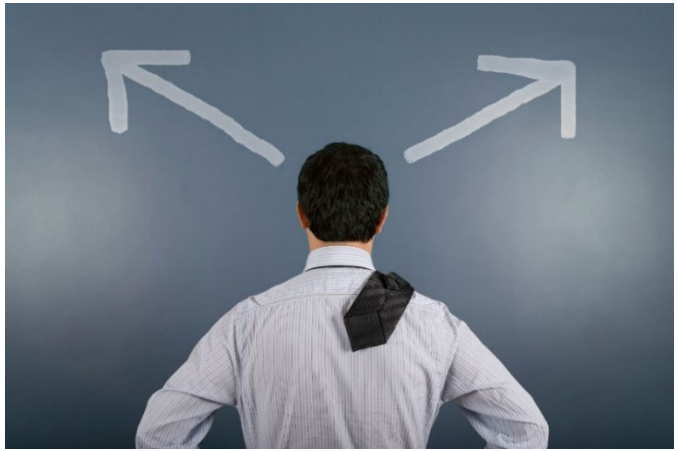
Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed

PIC/S Part II

Clause 2.16 - Any deviation from established procedures should be **documented and explained**. Critical deviations should be investigated, and the **investigation and its conclusions should be documented**.

Clause 6.53 - Written procedures should be established and followed for investigating **critical deviations or the failure of a batch of intermediate or API** to meet specifications. The investigation should **extend to other batches that may have been associated** with the specific failure or deviation.

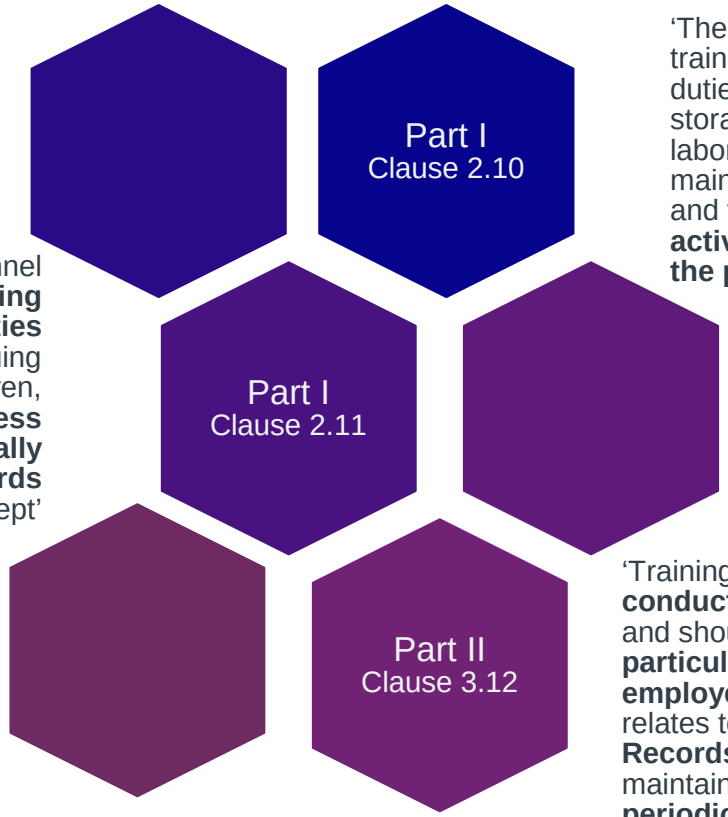
Investigation Deficiency Themes



Overview

- True root cause not identified
- Insufficient scope or detail of the issue
- Lack of Quality Risk Management
- Ineffective Corrective/ Preventative Actions (CAPAs)

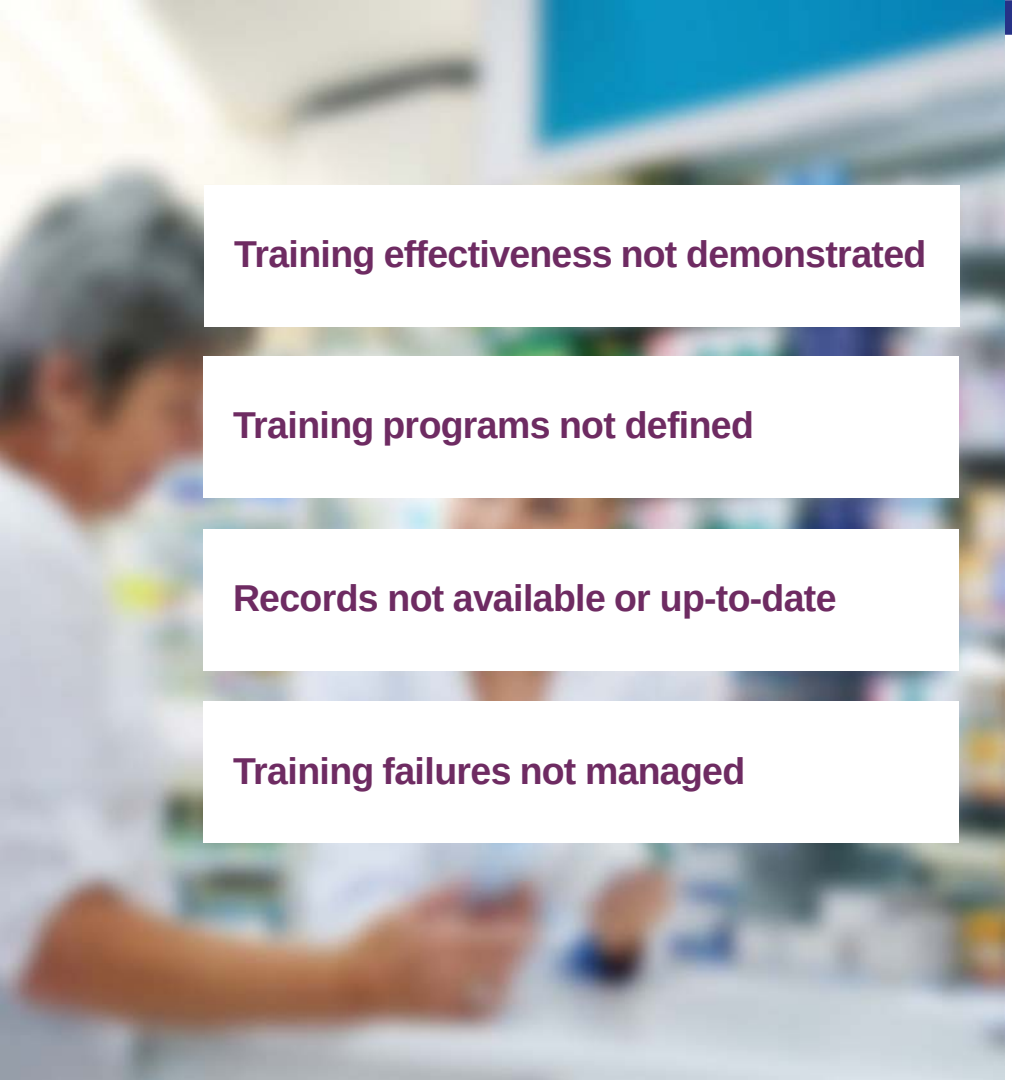
Training



‘The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other **personnel whose activities could affect the quality of the product**’

‘newly recruited personnel should receive **training appropriate to the duties assigned to them**. Continuing training should also be given, and its **practical effectiveness should be periodically assessed**….. **Training records** should be kept’

‘Training should be **regularly conducted by qualified individuals** and should cover, at a minimum, the **particular operations that the employee performs and GMP** as it relates to the employee's functions. **Records of training** should be maintained. Training should be **periodically assessed**’



Training effectiveness not demonstrated

Training programs not defined

Records not available or up-to-date

Training failures not managed

Improvements needed to…

- Provide an appropriate level of competency
- Ensure operator error is minimised
- Identify operational risks & knowledge gaps
- Standardise work practice
- Maintain validated processes & product quality

Documentation Systems

Part I Chapter 4 Principle

Good documentation…..**is key to operating in compliance with GMP requirements**

The various types of documents and media used should be **fully defined** in the manufacturer's Quality Management System

Documentation may exist in a variety of forms, including **paper-based, electronic or photographic media**

The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements….so that **ongoing application of the requirements may be demonstrated**

Part II section 6

Clause 6.10 - All documents related to the manufacture of intermediates or APIs should be **prepared, reviewed, approved and distributed according to written procedures**

Clause 6.11 - The issuance, revision, superseding and withdrawal of **all documents should be controlled** with maintenance of revision histories

Clause 6.14 - When entries are made in records, these should be made indelibly….and should **identify the person making the entry**. Corrections to entries should be dated and signed and leave the **original entry still readable**

Documentation Deficiencies

Overview

- Uncontrolled Document Systems - adoption of hybrid and digital formats during pandemic
- Good Documentation Practice not consistently applied
- Data Integrity issues throughout document lifecycle
- Procedures not accurate or sufficiently detailed

Document Management

Part I Clause 4.1

- All types of document should be **defined and adhered to**
- Requirements apply equally to **all forms** of document media
- Complex systems need to be **understood, well documented, validated, and adequate controls** should be in place
- Relationships and control measures….need to be stated for both **hybrid and homogenous systems**
- Appropriate controls...throughout the **retention period**

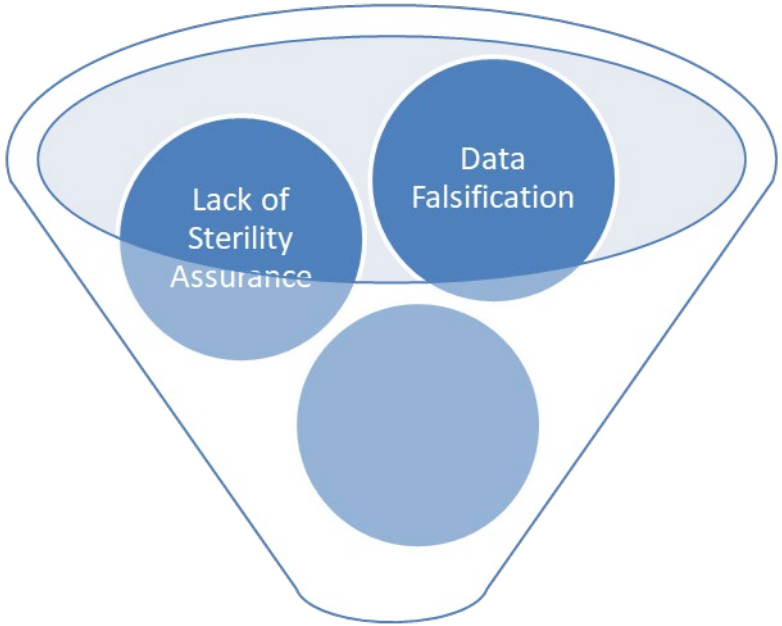
ElecDocumentationtronic System

- User Access & Controls
- Data Storage & Security
- System Validation & Governance
- Training requirements
- E-signatures

Changes to Document Management

- Change Control
- Risk Assessment
- Data Integrity & Compliance Review
- Vendor Qualification
- Validation Review & Plan
- Implementation Plan - include SOP updates
- System Failure Management/Business Continuity Plan
- Post Change Review

Critical Deficiency



- A practice or process has produced, or may result in, a **significant risk of producing a product that is harmful to the user**
- The manufacturer has engaged in **fraud, misrepresentation or falsification of products or data**

Additional Guidance

Documentation & Data Management

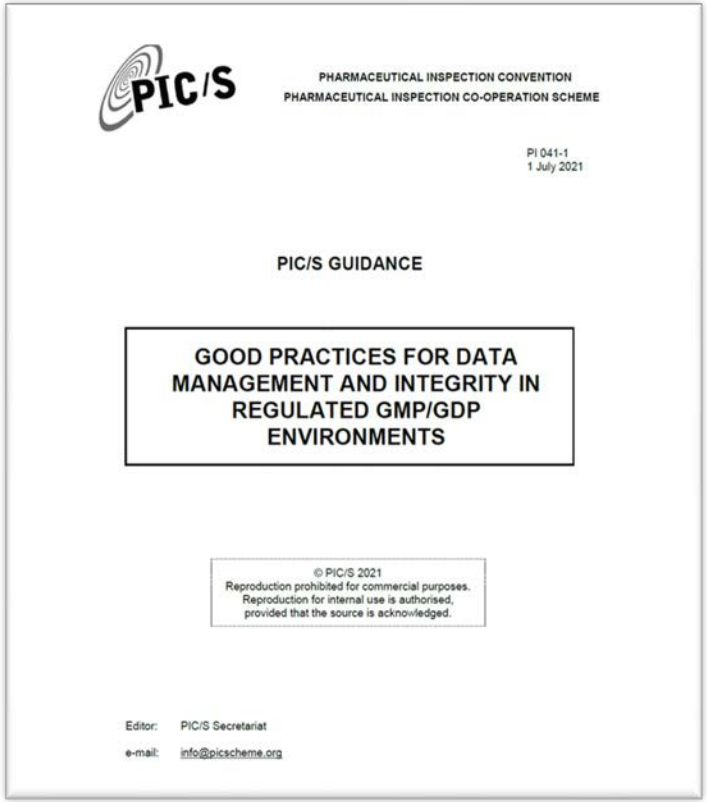
PIC/S Guidance PI041-1

ISPE

- ISPE GAMP® Guide: Records and Data Integrity
- ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems
- ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design

PDA Technical Reports

- TR84. Integrating Data Integrity Requirements into Manufacturing & Packing Operations
- TR80. Data Integrity Management System for Pharmaceutical Laboratories



PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1
1 July 2021

PIC/S GUIDANCE

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS

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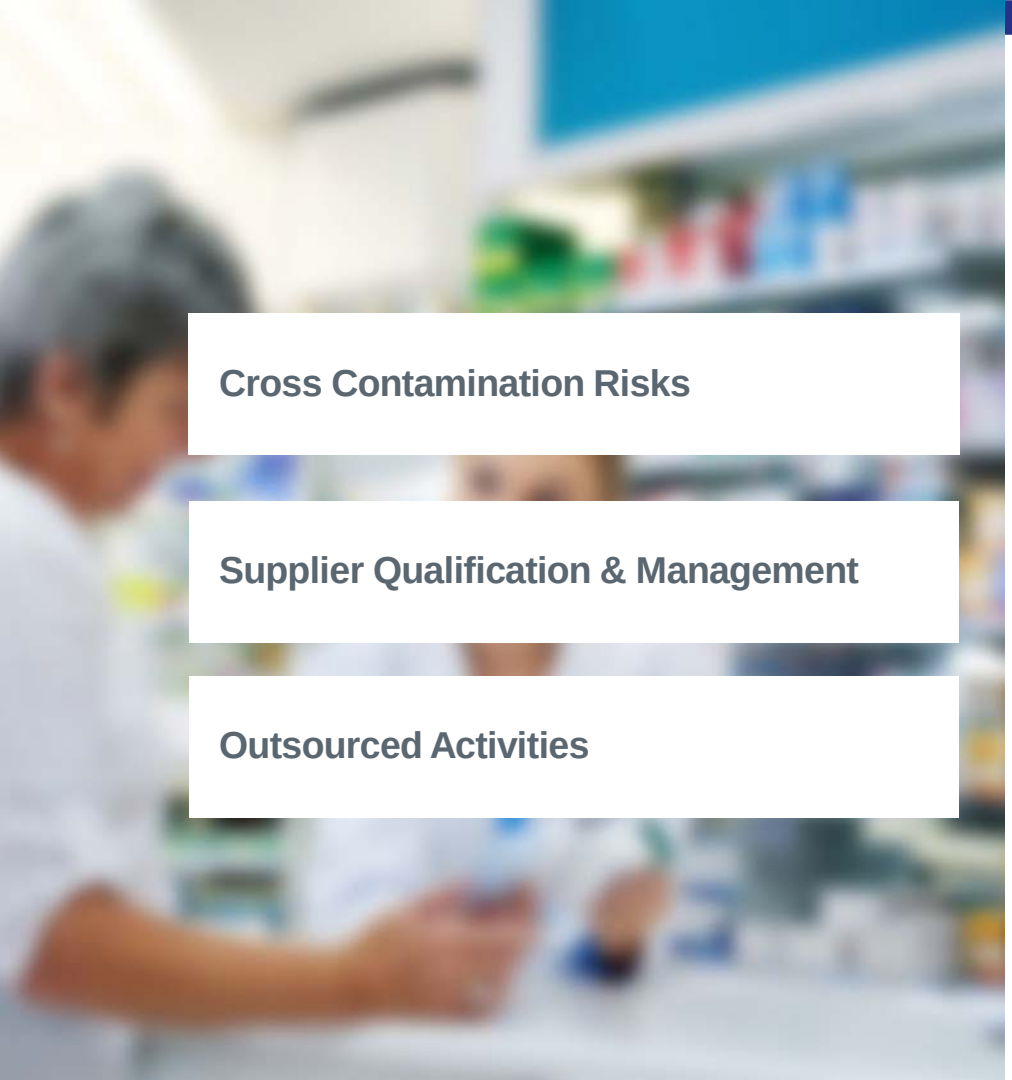
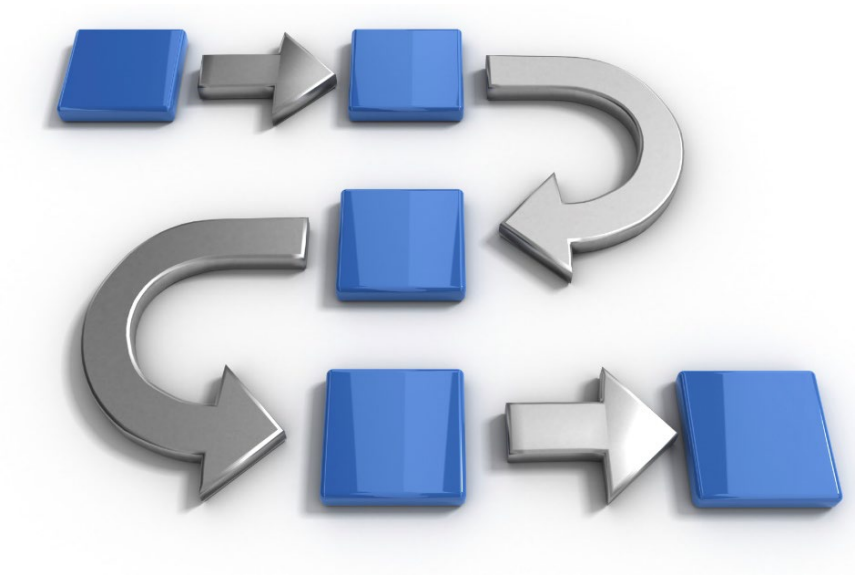


Additional common deficiencies

- Part I Clause 5.17 - 5.22
- Part I Clause 1.4 (vi) & Clause 5.27 - 5.29
- Part I Chapter 7

Recurring Deficiencies



Possible Reasons

Misinterpretation and poor understanding of GMP requirements

Focus of inspection and GMP clauses

Hybrid or e-systems not adequately assessed for compliance

Insufficient planning & resourcing

Participate in the Q&A

Verbal questions:

Raise your hand to ask a verbal question. A member of the GMP Forum staff will provide a roaming microphone.

Written questions:

Scan the QR code below or click the link in your calendar to access Slido via your mobile device. You can submit your question, and vote on other questions submitted.

Australian Government

Department of Health

Therapeutic Goods Administration

Coming up next in this room

Stephen Farrell
Director, GMP Clearance section
Manufacturing Quality Branch, TGA

Australian Sponsors & GMP