Class II Biologicals - Validations and Inspection Observations

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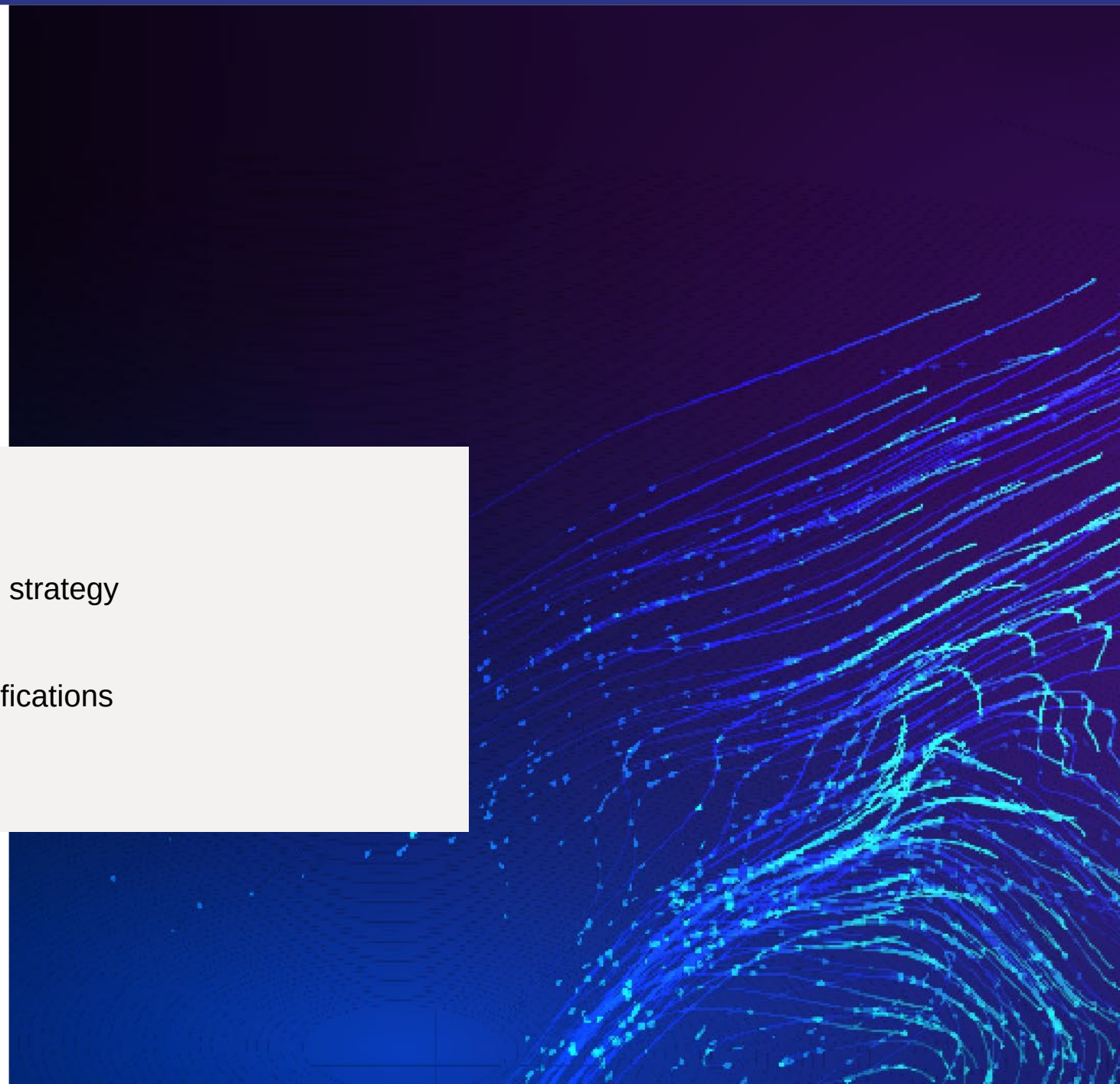
GMP FORUM 2024

Agenda

- Class 2 biologicals, definition and regulations
- GMP legislative requirements
- GMP requirements and the contamination control strategy
- Process Validation, Verification and qualifications
- Regulatory requirements for validations and qualifications
- Inspection observation
- Improvement



Definition of biologicals

[1]a thing made from, or that contains, human cells or human tissues, and that is used to:

- treat or prevent disease, ailment, defect or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to disease
- replace or modify a person's body parts

[2]and

- a thing that is a faecal microbiota transplant product
- a thing that comprises or contains live animal cells, tissues or organs

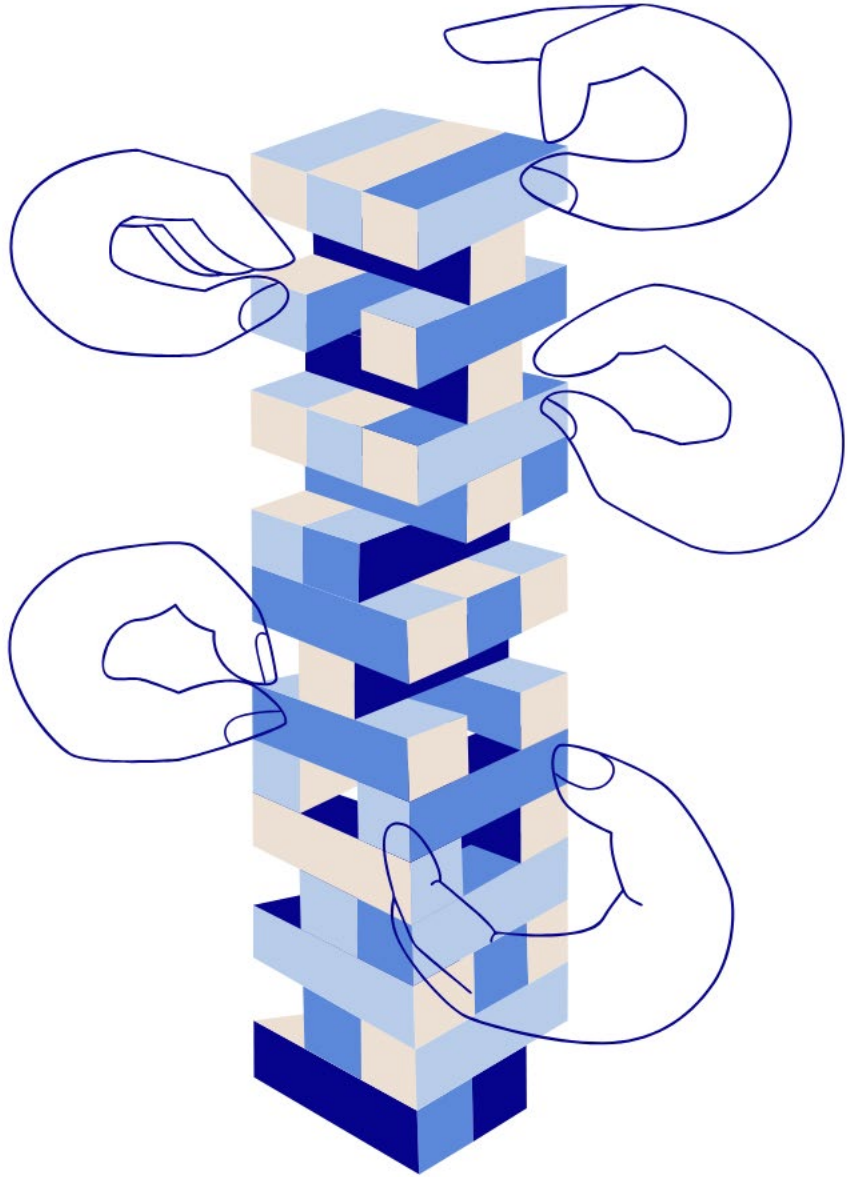
[1]The Act- The Therapeutic Goods ACT 1989 Section 32DEA(2) Meaning
[2]The Therapeutic Goods (Biologicals—Specified Things) Instrument 2021

Biologicals classification

Biologicals class 1-4.[1]

Risk- based classification

- Method of manipulation
  - Minimal vs non- minimal manipulation
- Intended use
  - homologous or none homologous
- level of external governance and clinical oversight



[1] the Regulation: Therapeutic Goods Regulation 1990- Schedule 16

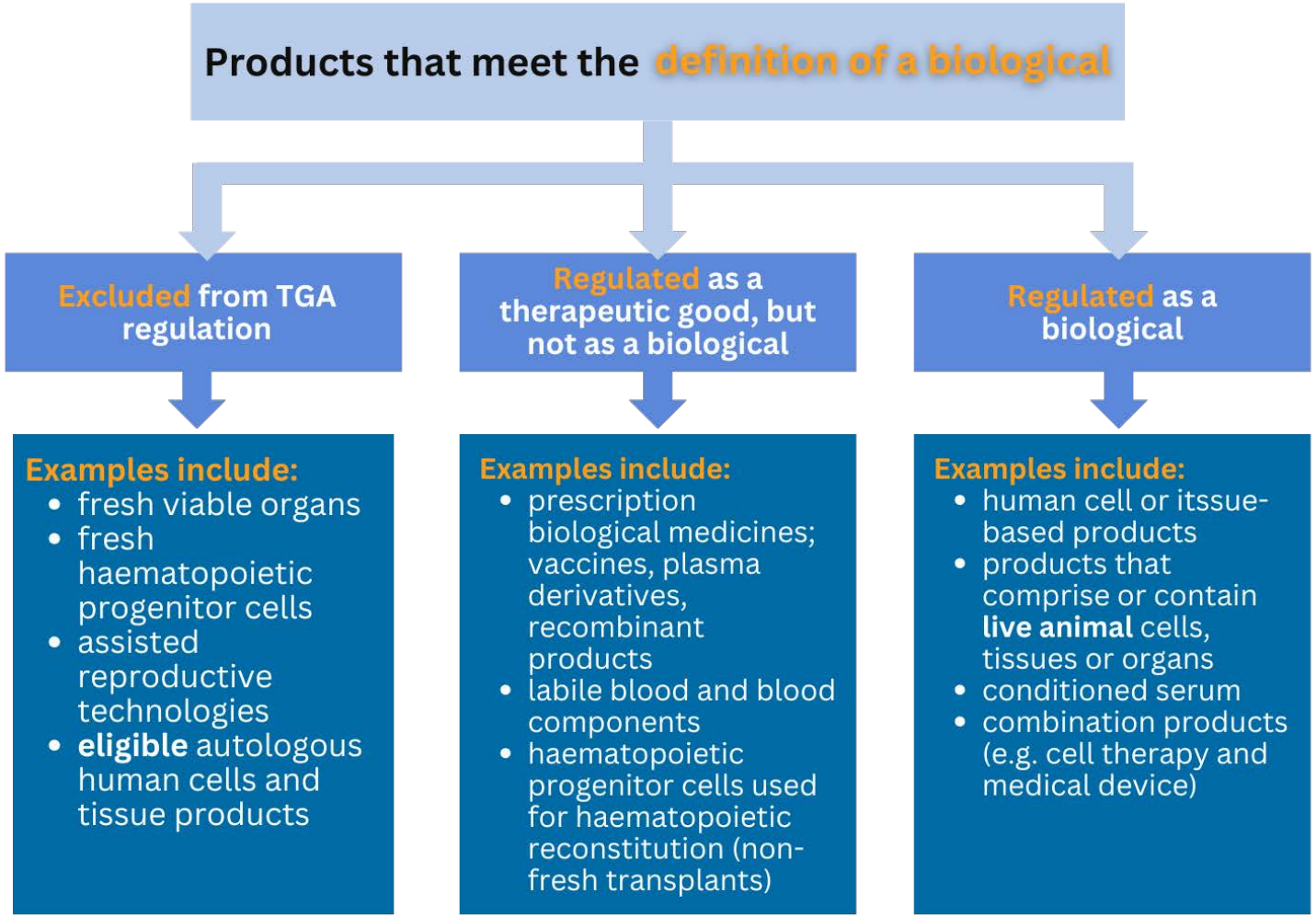
Biologicals classification

Class 1	Class 2	Class 3	Class 4
Low risk	Low risk	Medium risk	High risk
• Appropriate level of external governance and clinical oversight	• Homologous use • Minimal manipulation	• Homologous use with more than minimal manipulation OR • Non-homologous use with minimal manipulation or more than minimal manipulation	• Live animal cells, tissue or organ • Human cell and tissue modified to artificially introduce a function • Pluripotent stem cells • Derived from pluripotent stem cells

Regulation of Biological products

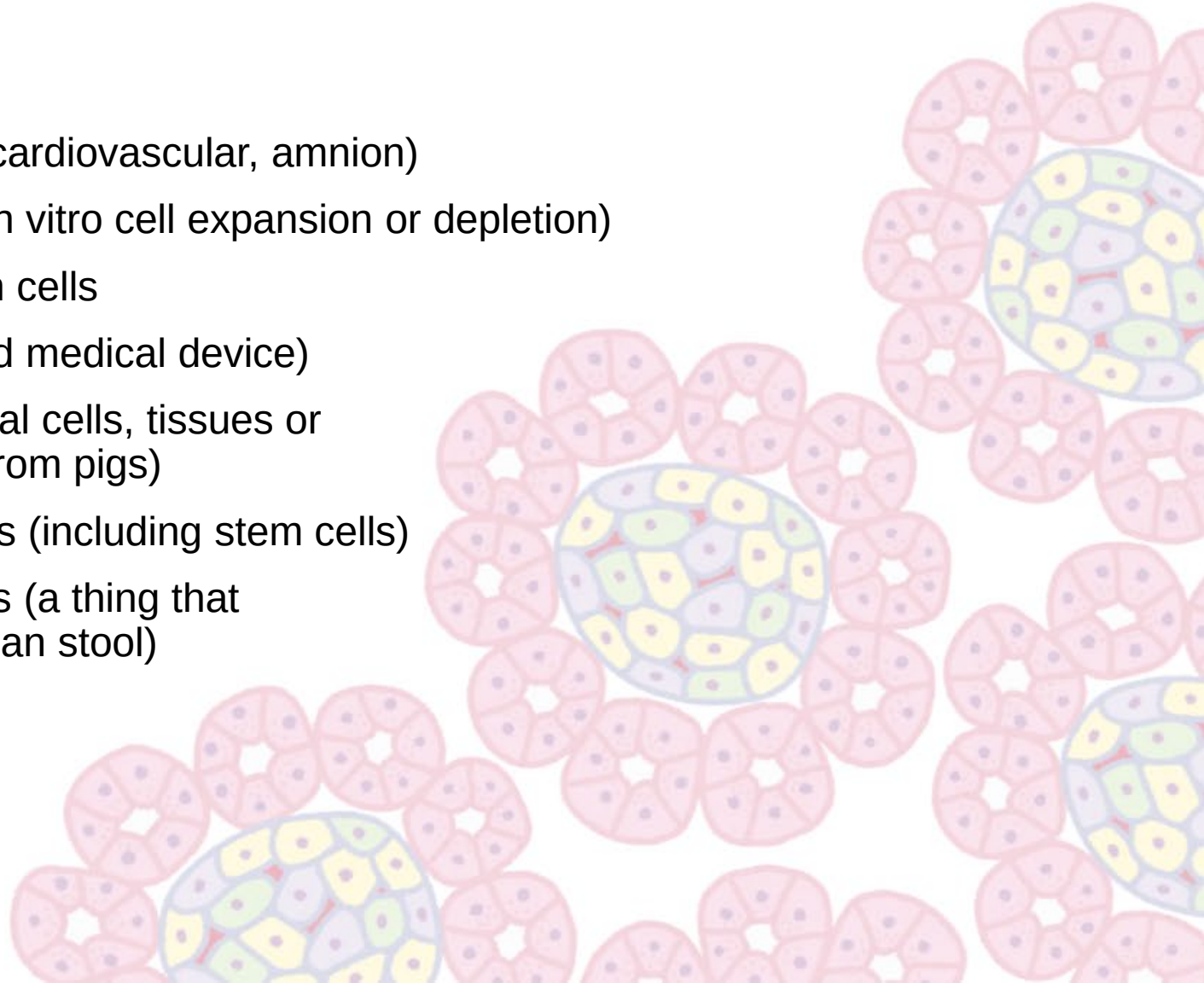
Regulated as biologicals:
Subject to all the Act requirements, including:

- good manufacturing practice- i.e., GMP Licence and certification
- inclusion in the Register- dossier
- demonstrate compliance with TGA standards for therapeutic goods
- adverse event reporting



Types of products regulated as biologicals

- tissue-based products (skin, bone, ocular, cardiovascular, amnion)
- cell-based products (genetically modified, in vitro cell expansion or depletion)
- immunotherapy products containing human cells
- combination products (e.g. cell therapy and medical device)
- products that comprise or contain live animal cells, tissues or organs (e.g. pancreatic islet cells isolated from pigs)
- autologous human cells and tissue products (including stem cells)
- faecal microbiota transplant (FMT) products (a thing that comprises, contains or is derived from human stool)



GMP legislative requirements

Therapeutic Goods Act 1989	• Part 3 - 3 Manufacturing Licensing and licence conditions requirements
Therapeutic Goods Regulations 1990	• PART 4 - Licensing of Manufacturers
Legislative instrument Therapeutic Goods (Manufacturing Principles) Determination	• The Australian Code for Good Manufacturing Practice - The Code • The PIC/S Guide to GMP

GMP Standards

The Code

- Blood, blood components, haematopoietic progenitor cells (HPCs) and biologicals that do not contain live animal cells, tissues or organ.
  - Class II Biological

PIC/S guide to GMP

- Products that comprise of or contain live animal cells, tissues and organs.

Excluding:

- Annex 4 and Annex 5- for Veterinary Medicinal products; and
- Annex 14- plasma derived products

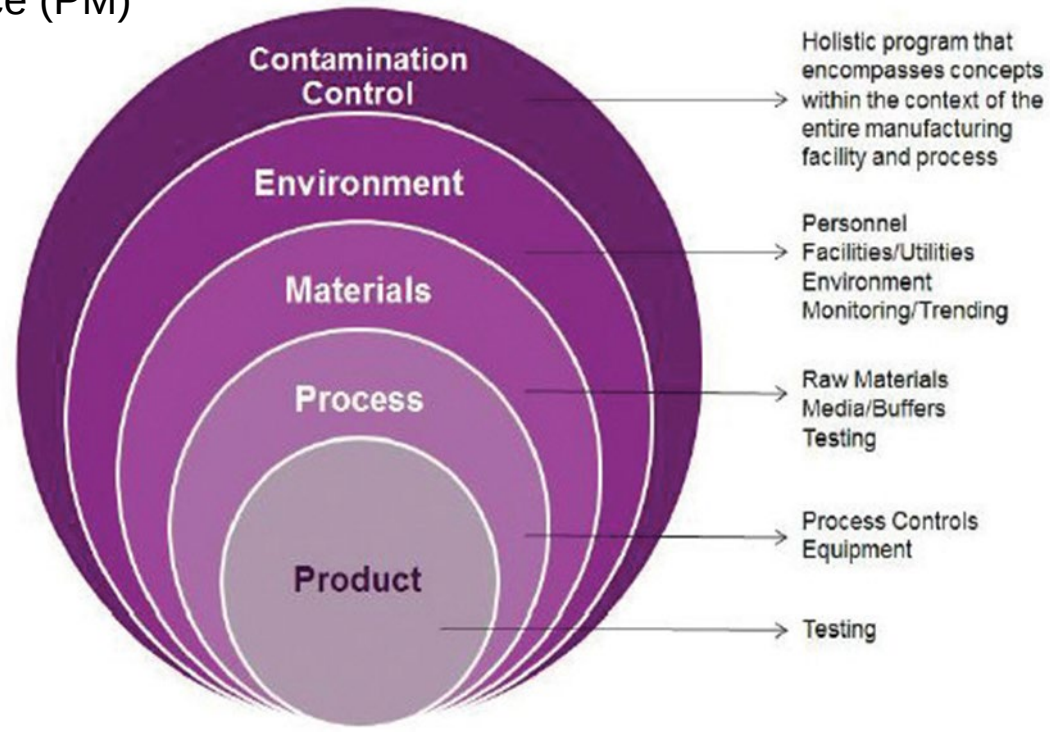
The Code (2013)

- Non- prescriptive
  - Allows flexibility for alternative processes and systems
  - justification based on published literature, international standards and guidelines and / or validations.
- Not product specific
  - Allow for application to new products and technologies e.g., Faecal Microbiota Transplant (FMT).
- Applies risk management approach
- Requires compliance with other standards for biologicals:
  - Annex 1 of the PIC/S Sterile products and low bioburden products
  - Therapeutic Goods Orders (TGOs): TGO 108, TGO 109, TGO 107 and TGO 105
  - TGAct – if TGO not available use BP/EP/USP

GMP requirements and the Contamination Control Strategy (CCS)

CCS is a system that considers all the integral elements of product manufacturing. It is a holistic strategy that considers all elements of the GMP requirements which collectively provide assurance of product quality and safety during manufacturing or preparation process.

- Facility – design and **qualification**
- HVAC system **qualification**
- Equipment design, **qualification** and preventative maintenance (PM)
- Monitoring system- detection of environmental contamination
- Clean and disinfection **validation**
- Personnel flow, training and gowning
- Material control and flow
- Vendor approval – quality and sterilisation assurance
- Process design and **validation**
- Quality control testing- **validation/ verification**



Source: Americanpharmaceutical.com

Process Validation, qualification and verification

Validation

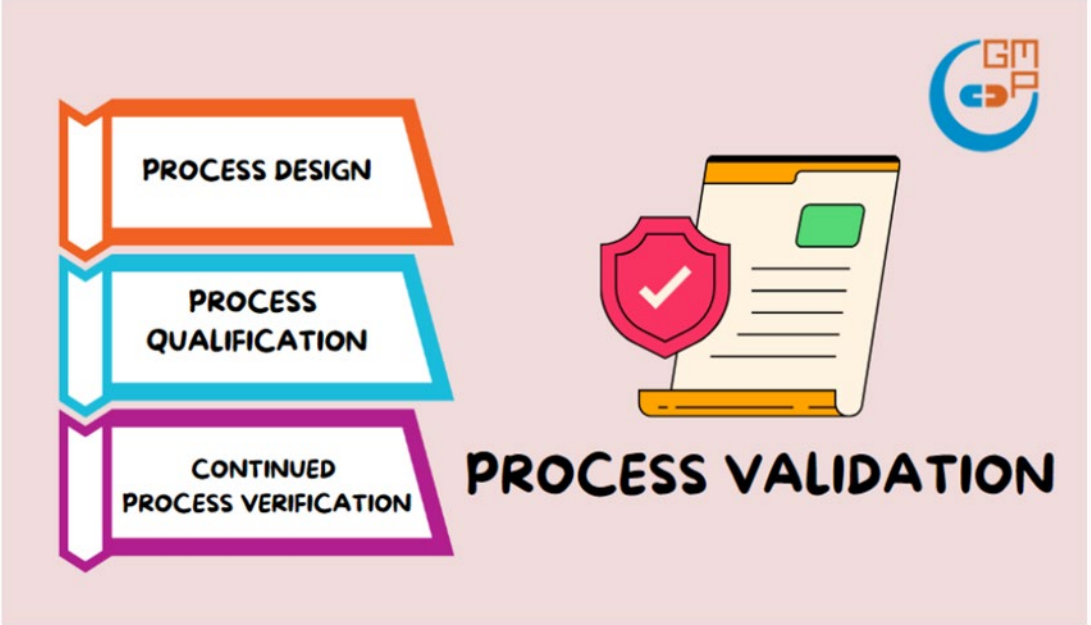
- Specific process will meet predetermined specifications.

Qualification

- installation of premises, systems or equipment meet predetermined and work appropriately.
- Part of a validation process

Verification:

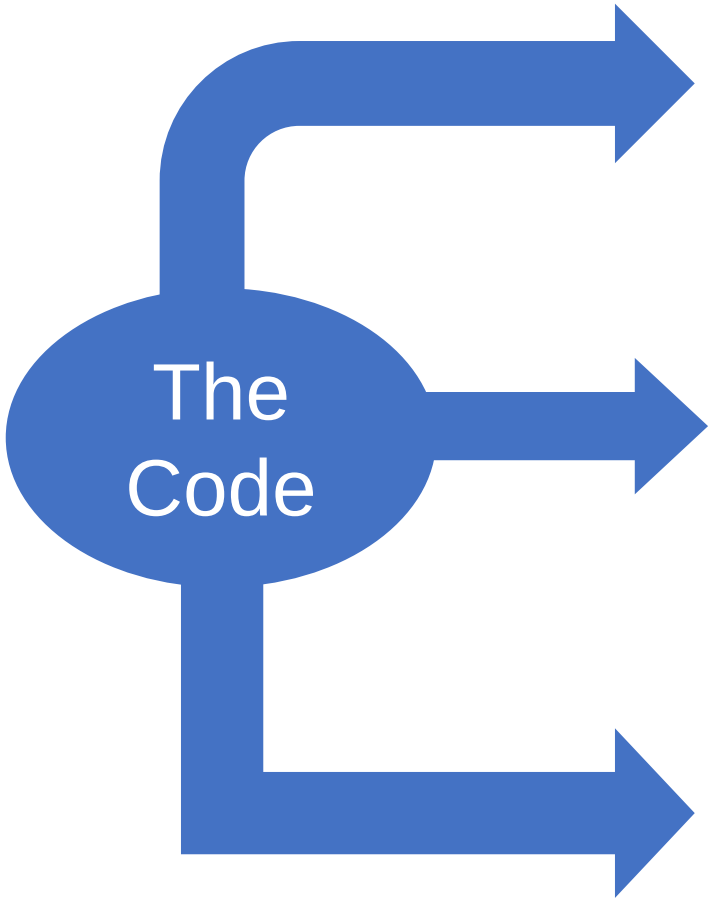
- A validated process remain in state of control.
- Suitability of a validated or a compendial analytical method under actual condition of use.



https://gmp.com.vn/process-validation-in-pharmaceutical-manufacturing-nen.html

FDA Guidance for Industry Process Validation: General Principles and Practices

Regulatory Requirements for Validation and Qualification



General validations

- VMP
- Quality control test method
- manufacturing process
- Significant changes
- Computer systems

Specific validations

- Aseptic process
- Cleaning and cleaning disinfectants
- Bioburden (validation/verification)
- EM program
- Transportation

Qualification

- Premises, facilities and equipment qualification
  - contingency plan equipment

Regulatory Requirements for Validation and qualification

TGO 109 Specific requirements

- Time frames and conditions:
  - storage and transportation
    - ✓retrieved tissue and grafts (shelf-life)
  - Tissue type and process method.
- Specifications
  - moisture content for freeze dried products, residual
    calcium for demineralised bones
- OR
  - Other conditions
    - ✓Validated
    - ✓Documented evidence- relevant scientific literature

Regulatory Requirements for Validations

TGO 109 general validation and guidance

- Validated Sampling method
- Using validated test method
  - Bioburden and product microbial contamination testing
  - Virus validation studies
  - Aseptic process validation
  - Osteoinductivity
  - Cryopreservation
  - Lyophilisation
  - Sterilisation method

Identified inspection observations - Aseptic Process simulation

The exercise that mimics the manufacturing process that;

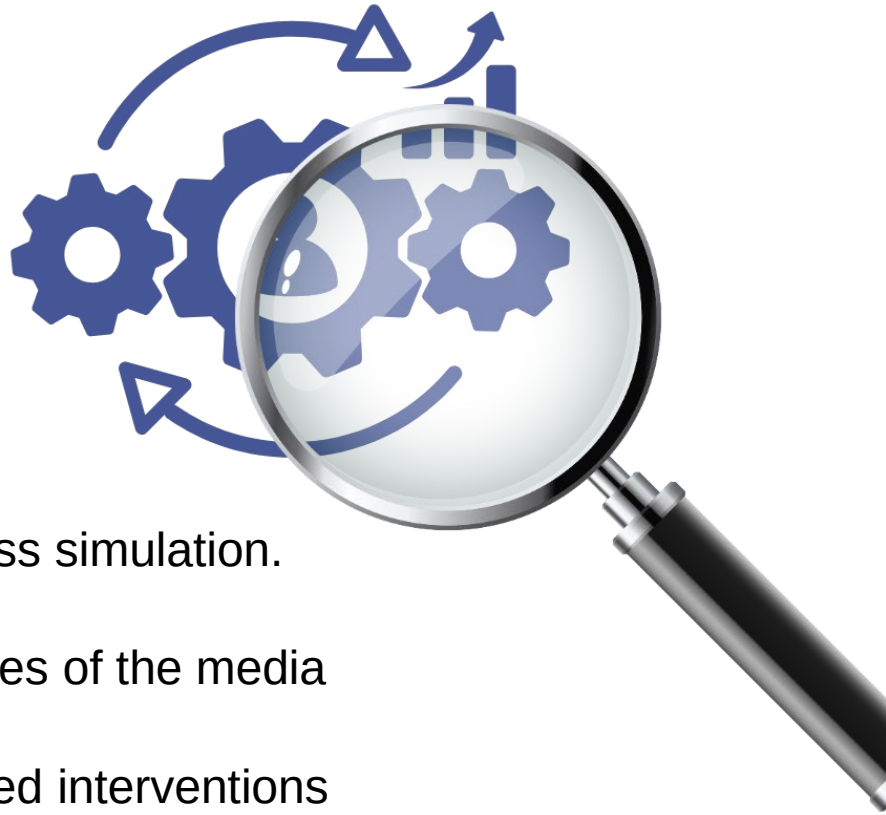
- covers all parts of the aseptic process
- include all aseptic manipulations
- include permissible worst-case conditions.

Specific requirement-The Code Clause 818

Figure 1: Points to consider when designing the media fill study.

Source: https://ispe.org/pharmaceutical-engineering/march-april-2022/validation-aseptic-processes-using-media-fill

Identified inspection observation – Aseptic Process simulation (APS)



- No APS in place- operator's qualification
- Inappropriate process design and validation
  - suitable sterile tissue surrogate material
  - Suitable sterile media
    - Growth promotion test for selected microorganisms
  - Sterility of the surrogate material tested at the end of the process simulation.
  - Tested media - representative of the entire process
    - no parts of the process alter the growth-promoting properties of the media
  - Risk management principles – focus on contamination control
    - Multiple configuration, maximum holding times, unscheduled interventions
  - Lack of knowledge - Standards and guidance documents
    - ISO 13408 Aseptic processing of health care products Part 1: General requirements; and
    - ISO 18362 Manufacture of cell-based health care products — Control of microbial risks during processing

Identified inspection observation - Cleaning and cleaning disinfectants

Identified observation:

- Non- validated cleaning/ disinfecting agents
  - Single vs multiple agent – resistance, controlling all types of microorganism, residual removal
- Agents that do not have expiry dates.
- Rationale for the contact time - Product information or validation.
- Contracted personnel – lack of training
- Inappropriately validation design - Risk - based assessment considering EM isolates, manufacture of different products with different microbial contamination load.
- The validation protocol - Lack of information- criteria and rational for the criteria, validated cleaning surfaces within the facility, contact time.
- Cleaning and disinfection processes of reusable instruments and consumables
  - Cycle Validation, including load configuration, residual study, etc.

Identified inspection observations - Transportation

Documented process and validation protocols

- Packaging configurations
- The validated storage conditions
- Transportation time including worst case scenarios
- Seasonal changes

Validations

- Old validations - representation of the current process
  - Review of validations - Changes to process(s), additional products, new shippers, new service providers
- Lack of details – actual practices
- Design of the study – validation protocol and report lack the required information

Specific requirement - The Code Clause 834

Identified inspection observations Environmental monitoring (EM) program

Why EM program is important?

- the environmental monitoring program is intended to verify a state of contamination control

What to consider - based on a Quality Risk Management

- how often to monitor
- where to monitor
- what samples to take
- which culture media to use
- incubation conditions to ensure that representative organism are detected.
- how to interpret data; and
- identifications of microorganisms to perform.

Specific requirement - The Code Clause 300 and 310

Identified inspection observations
Environmental monitoring program - continue

- Lack of risk – based approach designed EM program
  - considers air, personnel, product, materials, and waste flow.
- Selection of the EM Media
  - based on suitability for use to detect wide range of microorganism.
- No in - process EM
- EM is limited to air born particles, no viable microbial monitoring. [1]

Lack of Quality Control testing –

- Certificate of analysis vs QC testing - pre acceptance testing (PAT) for new batches of EM media
- Supplier evaluation and re- evaluation to ensure suitability of storage and transport conditions to maintain plates quality.

[1]ISO 14644-1 Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration. Specifies the classification of air cleanliness in terms of concentration of airborne particles in cleanrooms and Annex 1 of the PIC/s that references ISO 14644-1 requirements and provided guidance on controlled rooms classifications for viable microbial contamination.

Identified inspection observations - Bioburden and Microbial Contamination Testing

Old validations

- lack of review and revalidation

Validation protocol and report - insufficient information

- Tested samples conditions, validated time frames post collection, sample types and transportation conditions
- Insufficient discussion of results – unexpected results, unmet criteria results and impact on the test

Not all compendial microorganisms were included in the study

Identified observations from inspection - Back up equipment qualification

Back up equipment including:

- Storage equipment
- Processing equipment
- Testing equipment

Identified observations

- Not maintained according to routine equipment maintenance procedures
- Not qualified for the required intended use

Specific requirement- The Code Clause 324

Identified inspection observations – Gowning and de-gowning

- Suitable dedicated area
- Gowning qualification
- Periodic competency testing
- Suitability for use - full cover up

Conclusion

GMP compliance improvements ?

- Manufacturers with previous repeated basic (A3), now satisfactory compliance (A2)
- Management role
- Acknowledging gaps and planning what next
- Build QMS management knowledge across all teams- not just quality.
- Acknowledgement to some sites that although still maintaining basic compliance, however, improvement was also noted.

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