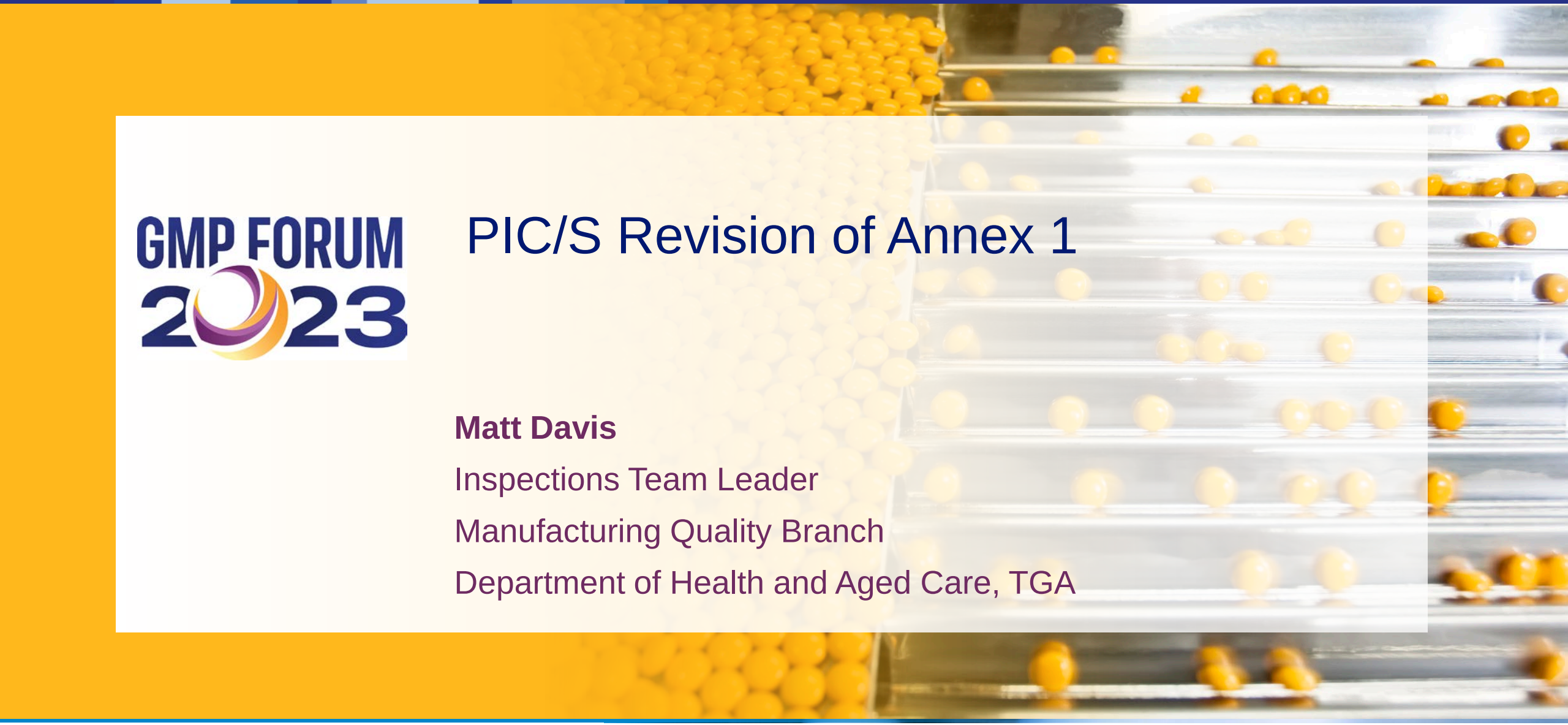


PIC/S Revision of Annex 1

Matt Davis

Inspections Team Leader

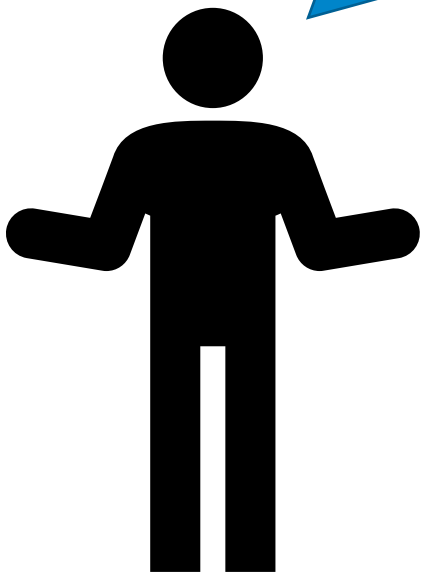
Manufacturing Quality Branch

Department of Health and Aged Care, TGA

Common concerns with Annex 1

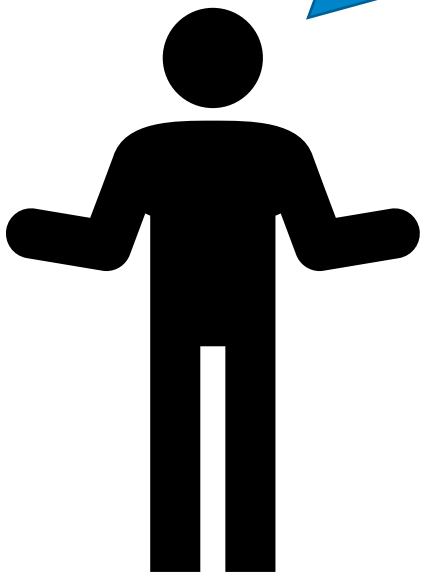
The new Annex 1 is a significant increase in requirements!

No, we simply clarified existing requirements, and provided new guidance where there wasn't any before!



Common concerns with Annex 1

The new Annex will render my existing site non-compliant!

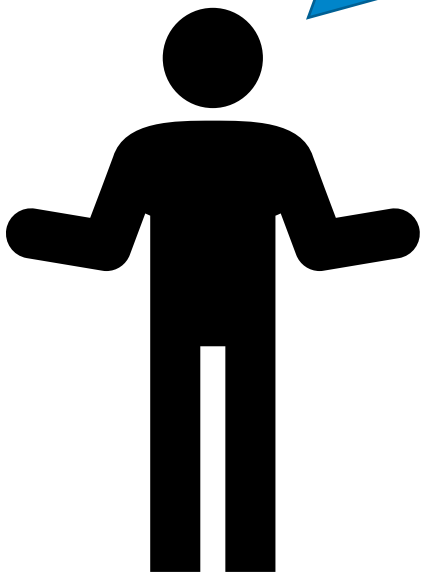


No, the changes to the Annex have been specifically written to allow existing technologies

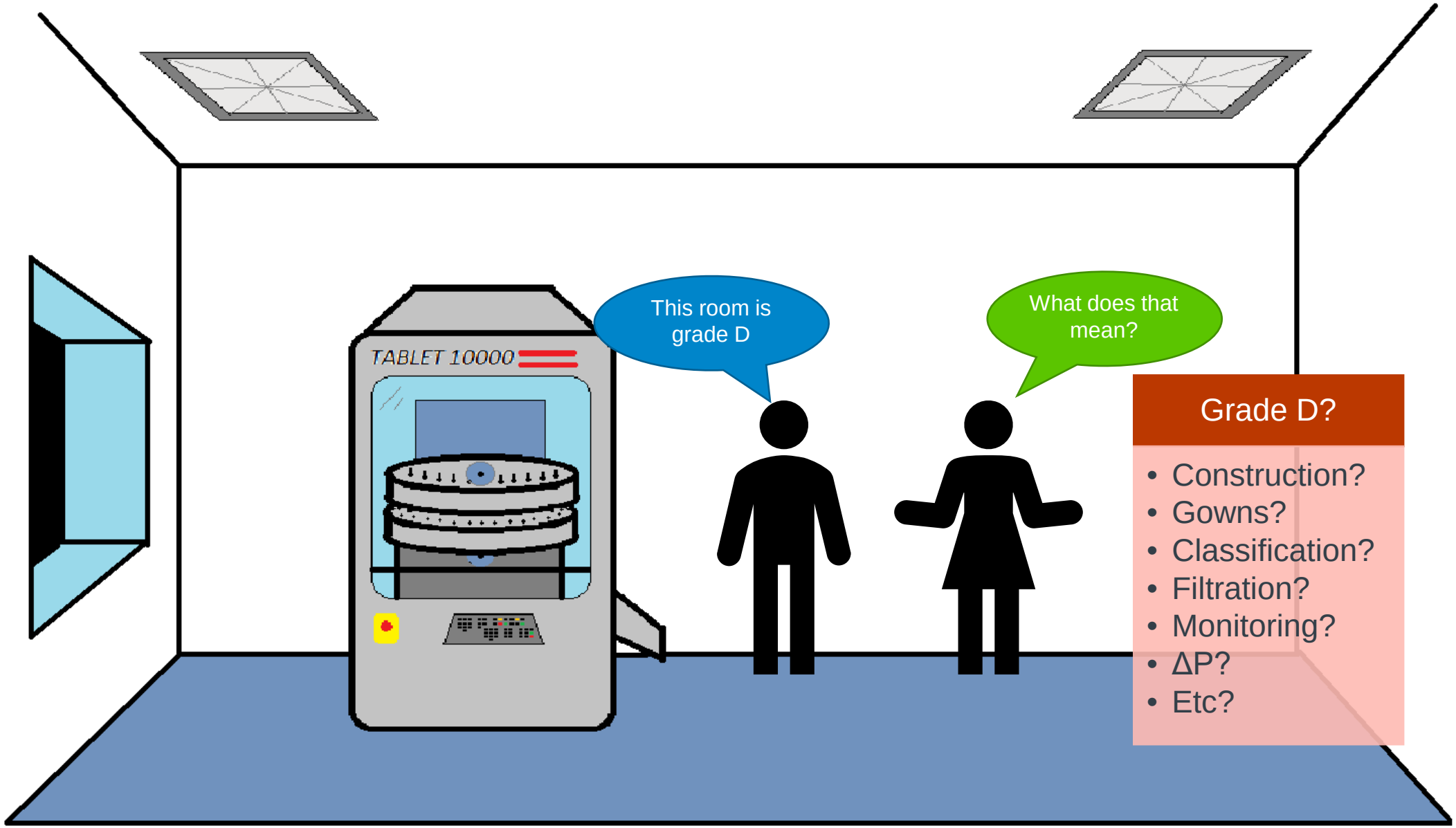
Common concerns with Annex 1

Annex 1 now applies to non-sterile goods!

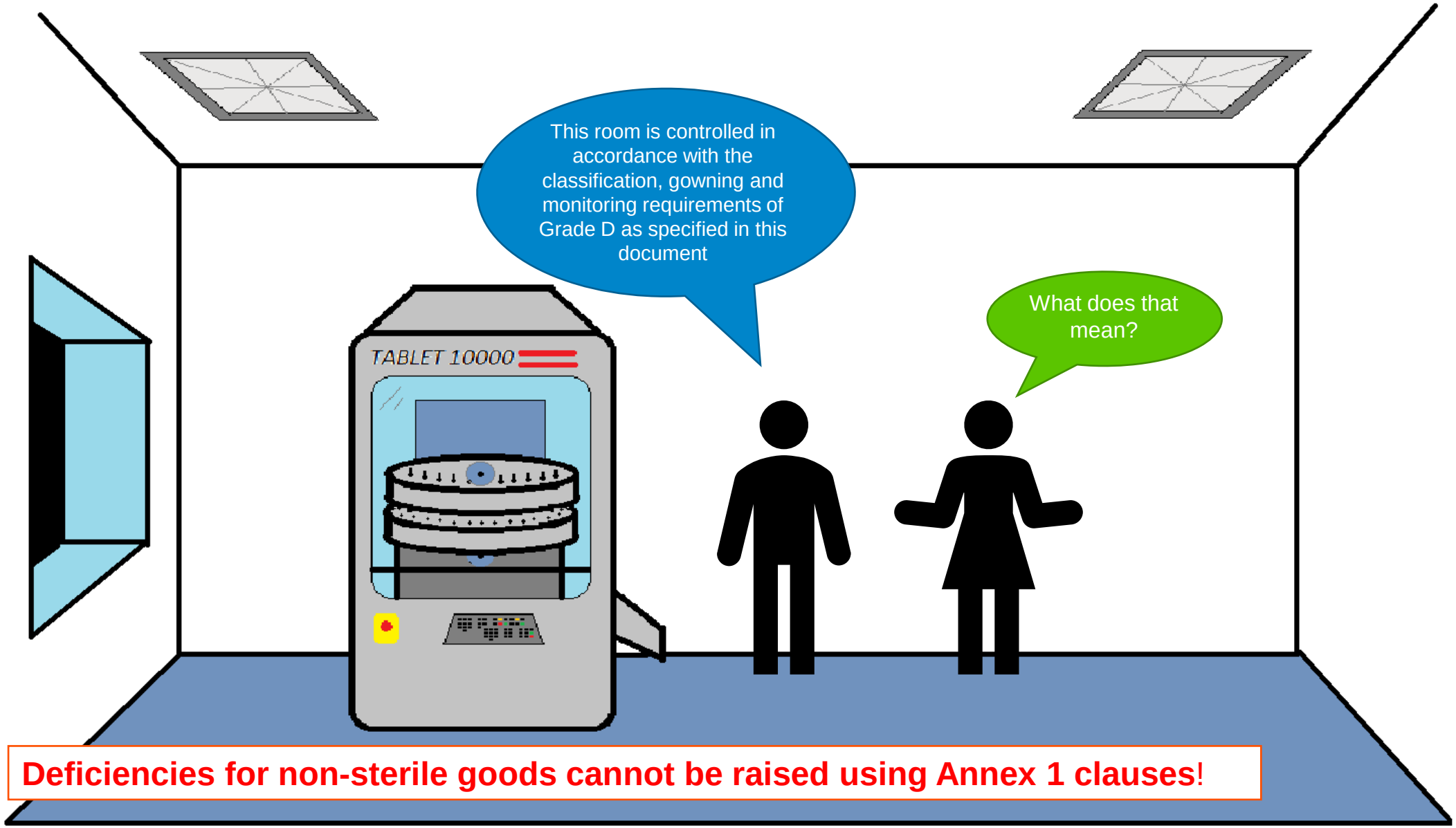
No, it doesn't*
(I need to explain)



Annex 1 and non-sterile medicines



Annex 1 and non-sterile medicines



Deficiencies for non-sterile goods cannot be raised using Annex 1 clauses!

Principles - QRM

2.2 "Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM"

QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.

Contamination Control Strategy elements

Quality Risk Management

Knowledge; Continuous Improvements

Organisational and Technical Measures

Personnel

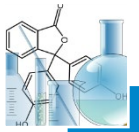
- Cultural considerations
- Appropriate education
- Suitable knowledge and experience
- Clothing considerations
- Gowning processes
- Training strategy
- Qualification for aseptic processing

Premises, Equipment& Utilities

- Location
- Design
- Capability
- Capacity
- Authorisations
- Validation life cycle
- Operating conditions
- Planned Preventative maintenance
- Monitoring and controls
- Cleaning and disinfection
- Consumables
- Water Sources
- Steam (s)
- HVAC design
- Gases

Production & Process

- Process design
- Sterility Assurance
- In-process controls
- Process risk assessments
- Process Validation
- Intermediate specifications
- PUPSIT
- Operating conditions
- Cleaning and disinfection
- Materials Management



Materials & Quality Control

- Specifications
- Materials management
- Parameters & attributes of
  - API
  - Excipients
  - Components
  - Process aids
  - Packaging
  - Intermediates
  - Bulk
  - Finished product

Outsourced activities

- Vendor assurance
- Materials management
- Component suppliers
- Sterilisation steps
- Validation experts
- Contracts
- Access to data
- Performance monitoring

Review

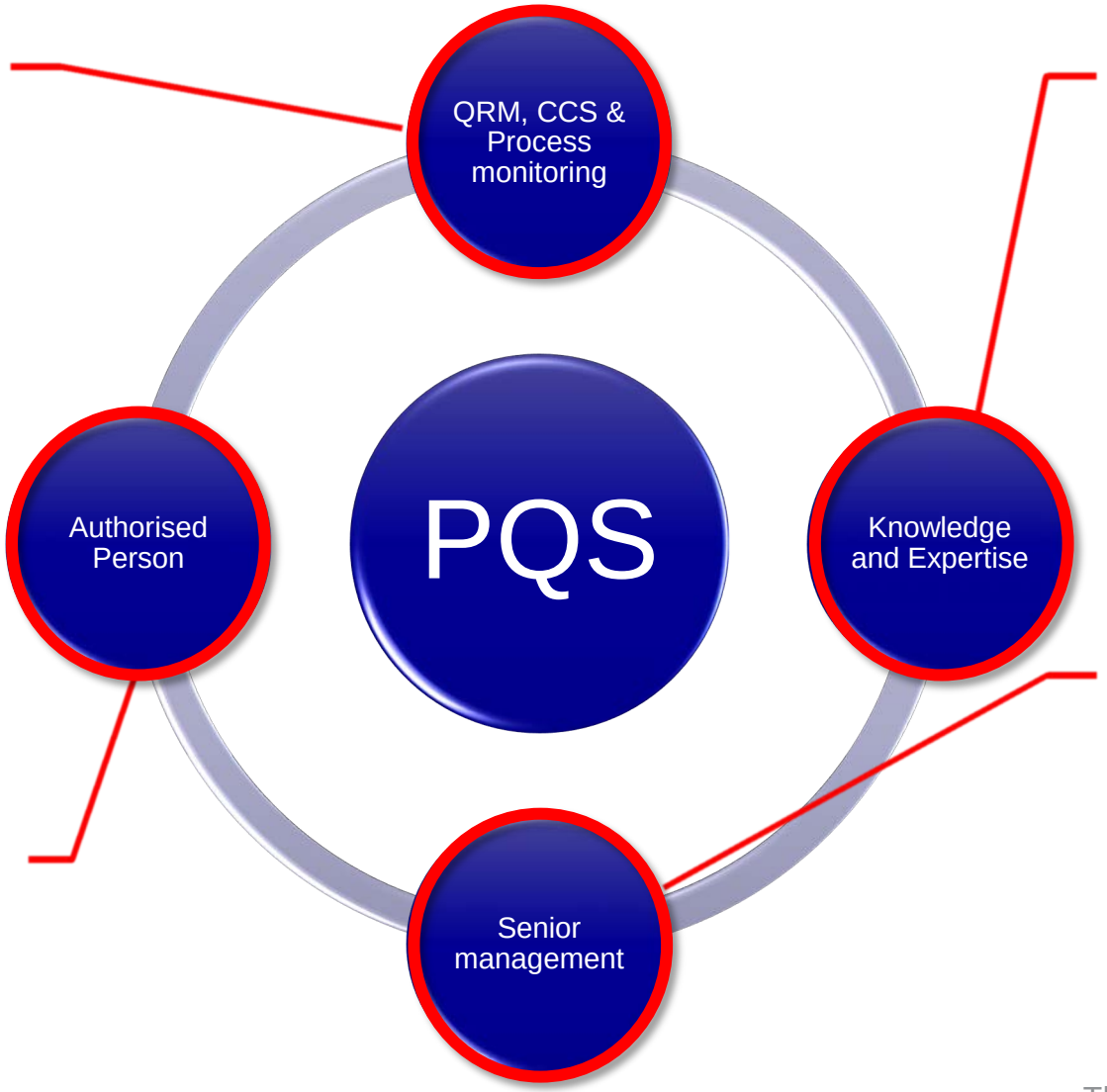
Risk assessments; Monitoring; Data

Pharmaceutical Quality System

Pharmaceutical Quality System

+3.1 *i) An effective risk management system is integrated into all areas of the product life cycle*

+3.1 *vii) Persons responsible for the certification/release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products*



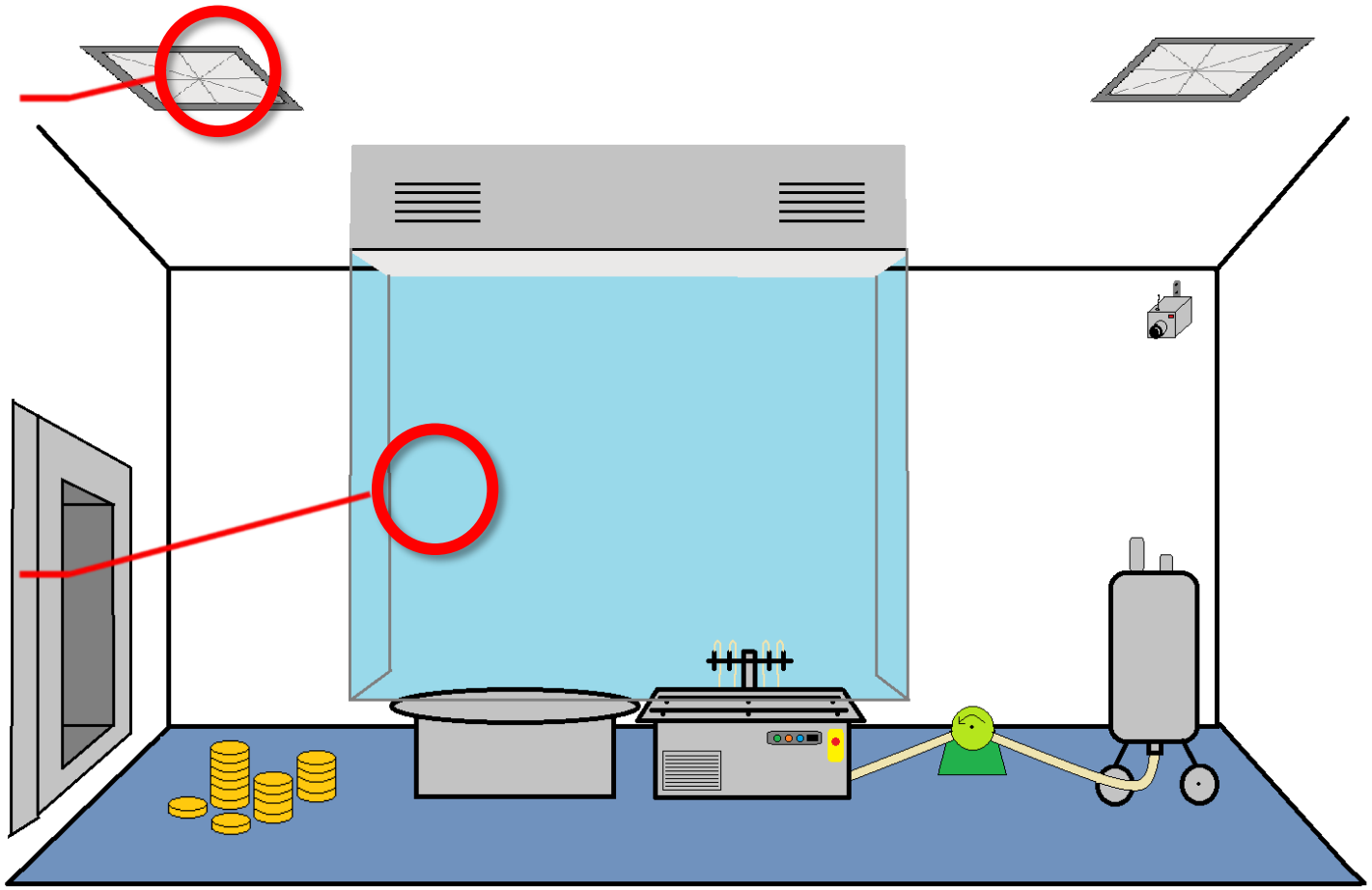
+3.1 *ii) The manufacturer has sufficient knowledge and expertise in relation to the products manufactured*

+3.1 *v) Senior management should effectively oversee the state of control throughout the facility and product lifecycle.*

Premises - Cleanroom Classification/Qualification

+4.25 Cleanroom and clean air equipment qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use…

+4.27 classification, particles equal to or greater than 0.5 and 5 µm should be measured…both at rest and in simulated operations.



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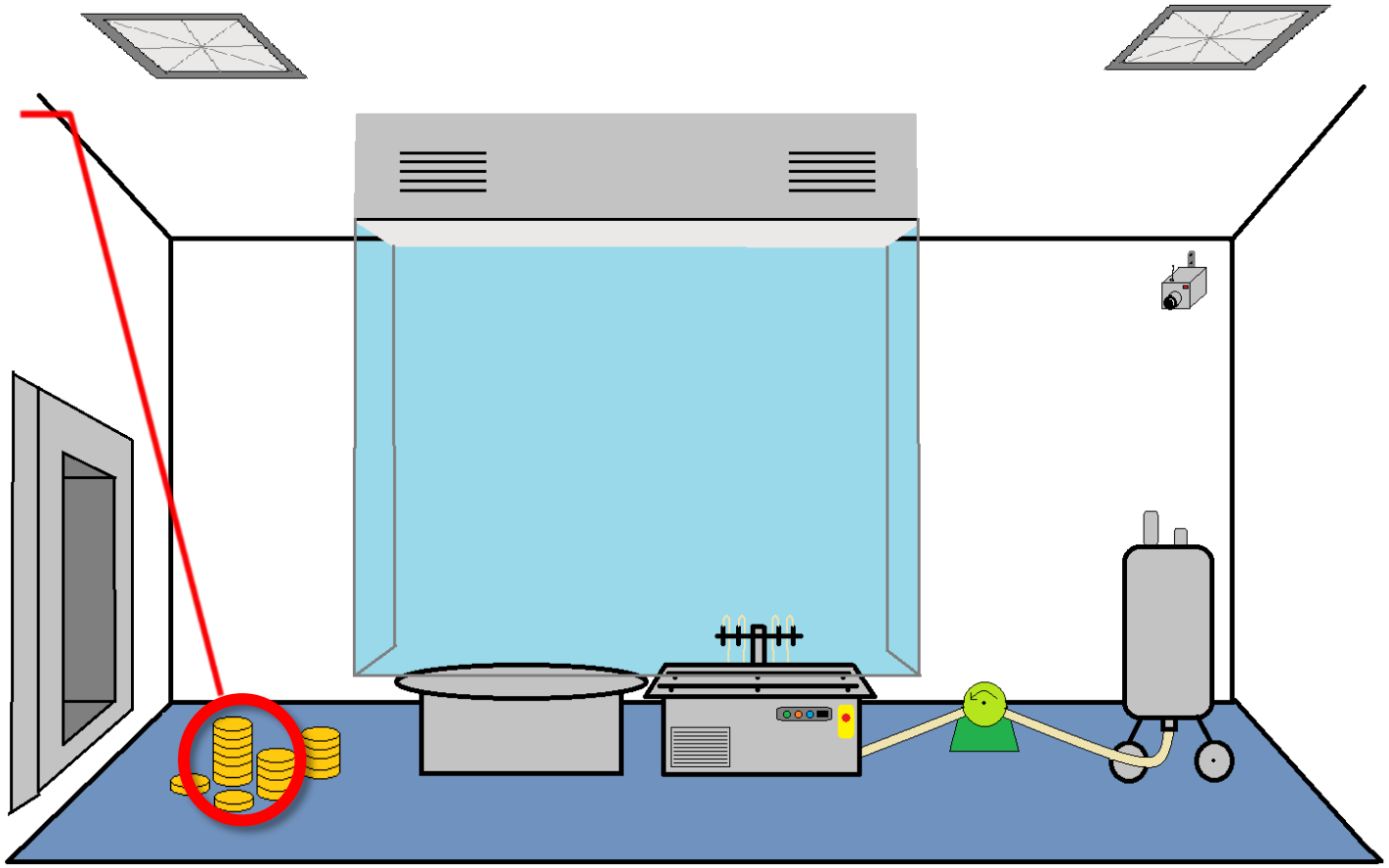
Grade	Maximum limits for Total particle ≥ 0.5 µm/m^3		Maximum limits for Total particle ≥ 5.0 µm/m^3	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified	Not specified
B	3 520	352 000	Not specified	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not predetermined	29 000	Not predetermined

Premises - Cleanroom Classification/Qualification

+4.25 v) microbial airborne and surface contamination
+ 4.31 sampling locations based on risk assessment and the results obtained from room classification, air visualization studies and process knowledge
+ both “at rest” and “in operation” states need to be qualified



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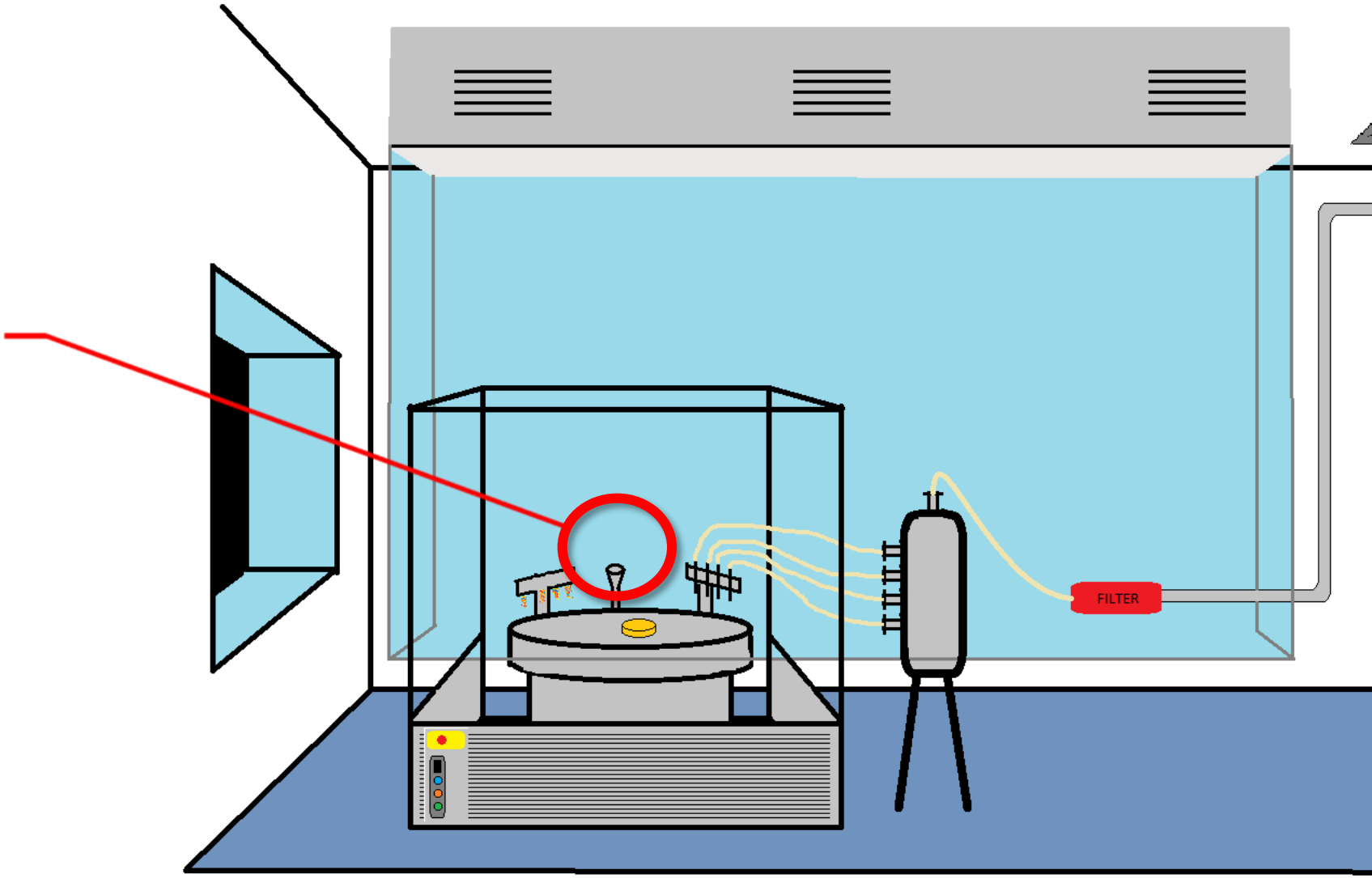
Grade	Air sample CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours (a)	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

Premises-Cleanroom Monitoring

+9.9 Total particle monitoring +9.17
- Both ≥0.5 and ≥5 µm monitored
- Sample rate at least 28L/min
+9.20 If contaminants present: frequency sufficient to demonstrate compliance pre and post exposure



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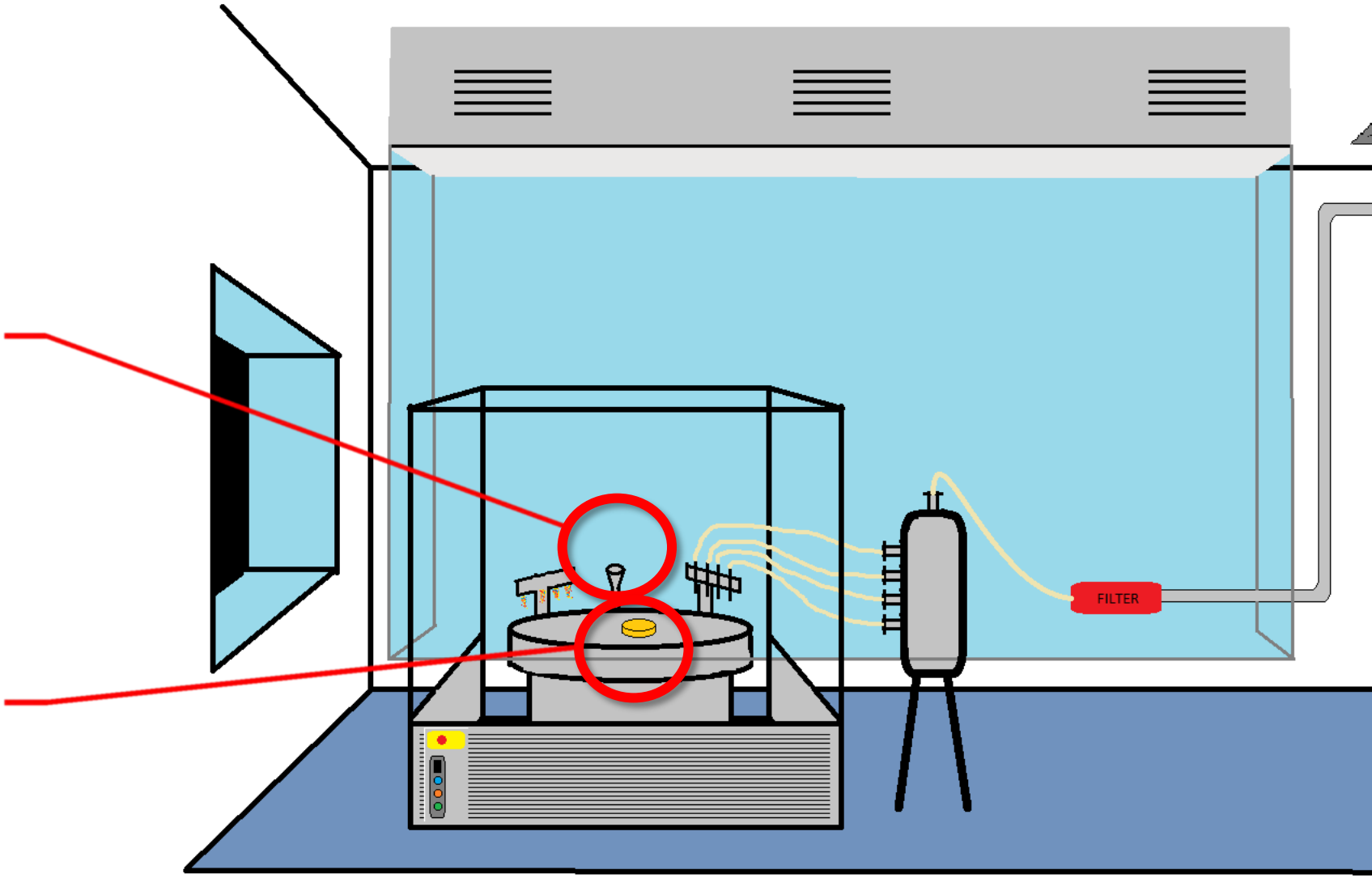
+9.25 Viable particle monitoring
- Includes personnel
+9.31 All A&B isolates identified to species level
C&D isolates ID when >limit or problematic organisms



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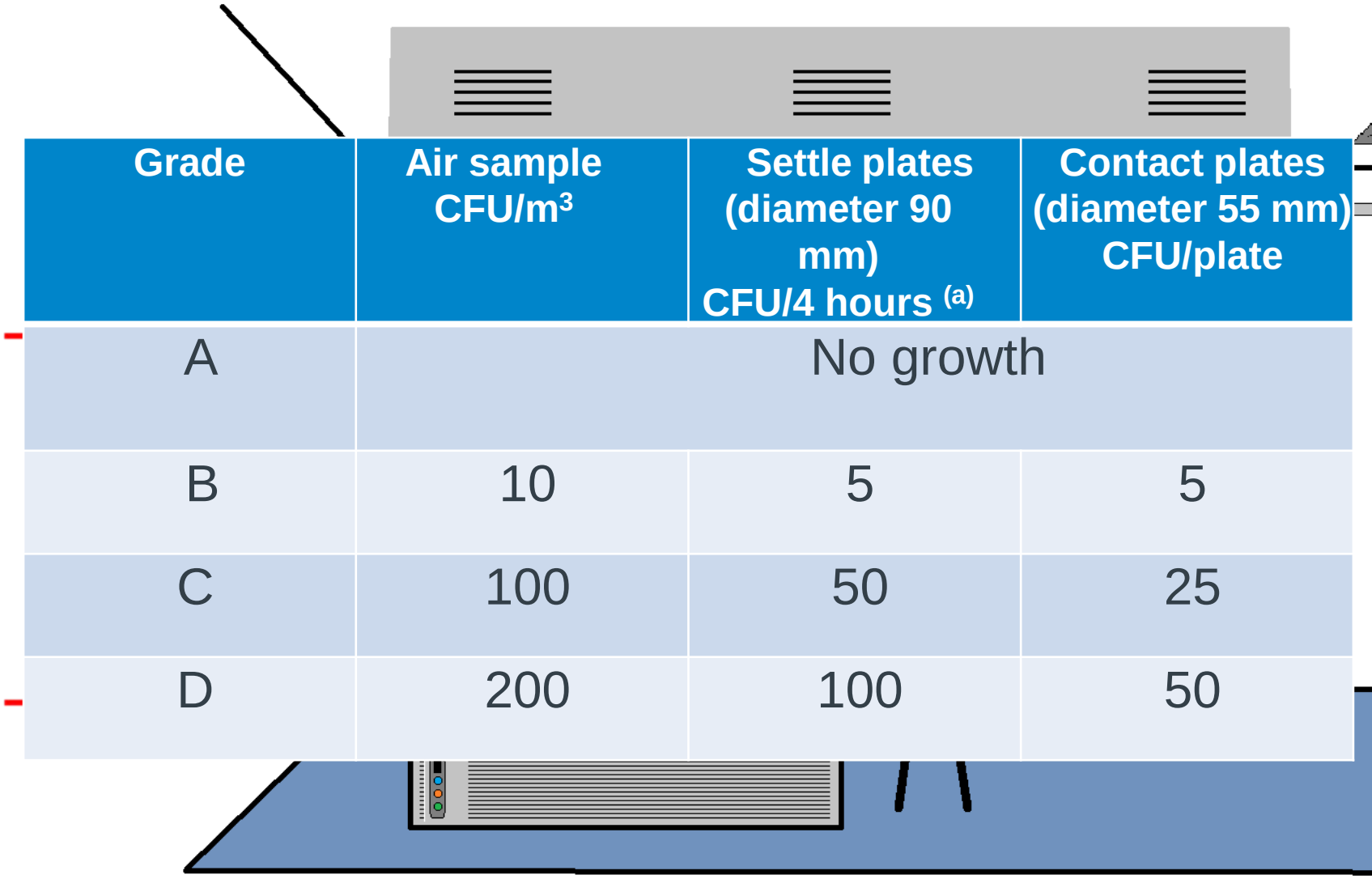
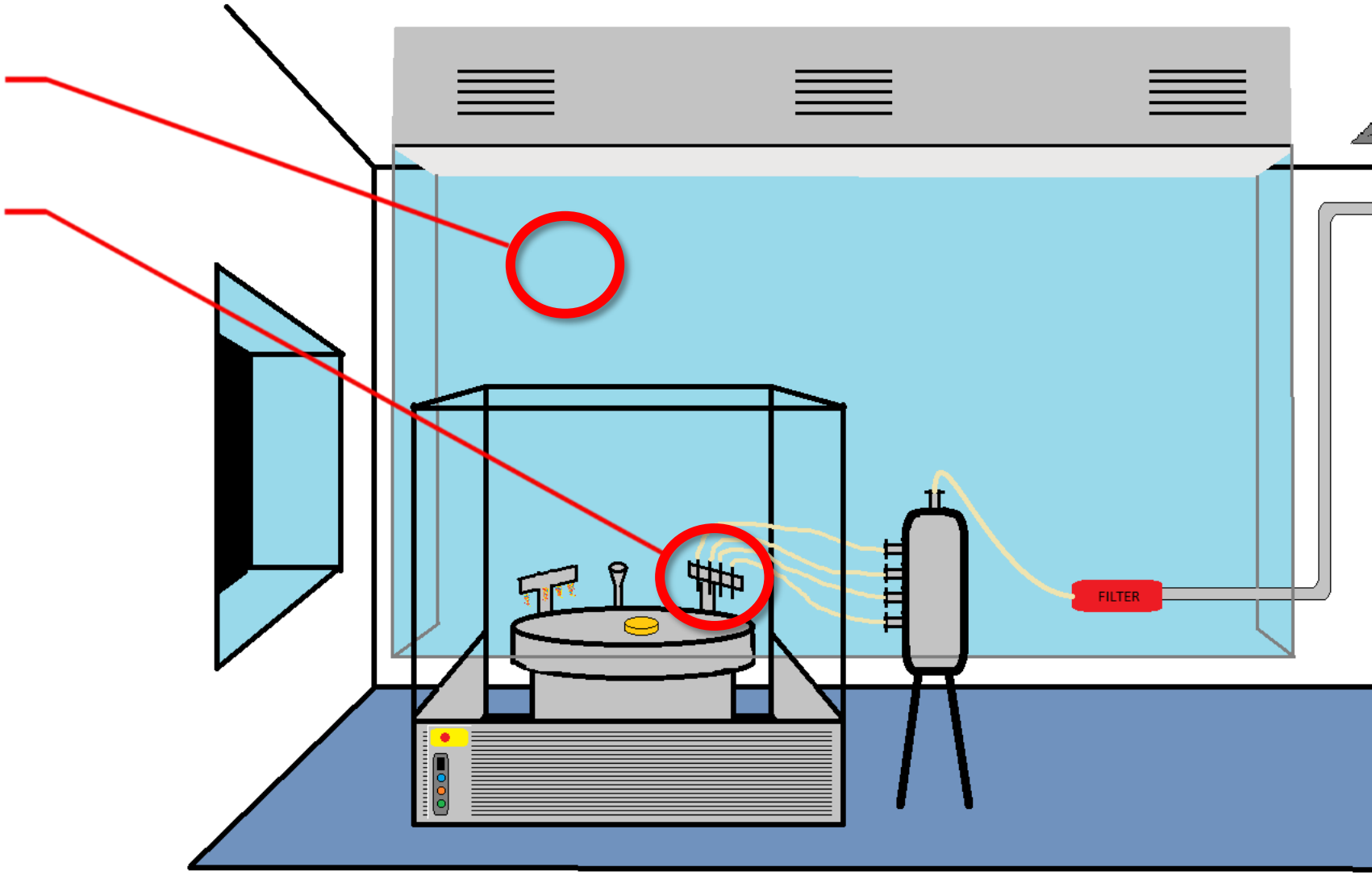


Premises-Cleanroom Monitoring

+9.2 Temperature, %RH and ‘other specific characteristics’

+9.2 Aseptic Processing Simulation (APS) …



APS

+9.34 Interventions:
- Known inherent interventions
- Include worst-case interventions
- Frequency and manner reflective of routine operations
- Based on design of process and risk to sterility

+9.36 Design of APS:
- Shifts
- Campaign operations
- Use of chaser fills

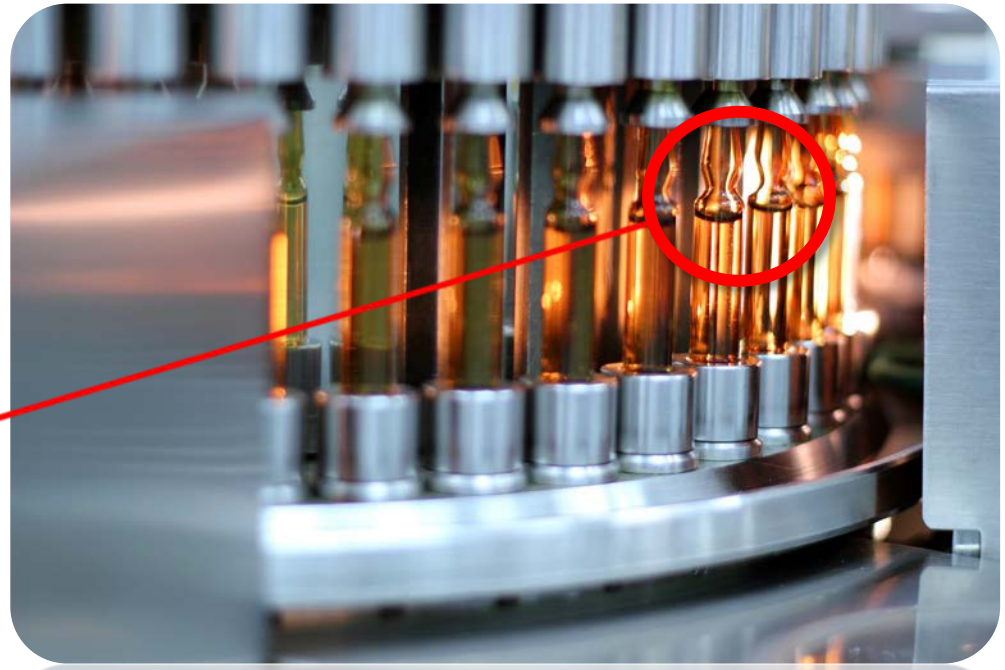
+9.35 APS should not be used to justify practices that pose unnecessary contamination risks.

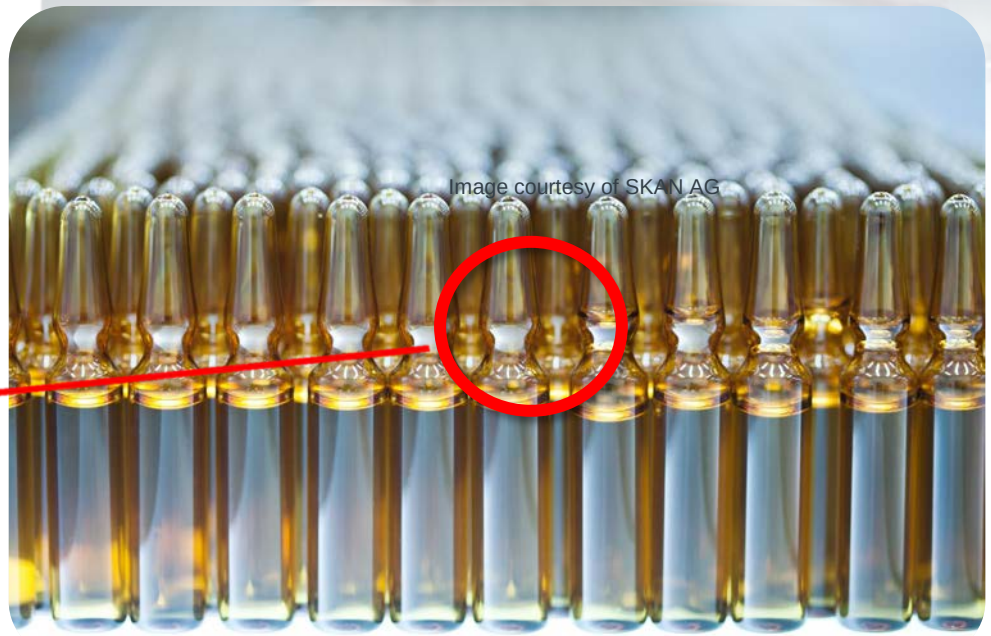
APS

+9.41 Unit inclusion/exclusion
- Only reject units typically rejected during normal operations
- Process knowledge - Units rejected during set-up or line clearance incubated – but not included in acceptance criteria

+ 9.46 Target now ZERO…any growth = failed APS.
- Normally 3 repeat APS required

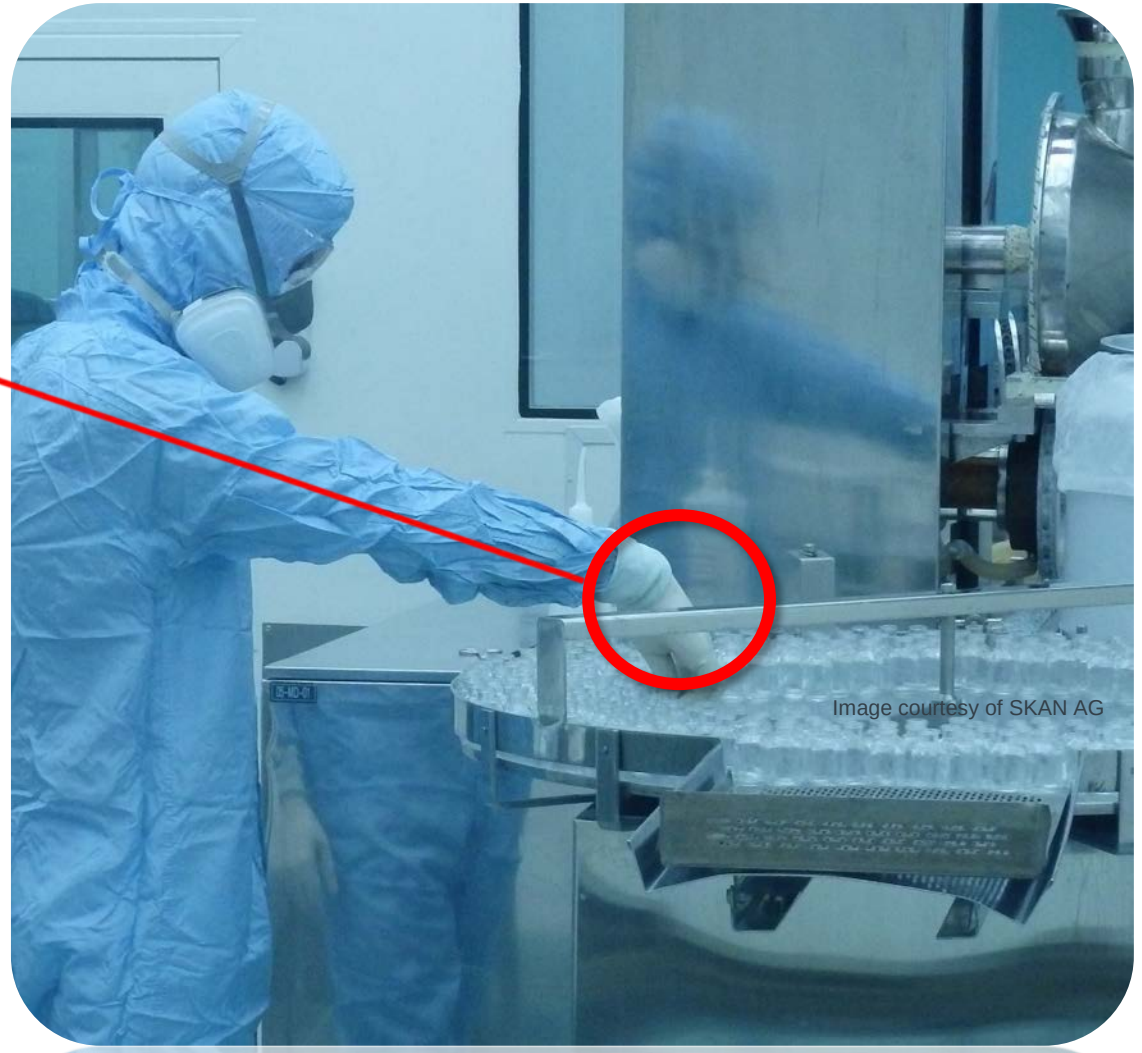
+9.47 APS can only be aborted where similar circumstances would result in batch cancellation + investigation





APS

+9.39 Manual filling:
- Each process and operator 3 APS
- APS each operator every 6 months
- APS = routine batch size



Barrier technologies

+ 4.21 System integrity:
Isolators:
- Regular system and glove leak testing
- At least at the beginning and end of each batch/campaign
- Systematic visual inspection during use

Images courtesy of SKAN AG

Barrier technologies

+ 4.21 System integrity:
RABS:
- Sterilisation of gloves before installation
- Sterilisation or bio-decontamination prior to each manufacturing campaign
- Disinfection after exposure to background environment, e.g. door opening
- Systematic visual inspection during use, integrity testing periodically

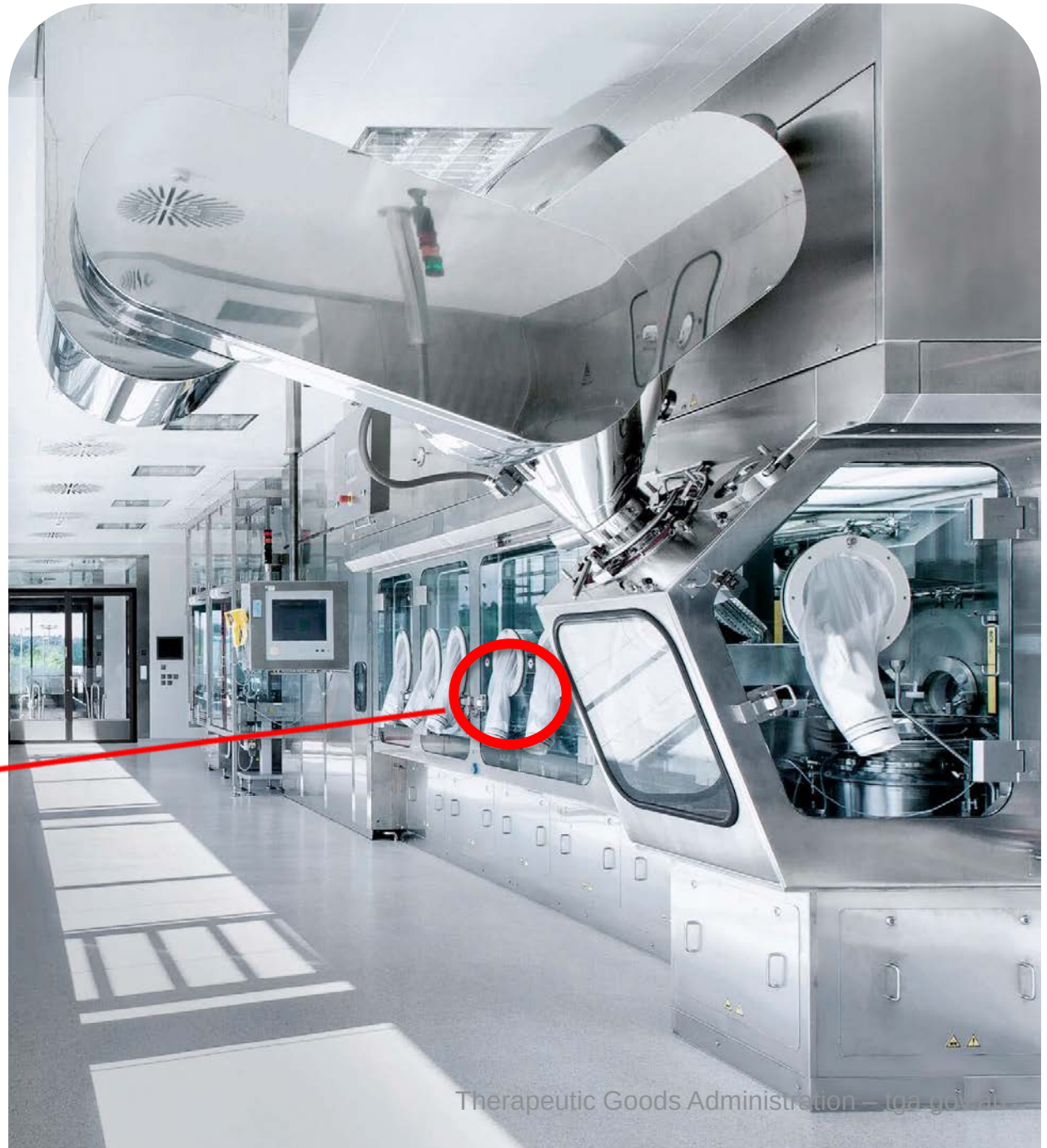
Images courtesy of SKAN AG

Barrier technologies

+4.22 Validated decontamination methods - sporicidal

+ Evidence that cleaning agent doesn't affect product produced

+Automated decontamination for isolators, validated for RABS

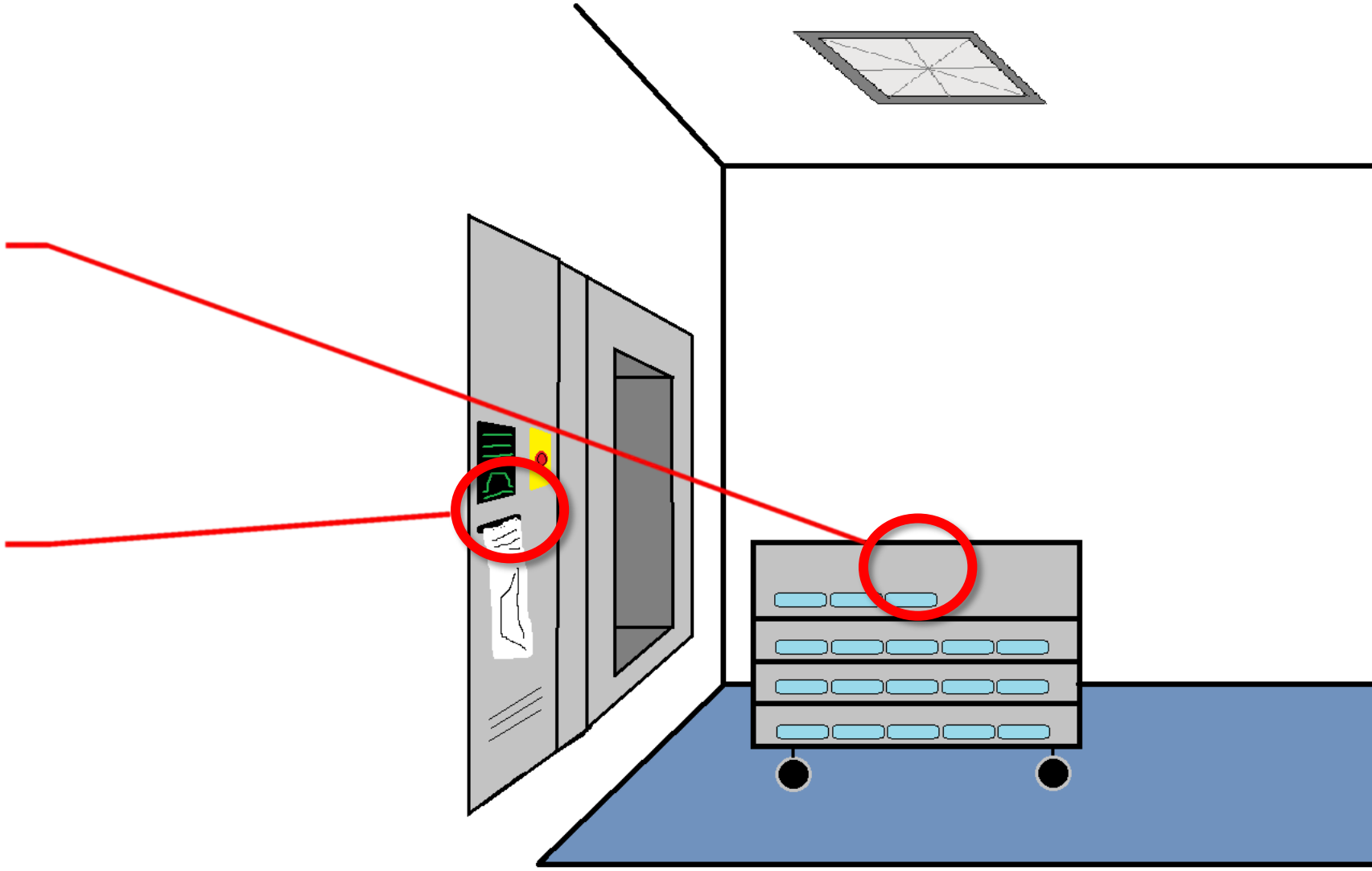


Images courtesy of SKAN AG

Sterilisation

+ 8.38 min/max load sterilisation validated
+ 8.39 Annual revalidation of worst case load patters…other loads revalidated based on CCS

+ 8.50 redundancy in control and monitoring systems
+ 8.52 Load probe temperature control prior to cycle commencement



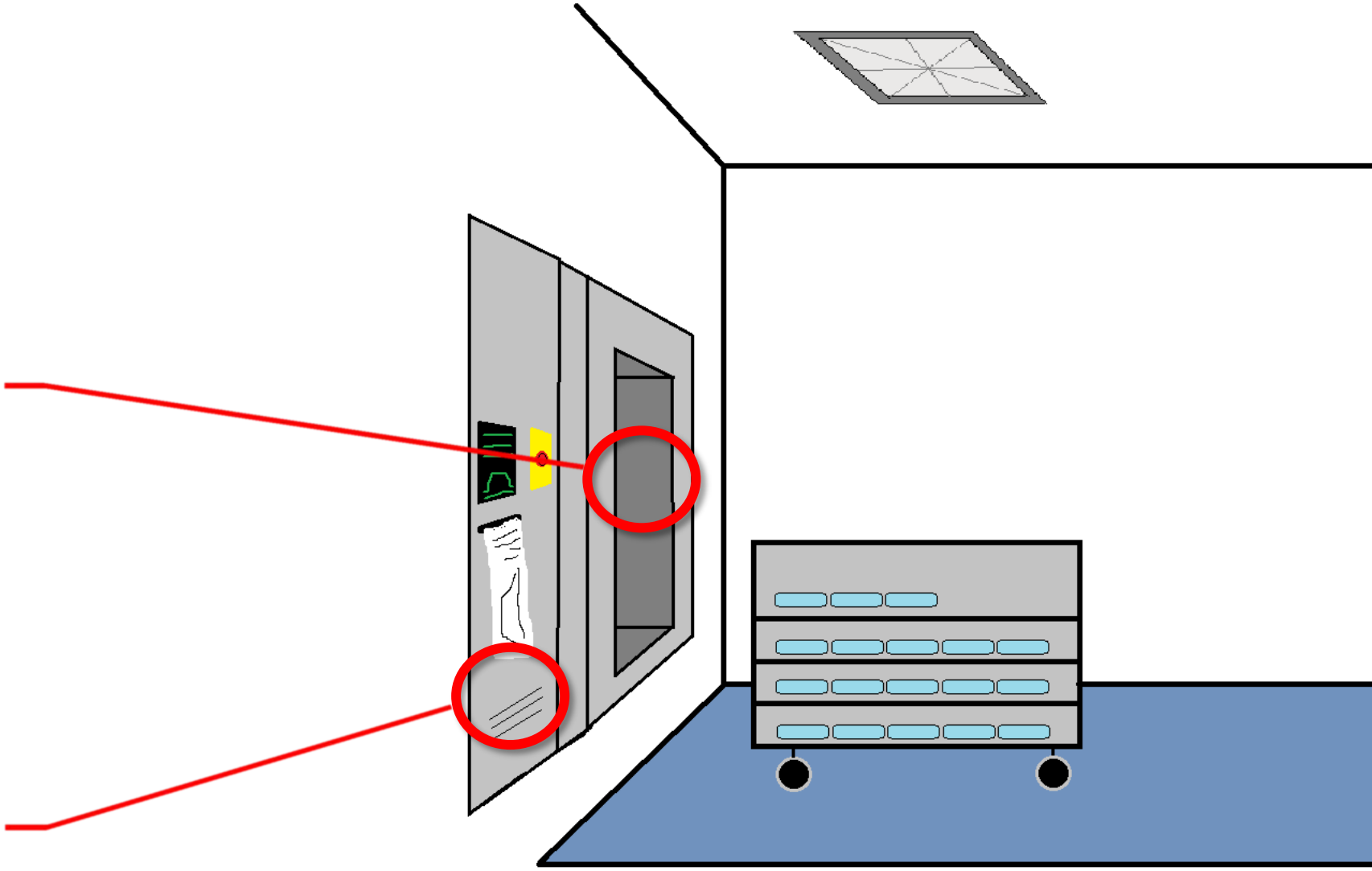
Sterilisation

+ 8.59 Porous loads:
- equilibration time
- exposure time
- correlation of pressure and temperature
- minimum/maximum temperature range during
- exposure

+ 8.59 Liquids loads:
temperature, time and/or F_0

Autoclaves:
+ 8.60 Weekly leak test for vacuum phase cycles and when used to hold sterile equipment

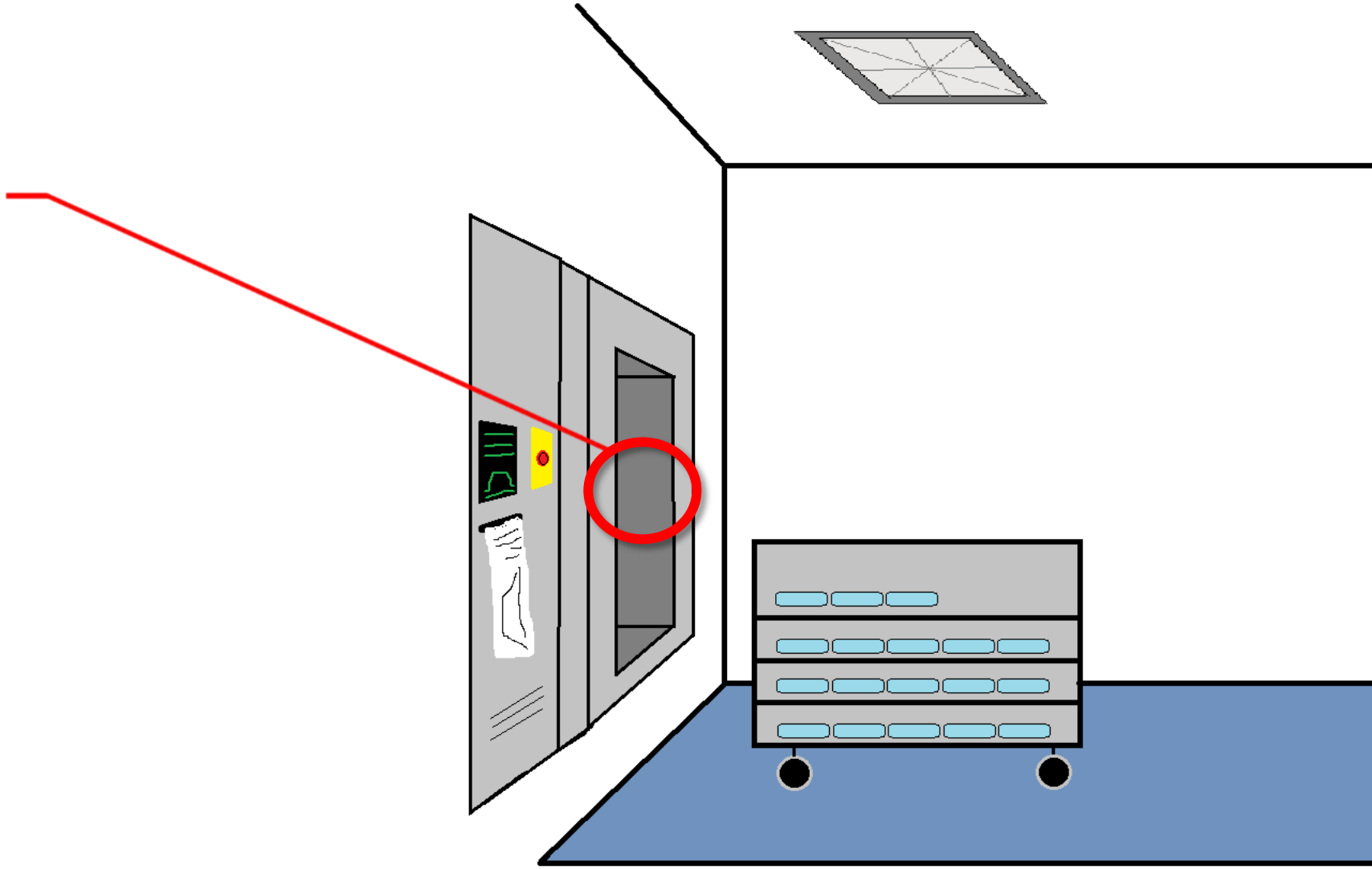
+8.61 Daily air-removal test, or use of air detector



Sterilisation

+8.62 prevention of container distortion

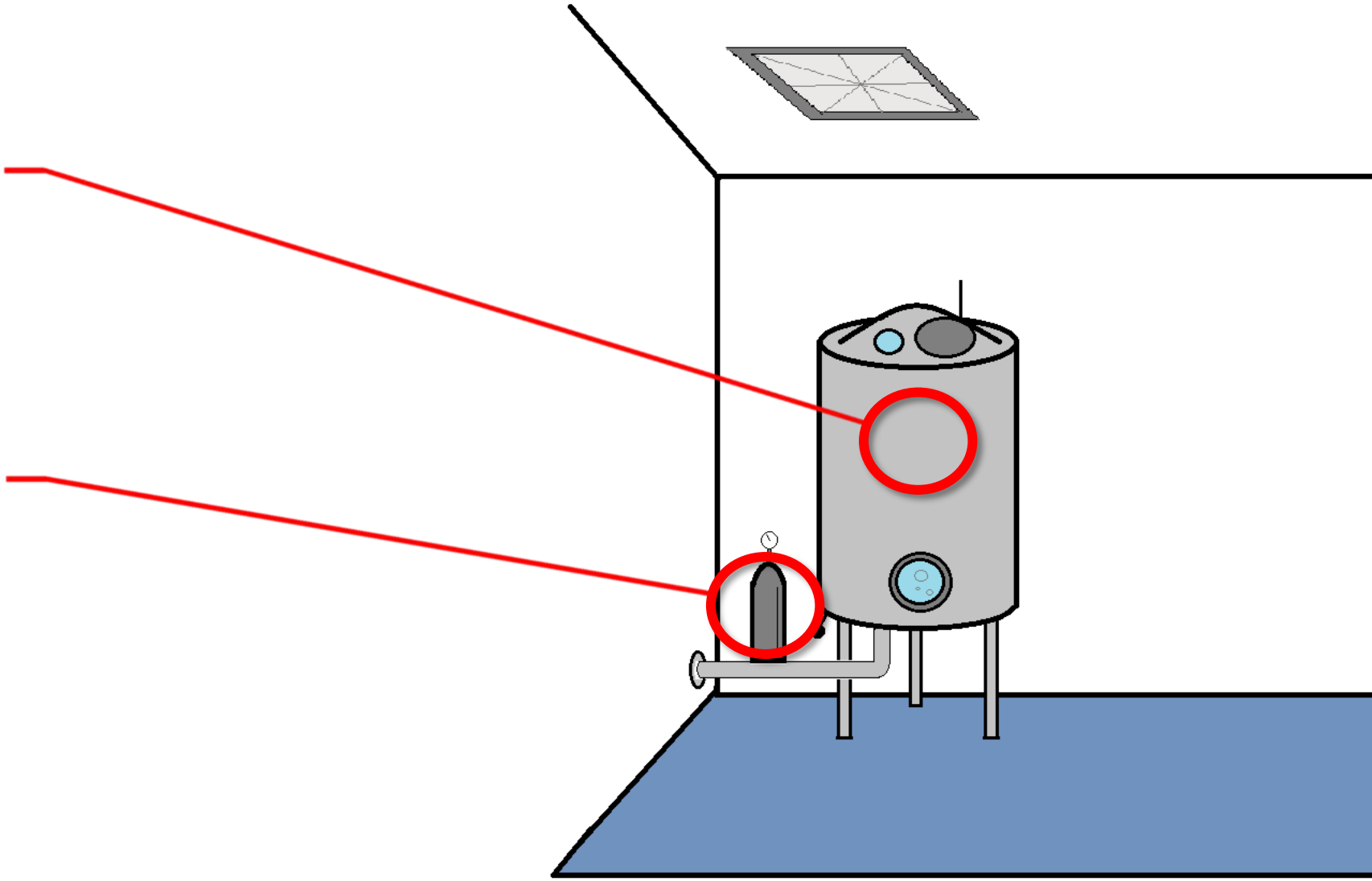
+8.64 super-heated water cycles – spray/drain checks



Sterilisation

+8.63 SIP
- Validated
- Cycles monitored
- +ve pressure maintained

+8.82 Design of filtration system
+8.85 Validated in line with ISO13408-2
+8.87 PUPSIT
+8.94 Single use of filters

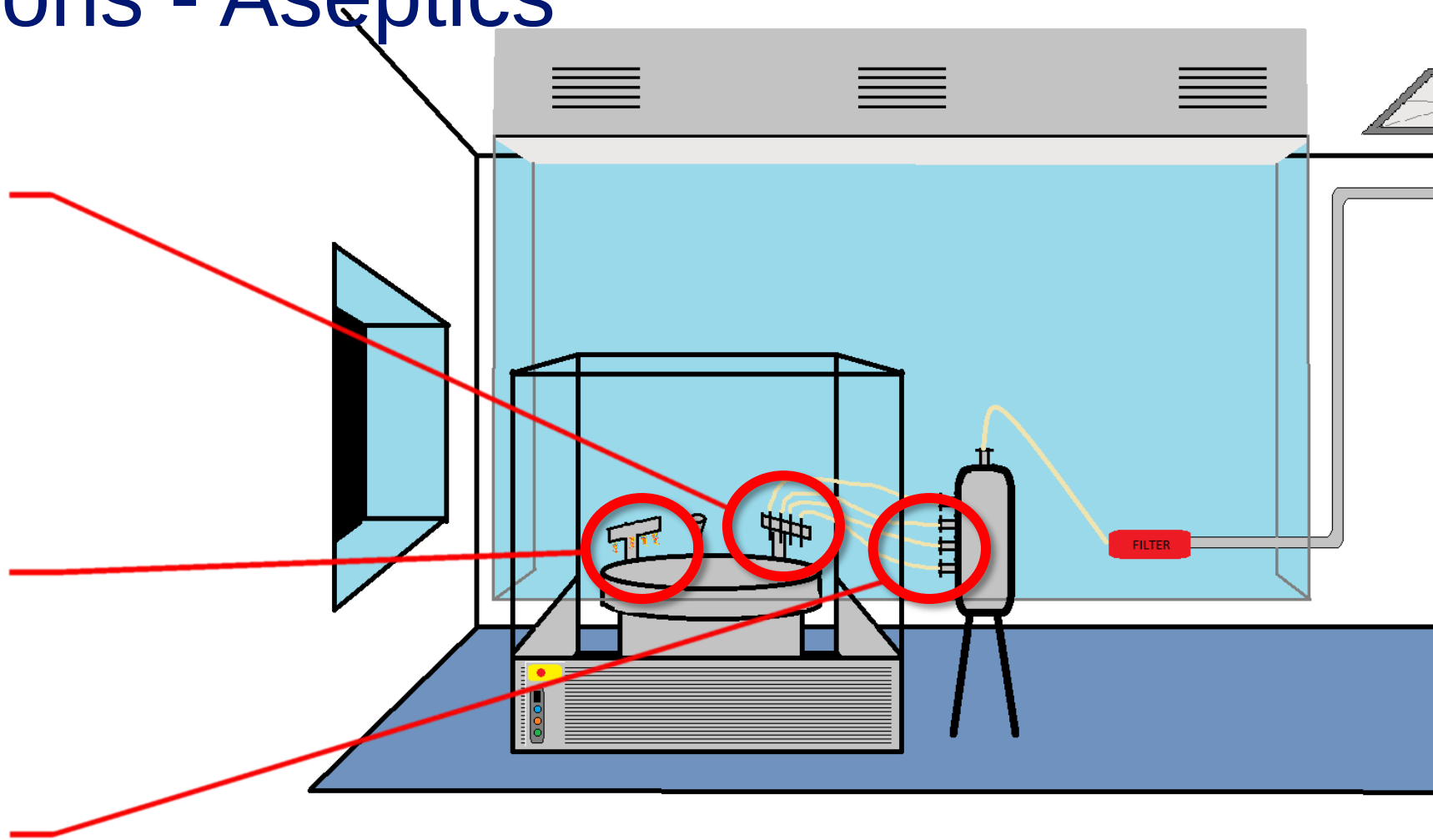


Critical Operations - Aseptics

+5.2 For aseptics - all direct and indirect contact parts sterilised

+8.16
- Authorised list of interventions
- Interventions designed – QRM – Media fills
- Engineering solutions for all interventions/tools
- Non-qualified interventions managed as a deviation

+8.131
Single use systems



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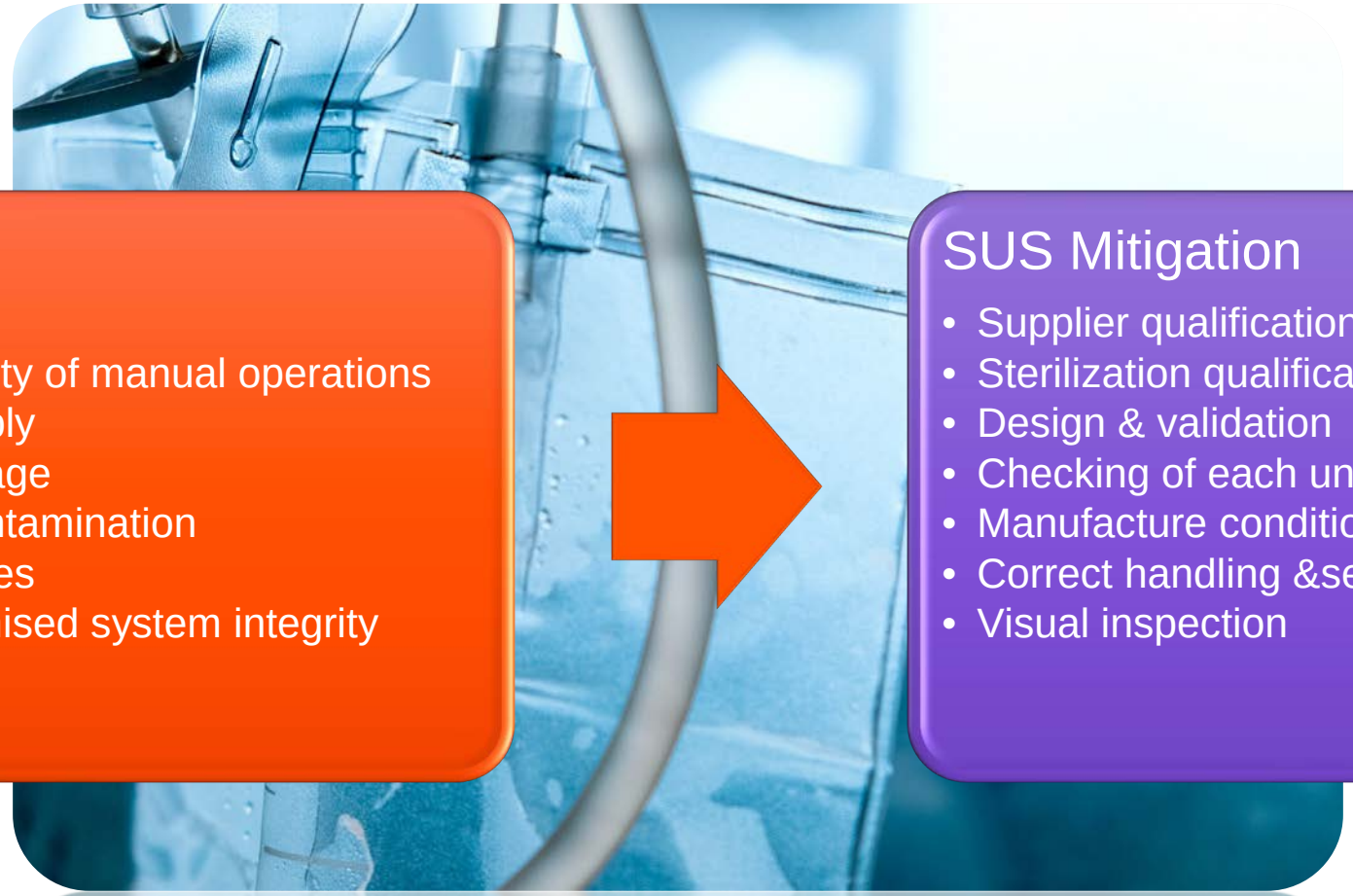


SUS Risks

- Fragile bags
- Number and complexity of manual operations
- Complexity of assembly
- Risk of hole and leakage
- Risk of particulate contamination
- Extractables/leachables
- Potential for compromised system integrity during unpacking

SUS Mitigation

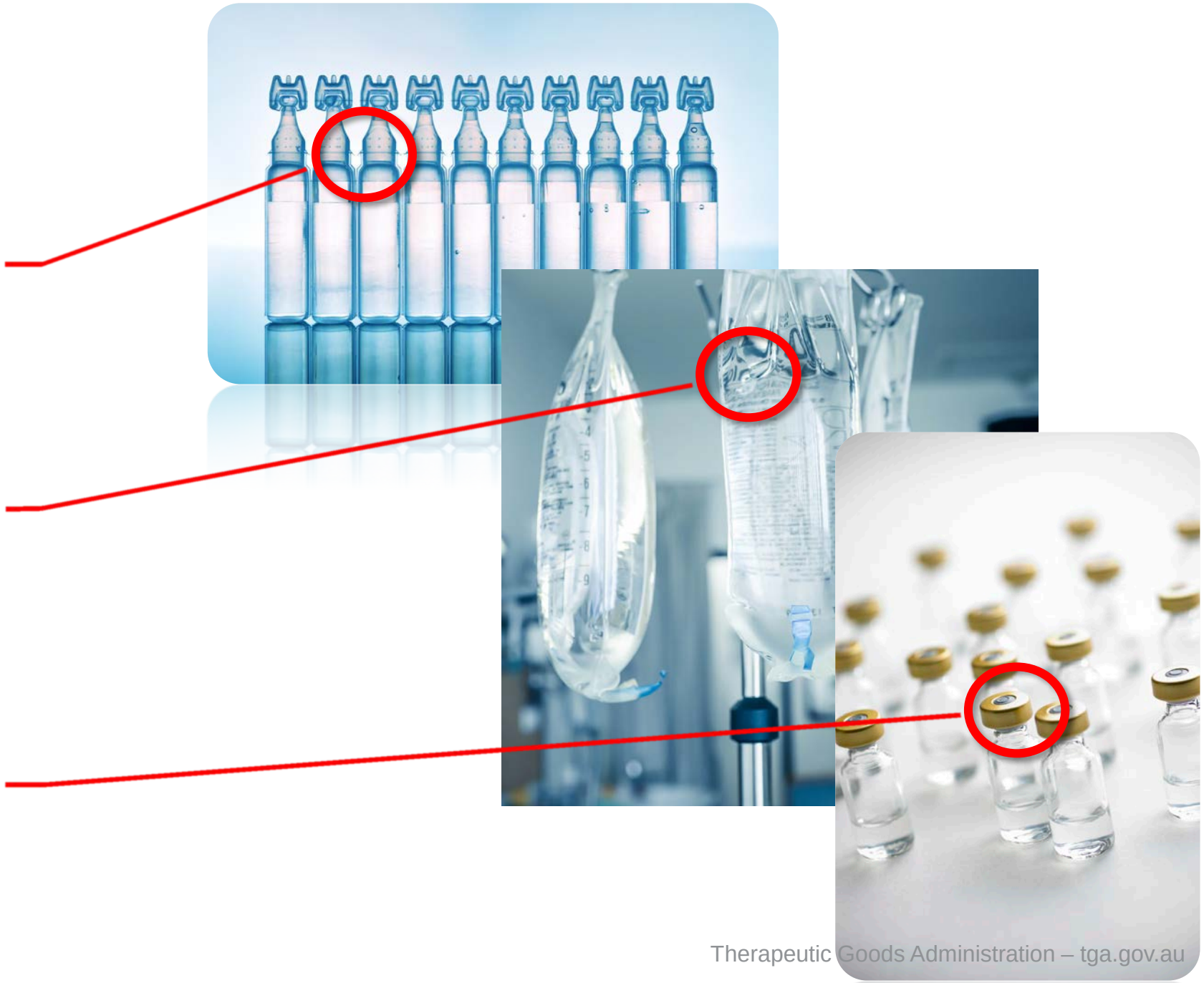
- Supplier qualification
- Sterilization qualification
- Design & validation
- Checking of each unit upon reception
- Manufacture conditions
- Correct handling &set up
- Visual inspection

IPQC

+8.22 Fusion sealed SVP – 100% integrity tested

+8.22 Fusion sealed LVP – Reduced sampling where justified:
- Consistency of process
- High level of process control

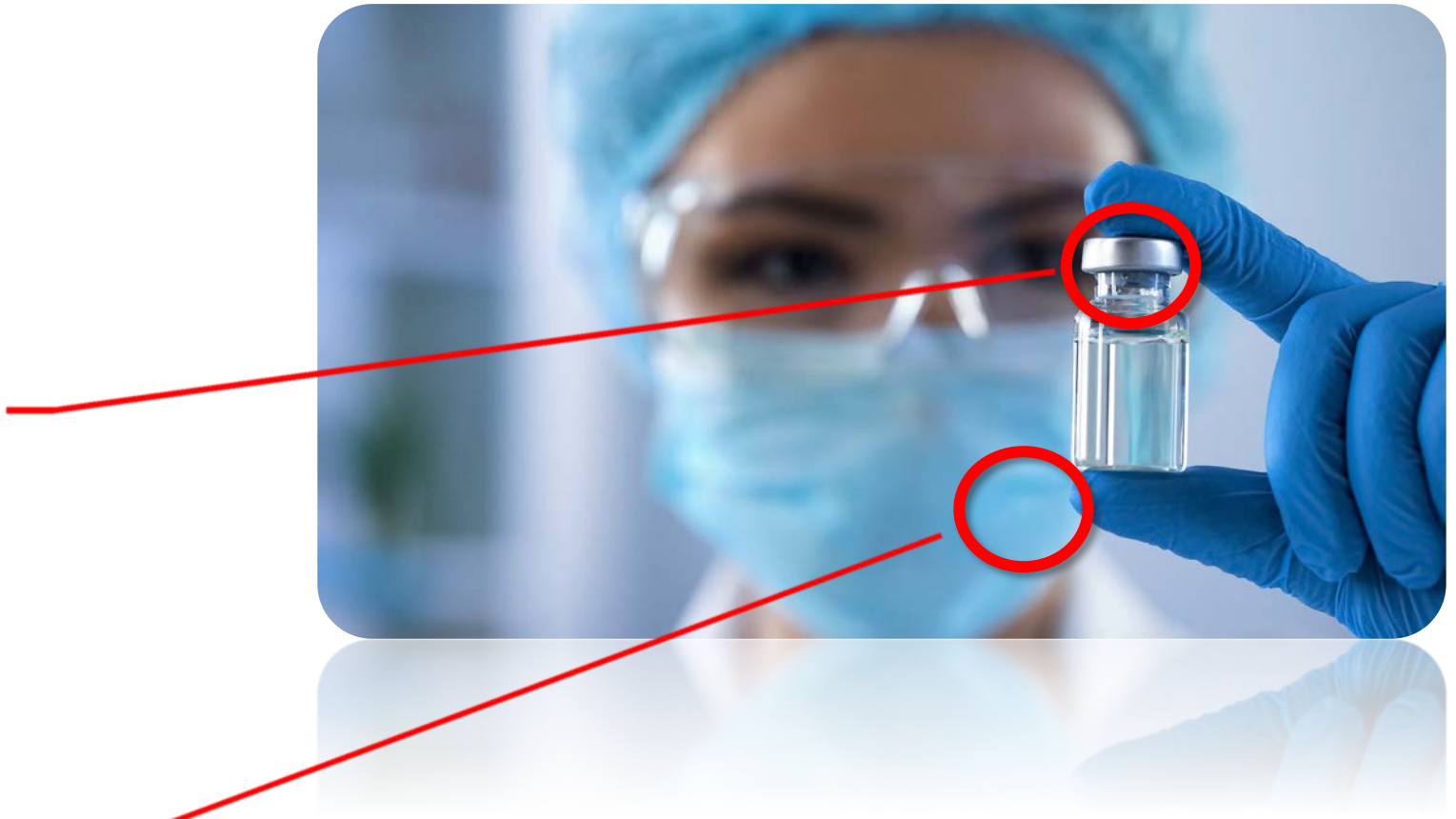
+8.23 Non-fusion sealed:
- Sampling where justified:
- Knowledge of CC system
- Supplier management and process knowledge
- High process control



IPQC

+8.31 Visual inspection
- Controlled conditions
- Annual qualification
+8.32 Automated systems
- Knapp testing
- Challenge units during set-up
+8.33 Monitoring, recording and trending of defects

+8.30 Visual inspection
- Categorization of defects
- Investigation of OOT results
- If AQL is used, no critical defects permitted (addresses USP <790>)



IPQC

+10.3 Bioburden representative of worst case

+10.4 Organisms identified and impact on sterilisation process assessed

Next steps

- Adoption strategy
- Gap analysis
- Engagement with SM-TWG

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 and Aged Care

Therapeutic Goods Administration

Coming up next in this room

Lynn Talomsin
Senior GMP Inspector

Adoption of future PIC/S revisions