Australian Government
Department of Health
Therapeutic Goods Administration

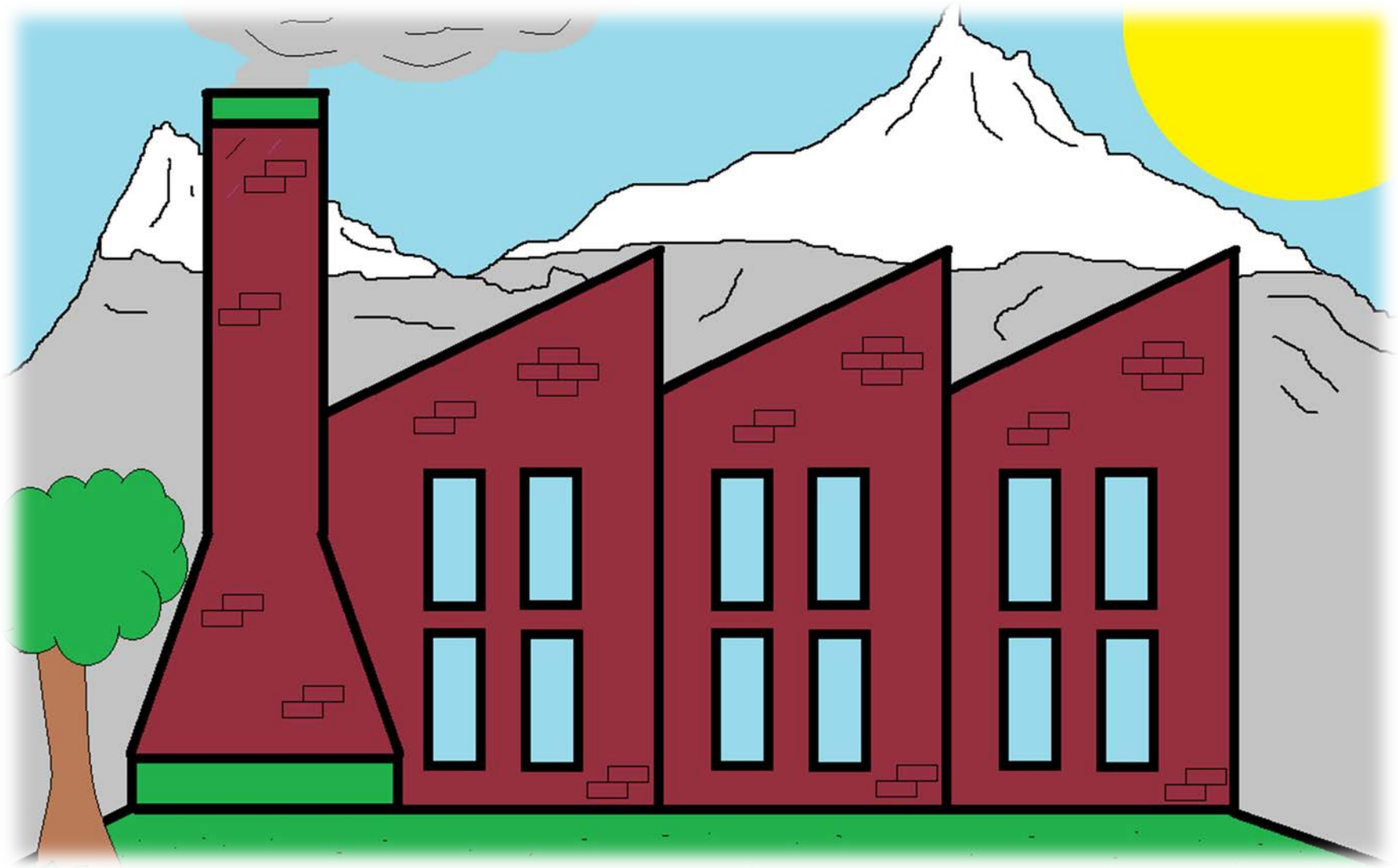
Sterile medicines - lessons from StrugglePharm

Matt Davis
Inspections Team Leader
Manufacturing Quality Branch
Medical Devices and Product Quality Division
Therapeutic Goods Administration

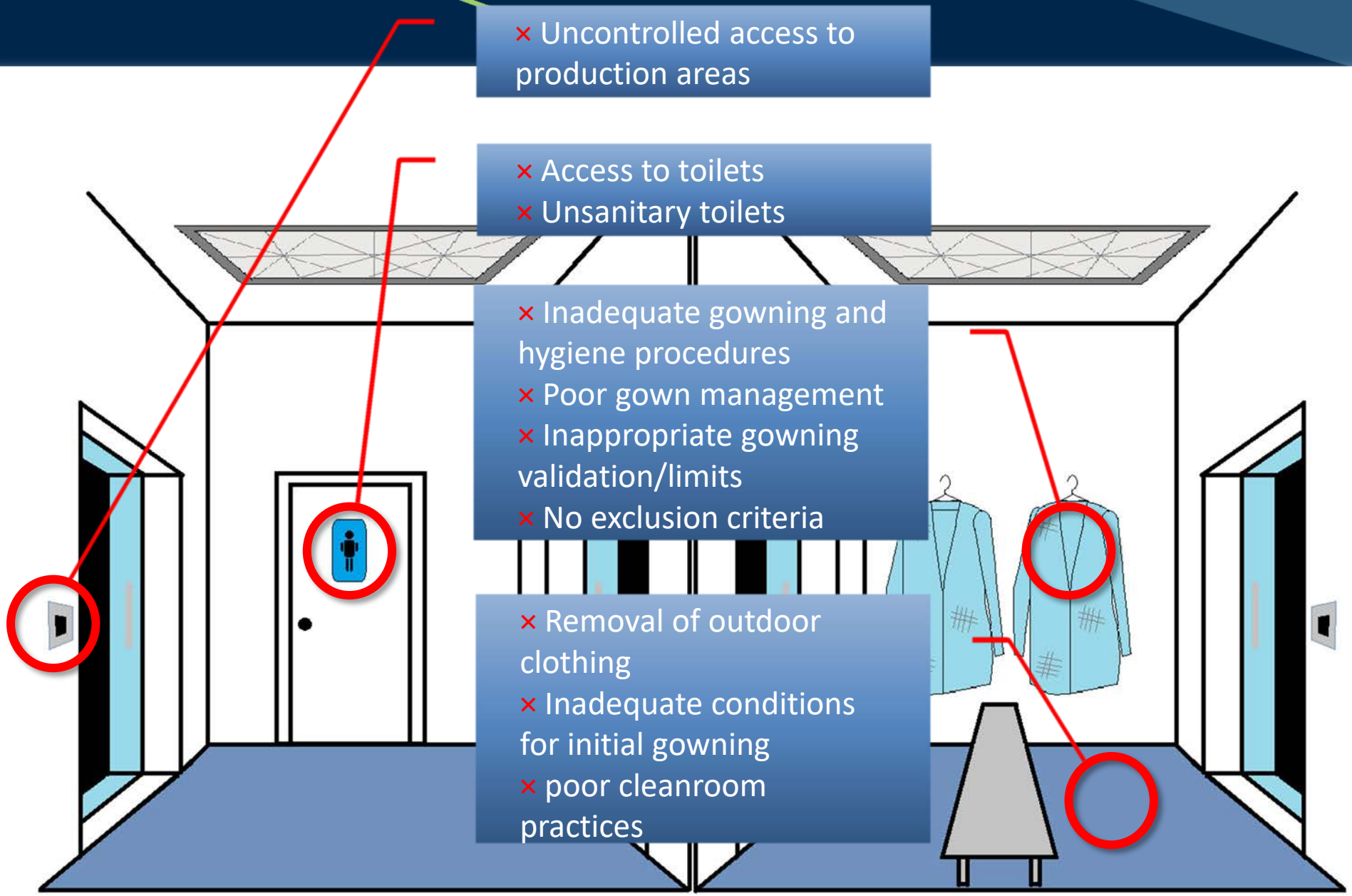
14/05/2021

TGA Health Safety Regulation

Welcome to StrugglePharm!



Gowning up

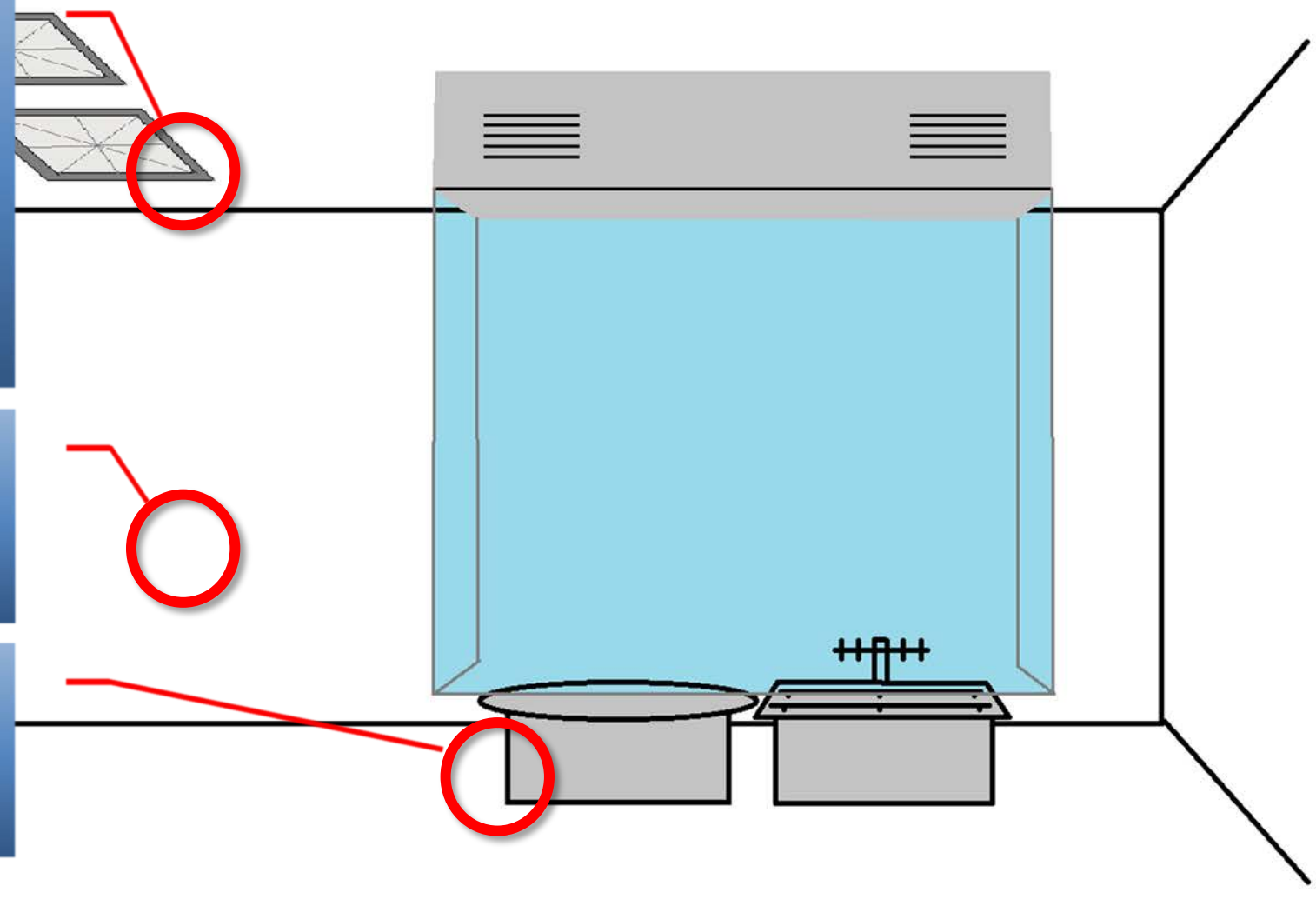

× Uncontrolled access to production areas
× Access to toilets
× Unsanitary toilets
× Inadequate gowning and hygiene procedures
× Poor gown management
× Inappropriate gowning validation/limits
× No exclusion criteria
× Removal of outdoor clothing
× Inadequate conditions for initial gowning
× poor cleanroom practices

Clean room classification and condition

× ISO 14644.1
- Defined test protocol
- Installed filter test
- Airflow vol./velocity
- Airflow visualisation
- Number of locations
- Sample volumes
- Leak testing
- Report verification

× Facility condition
- Walls
- Floors
- Joints

× Equipment condition
- Cleanliness
- Rust
- Damage



Preparation

× Dedicated tooling

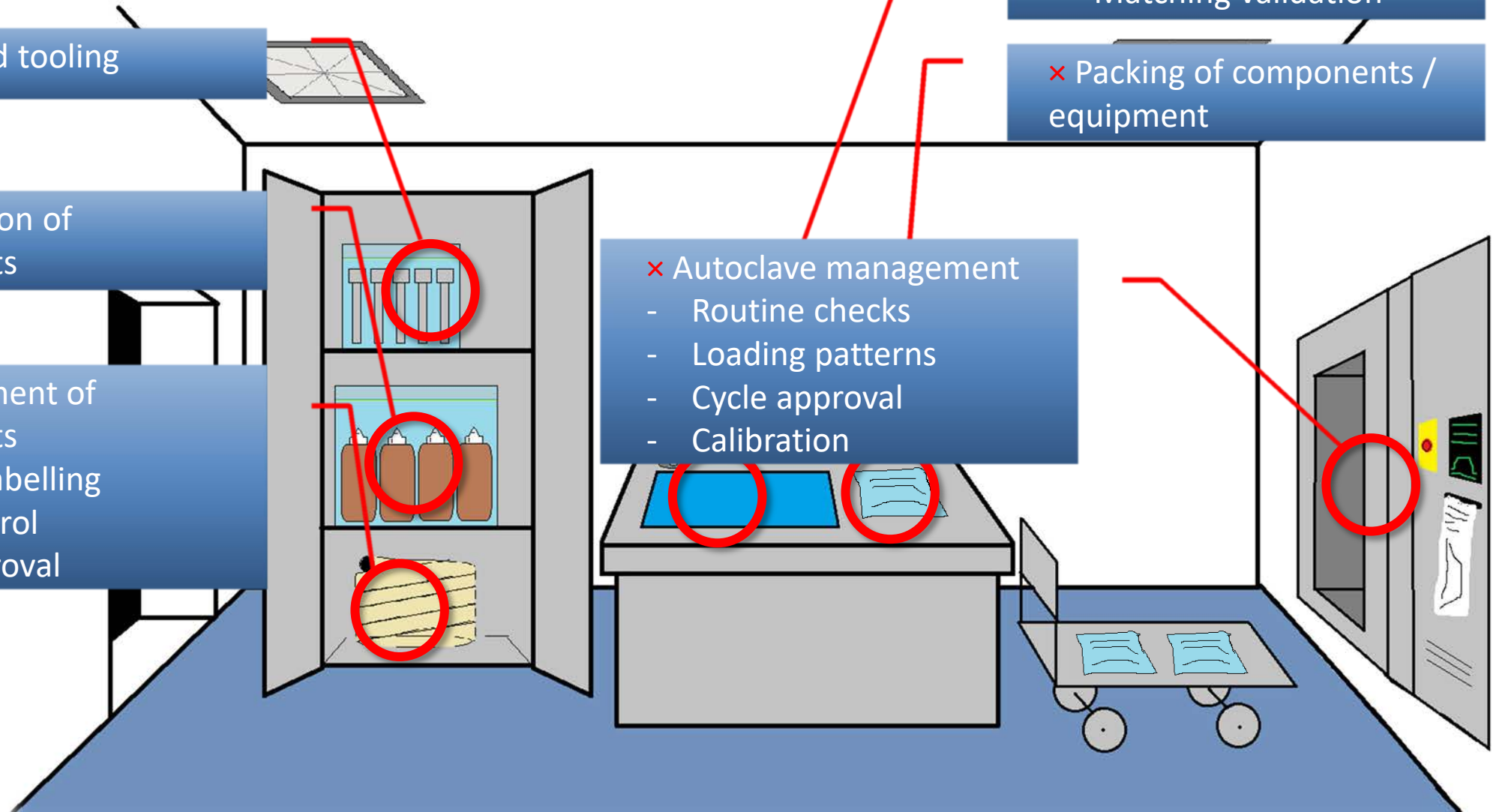
× Cleaning
- Defined procedures
- Matching validation

× Packing of components / equipment

× Sterilisation of components

× Autoclave management
- Routine checks
- Loading patterns
- Cycle approval
- Calibration

× Management of components
- Status labelling
- Lot control
- QA approval



Vial processing

× Cycle validation

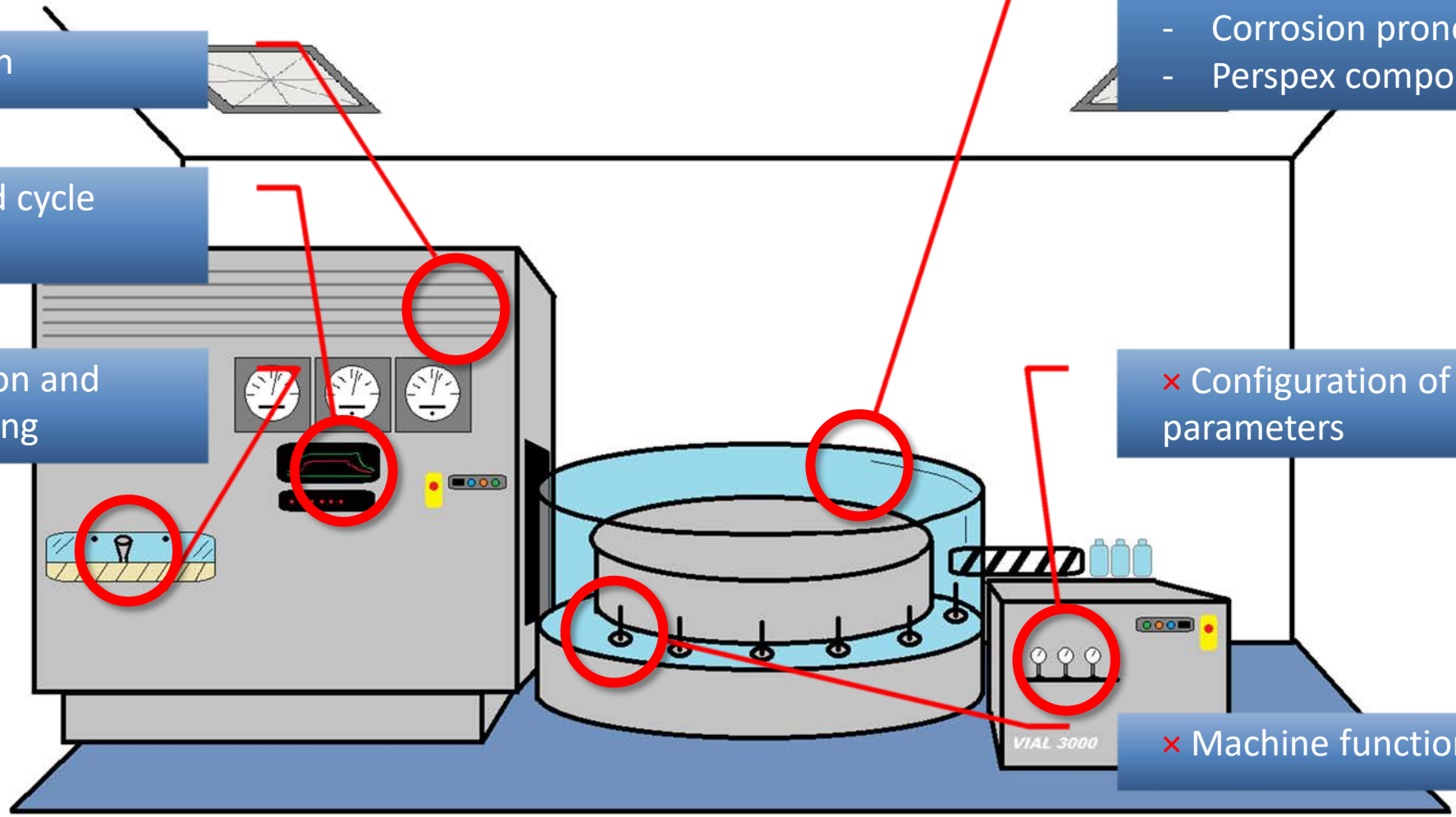
× Calibration and cycle monitoring

× ISO classification and routine monitoring

× Maintenance
- Water filters
- Corrosion prone
- Perspex components

× Configuration of critical parameters

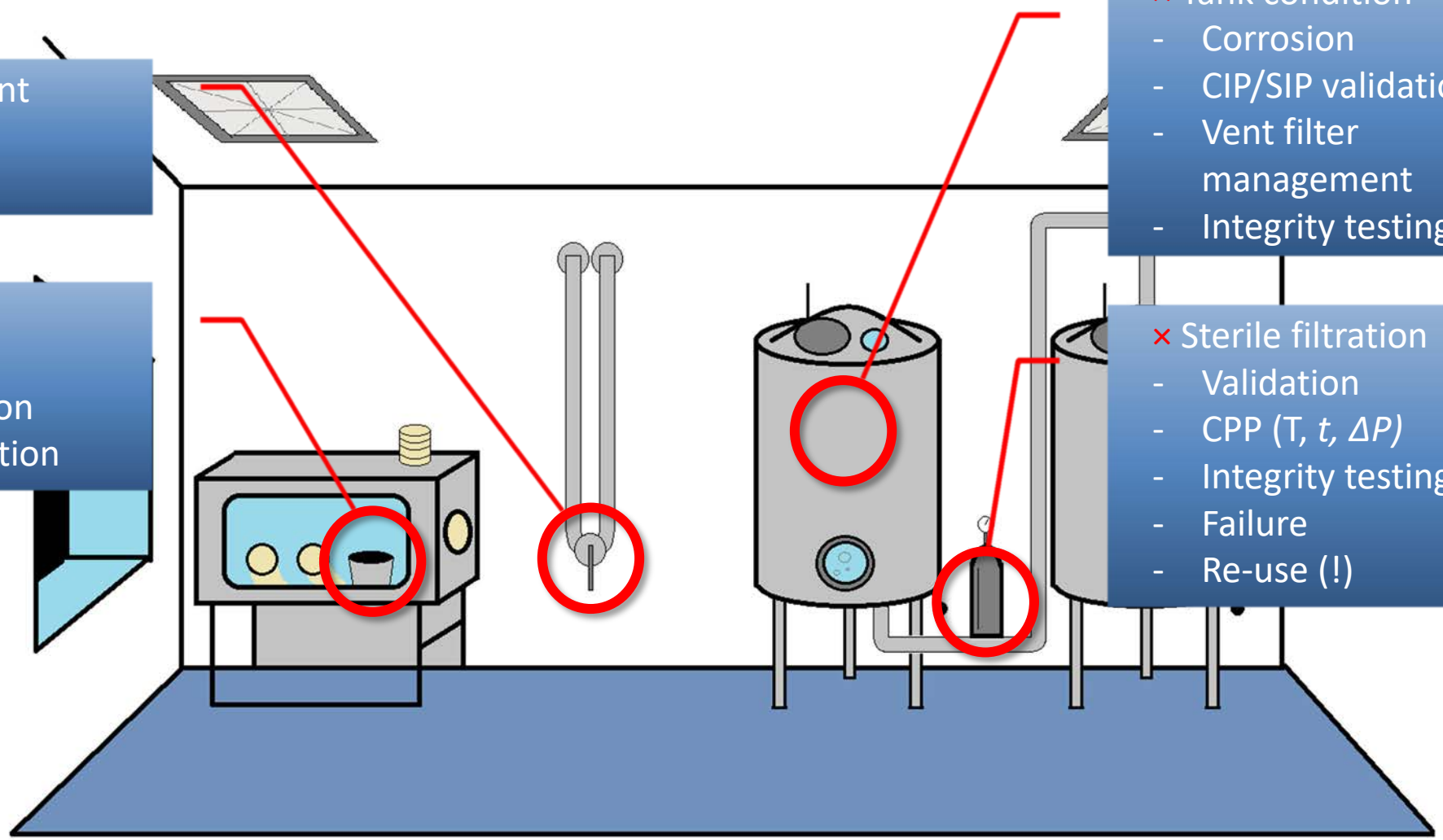
× Machine function



Solution preparation

× Water management
- Monitoring
- Sanitisation

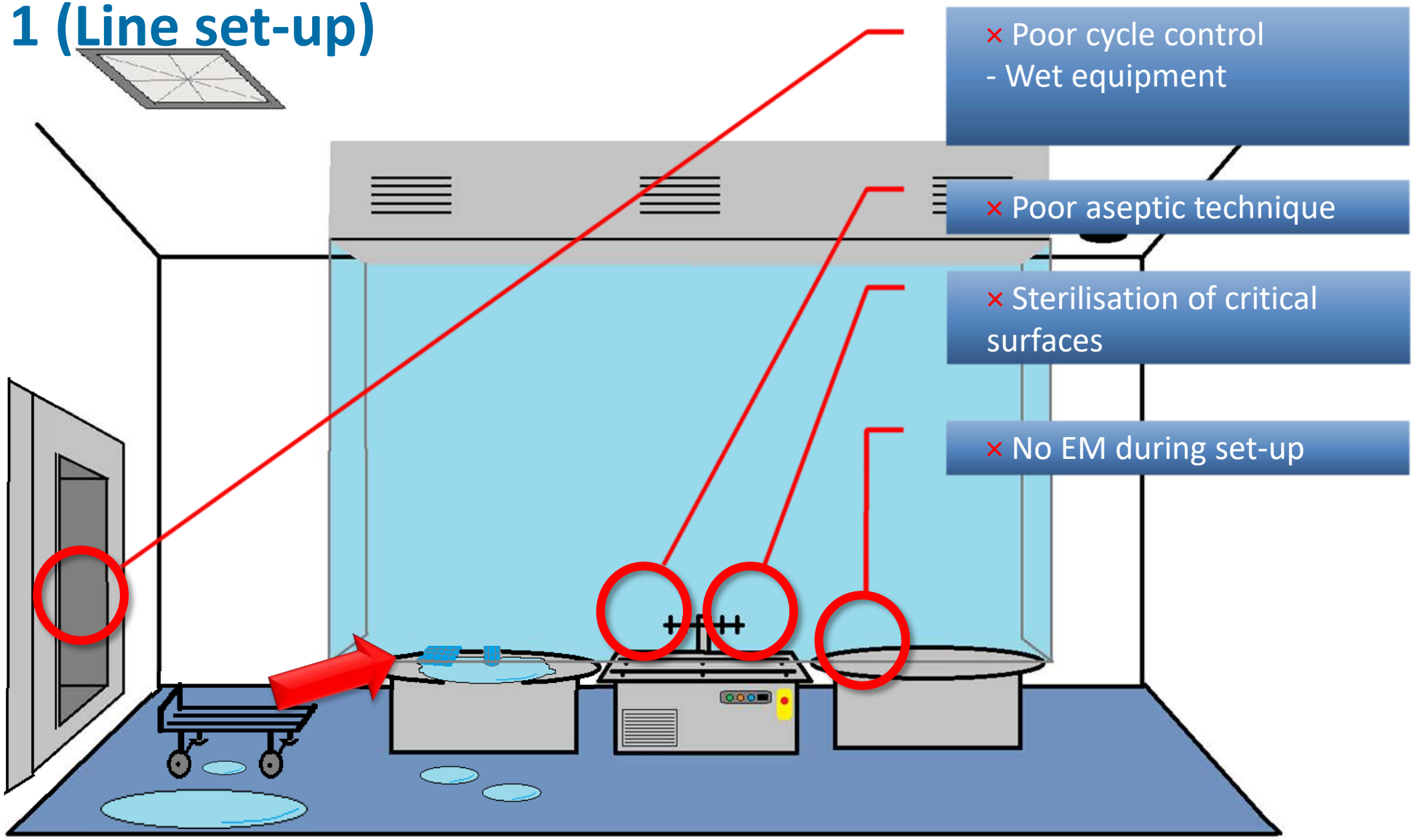
× Dispensing
- Cleanliness
- Cleaning validation
- Cross-contamination



× Tank condition
- Corrosion
- CIP/SIP validation
- Vent filter management
- Integrity testing

× Sterile filtration
- Validation
- CPP (T, *t*, *ΔP*)
- Integrity testing
- Failure
- Re-use (!)

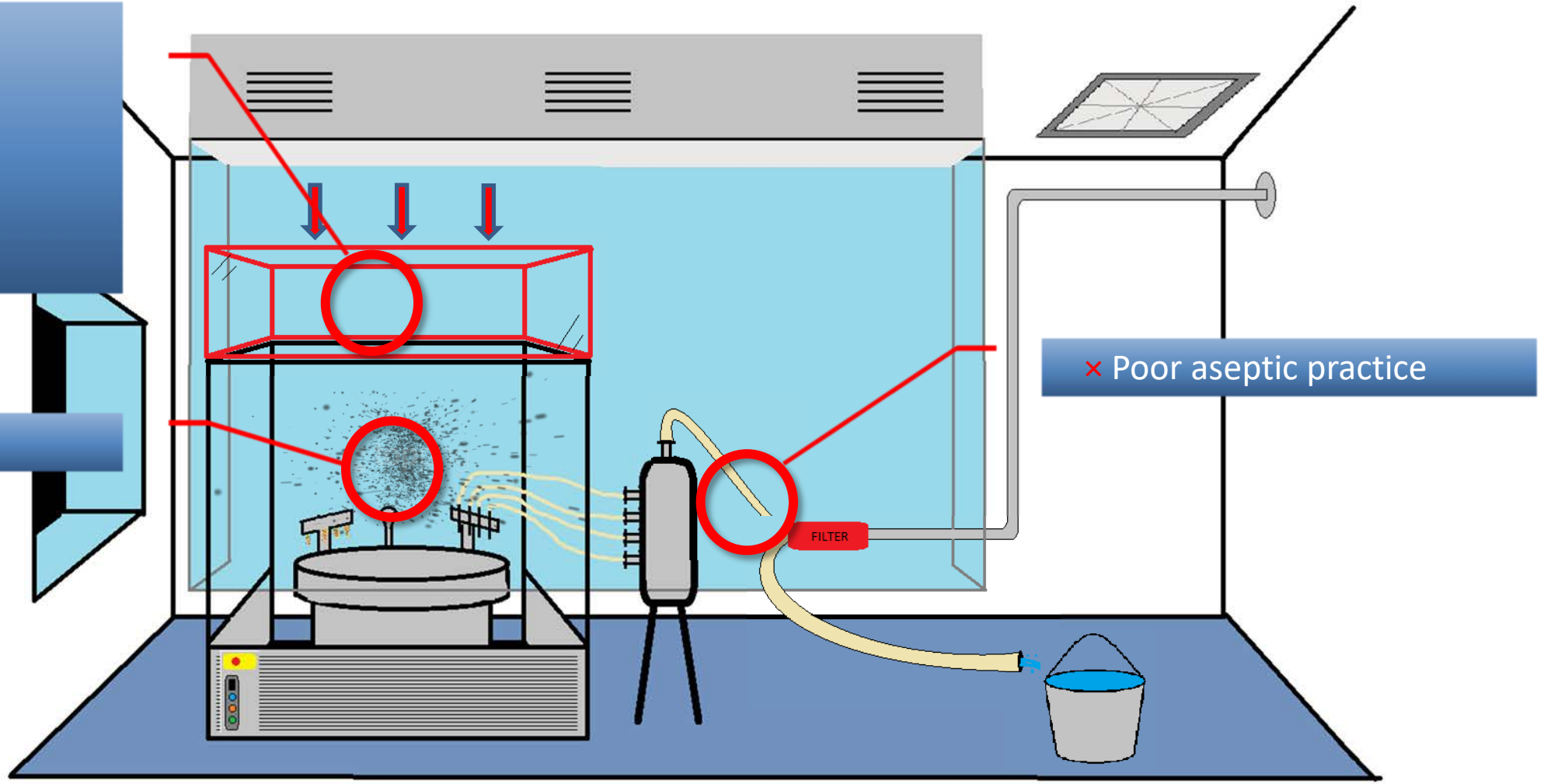
Aseptic filling 1 (Line set-up)



Aseptic filling 2 (Ampoule filling)

- × No change control
- × No review of HVAC
- × No re-classification
- × No media fills
- × Batches released
- × Site AP aware!

× Particle excursions



× Poor aseptic practice

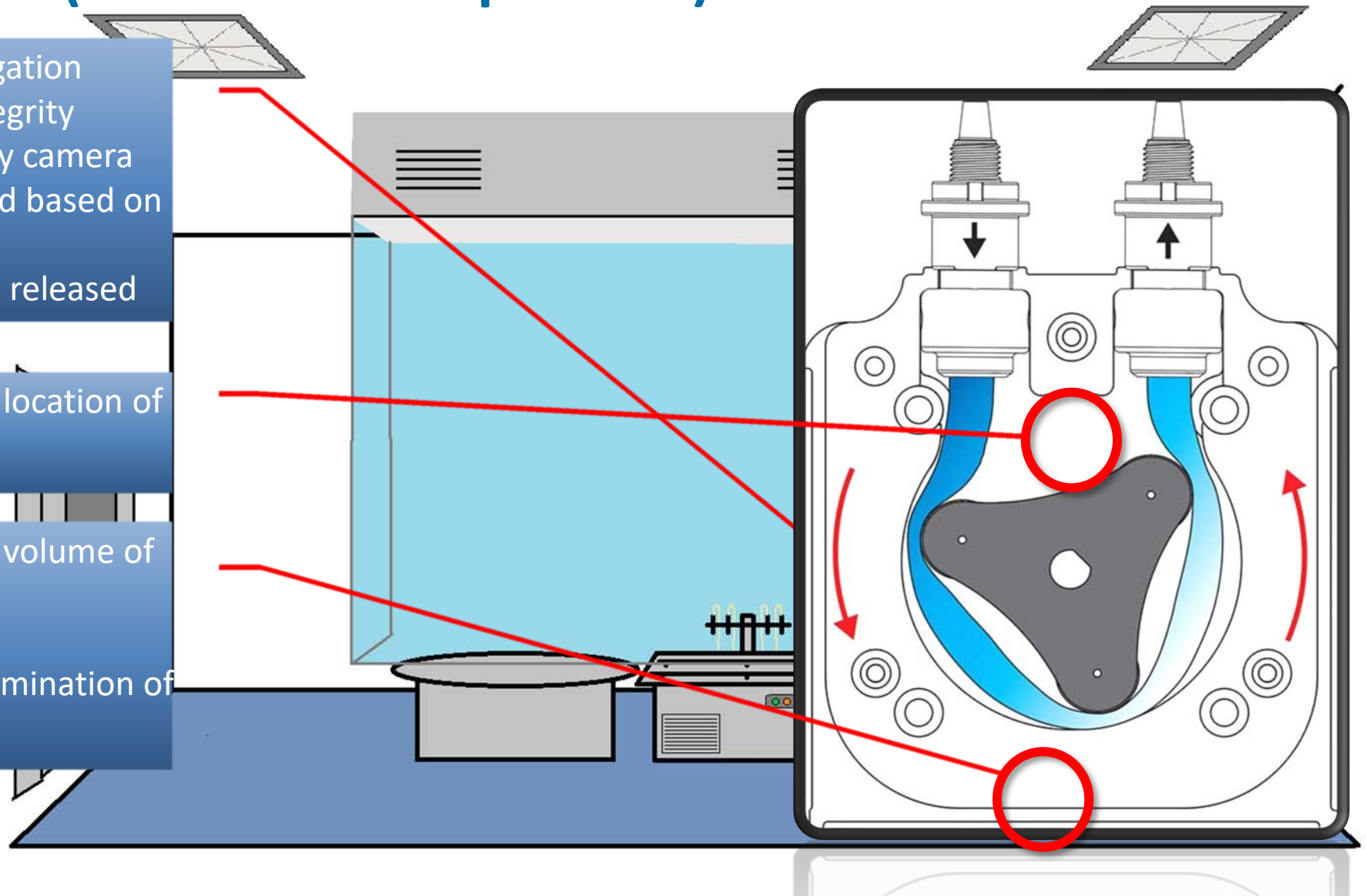
Aseptic filling 3 (Non-filterable product)

× Deviation investigation
- Loss of tube integrity
- Leak detected by camera
- Batch segregated based on times
- Portion of batch released

× No knowledge of location of leak

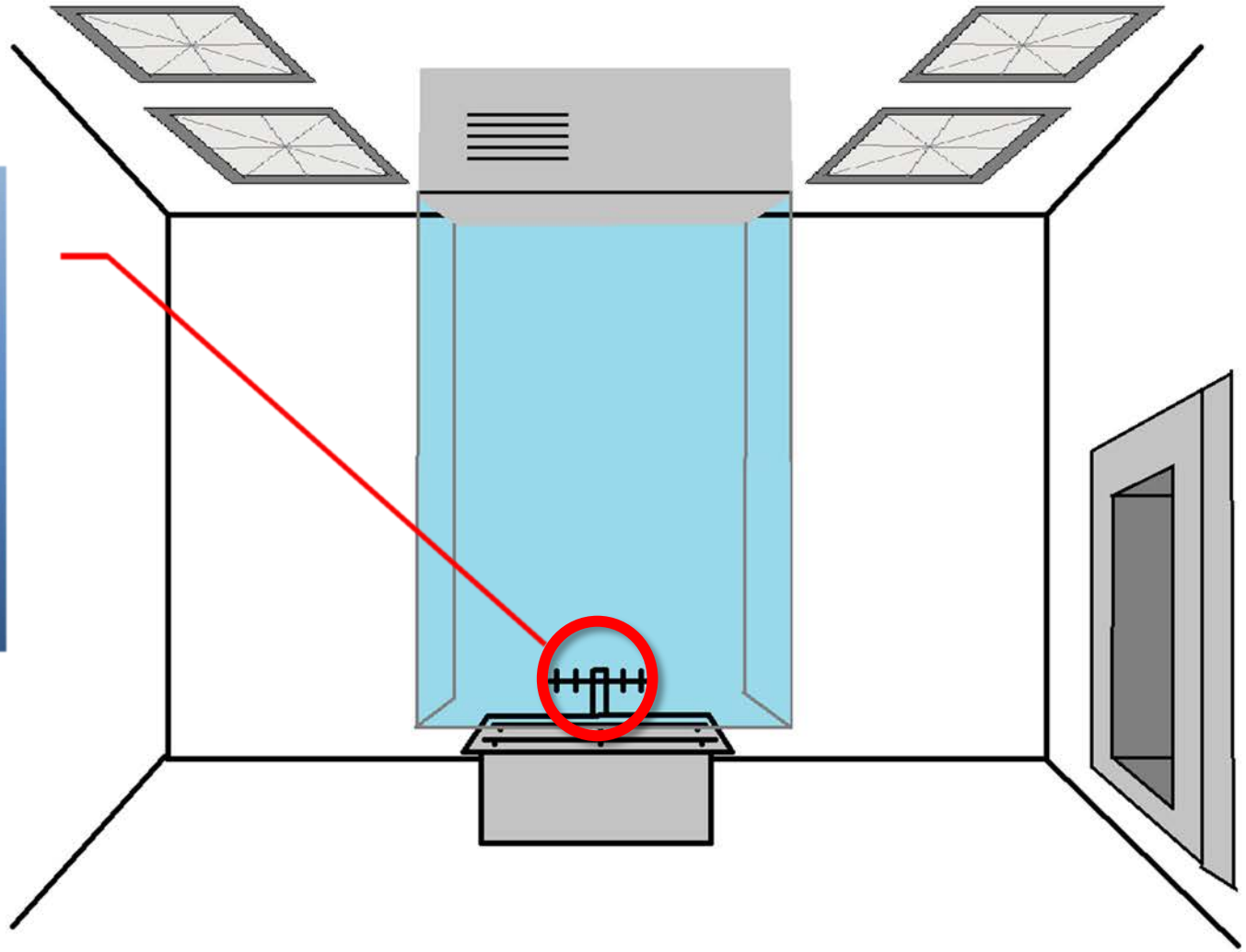
× No knowledge of volume of drip reservoir

× Inadequate determination of breach of sterility



Media fills (APS)

- × Inadequate program design
- × Frequency
- × Ensure all operator involvement
- × Acceptance criteria
- × Investigation of failures
- × Invalidation of positive units

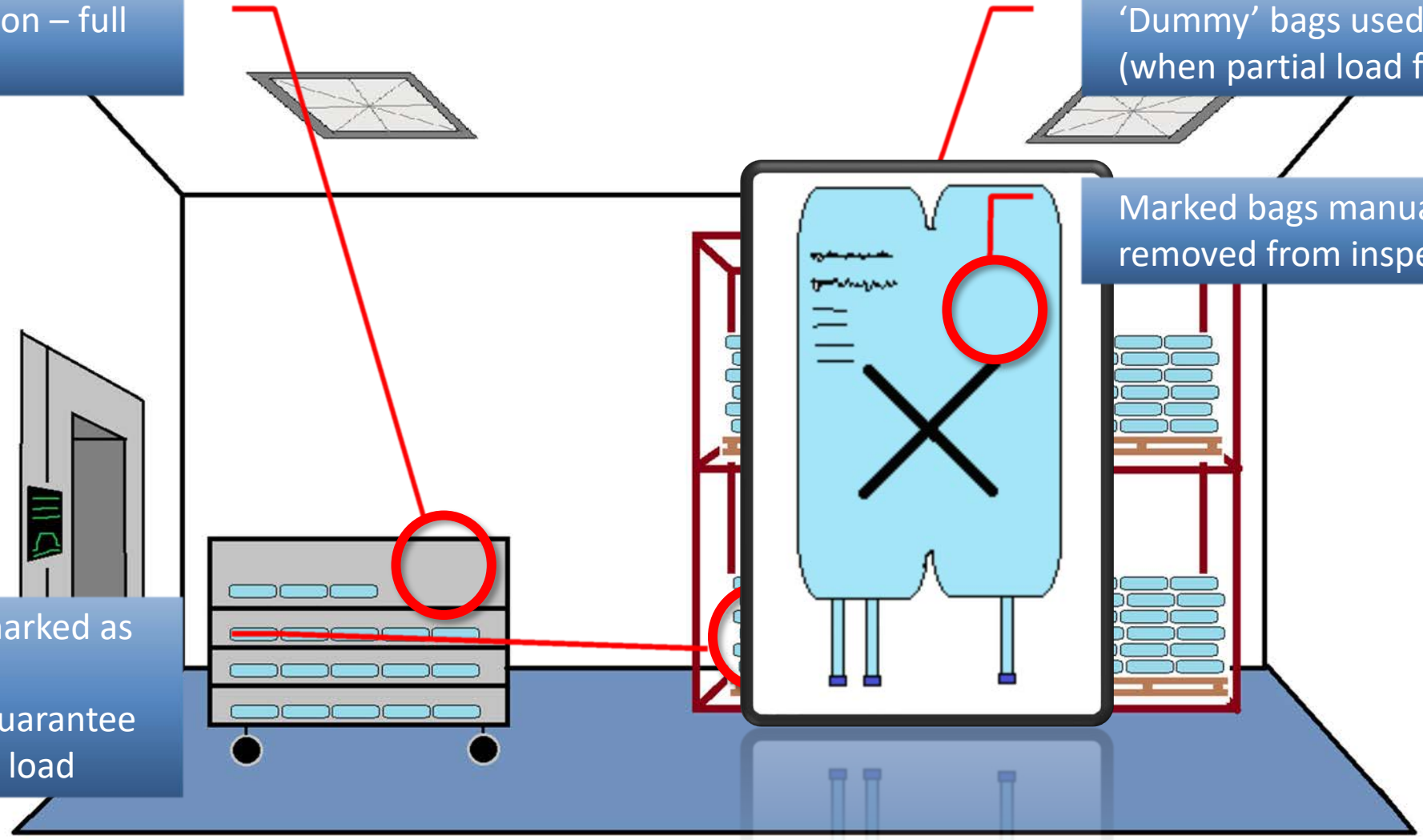


Terminal sterilisation (LVP)

Validated sterilisation – full cycle only

‘Dummy’ bags used to fill load (when partial load filled)

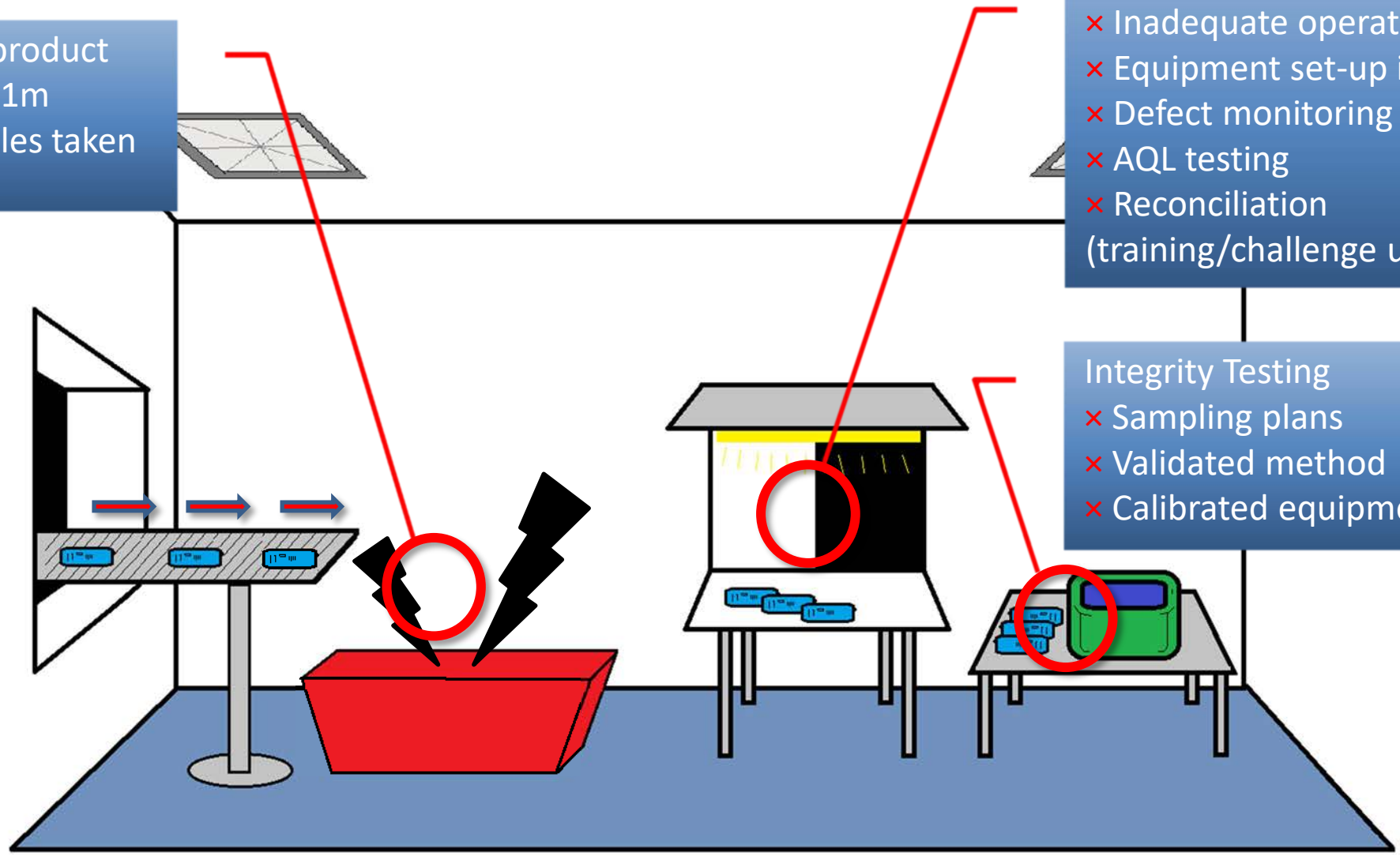
Marked bags manually removed from inspection line



× Many bags not marked as ‘dummy’ bags
× Not possible to guarantee removal from each load

Packaging and visual inspection

Handling of packed product
× Product dropped >1m
× Integrity test samples taken before drop



Visual Inspection
× Inadequate operator training
× Equipment set-up issues
× Defect monitoring
× AQL testing
× Reconciliation (training/challenge units)

Integrity Testing
× Sampling plans
× Validated method
× Calibrated equipment

Quality Control (microbiology)

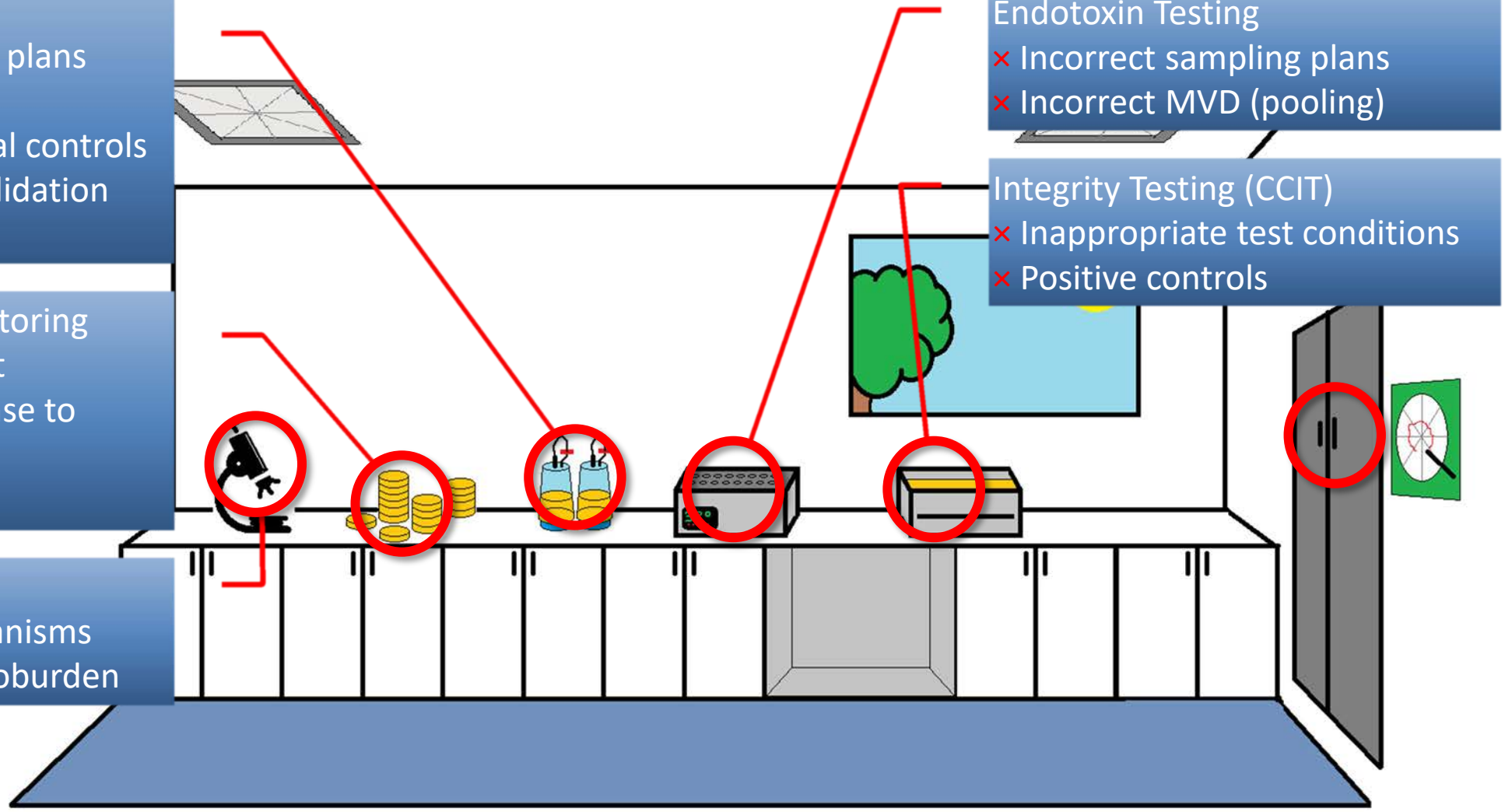
Sterility testing
× Incorrect sampling plans
× Lack of validation
× Poor environmental controls
× Inappropriate invalidation approach.

Environmental Monitoring
× No risk assessment
× Inadequate response to excursions
× Data integrity

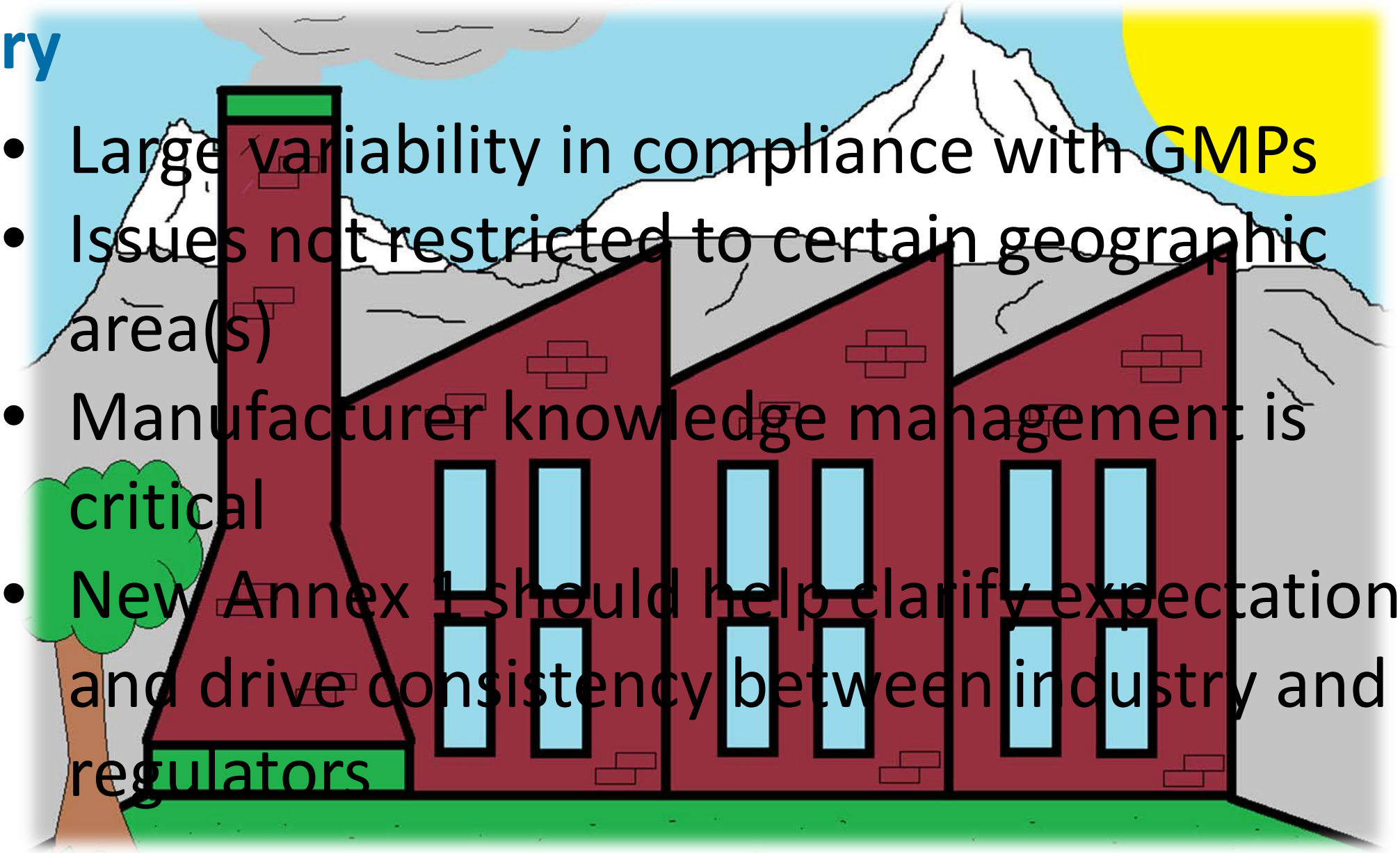
× ID policy
× Objectionable organisms
× Pre-sterilisation bioburden

Endotoxin Testing
× Incorrect sampling plans
× Incorrect MVD (pooling)

Integrity Testing (CCIT)
× Inappropriate test conditions
× Positive controls



Summary



- Large variability in compliance with GMPs
- Issues not restricted to certain geographic area(s)
- Manufacturer knowledge management is critical
- New Annex 1 should help clarify expectations and drive consistency between industry and regulators

Australian Government

Department of Health

Therapeutic Goods Administration