SUMMARY OF REVISING ANNEX 1
&
Discussed Points During Revision

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November, 16th 2019

Content Table

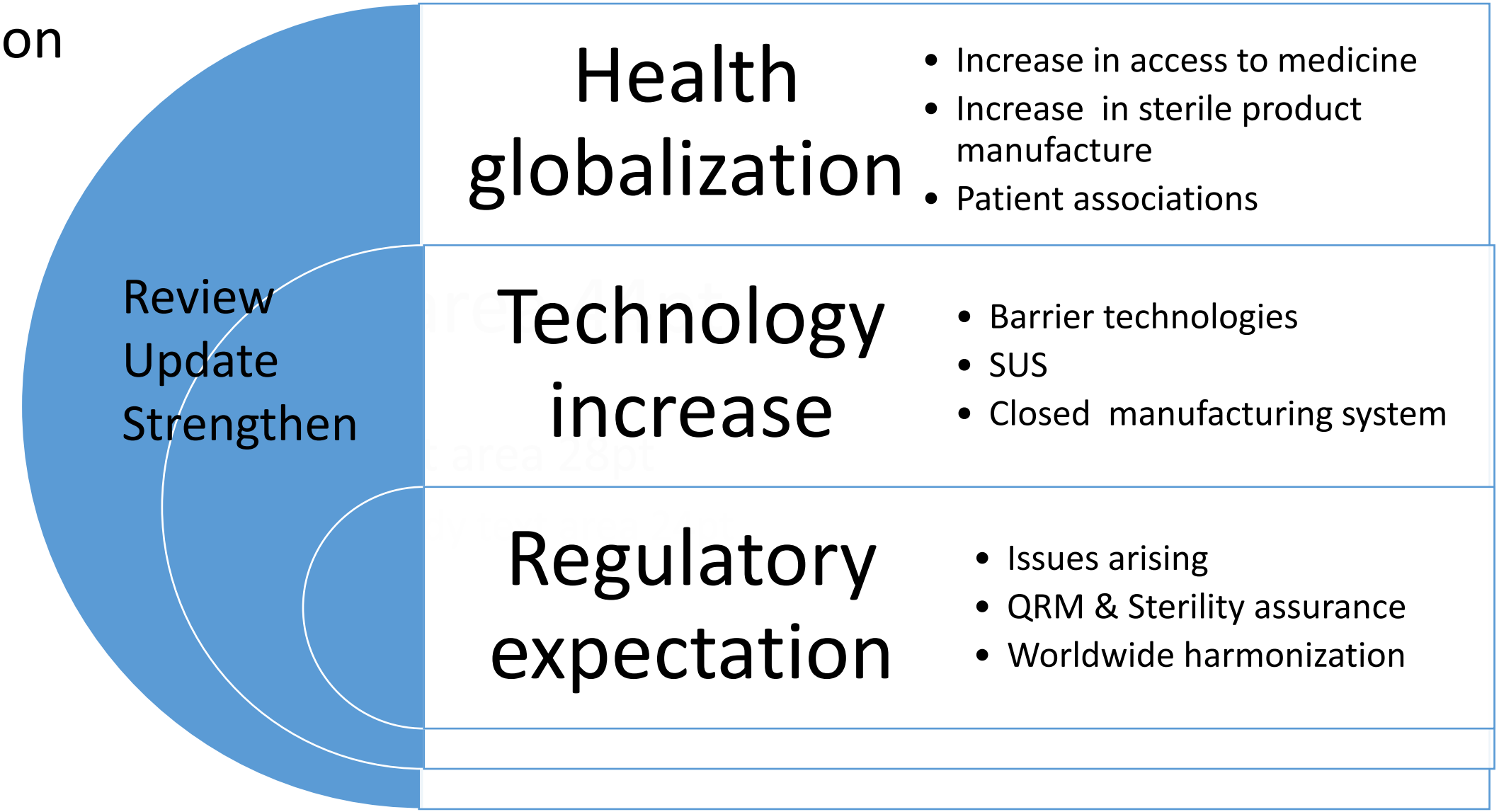
SOURCE & COMPLEXITIES

SOURCES & COMPLEXITIES

Shawn Donnan, World Trade Editor

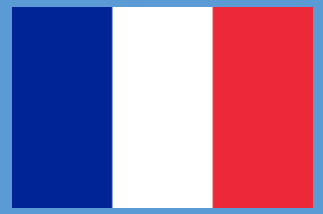
DRAFT ANNEX 1

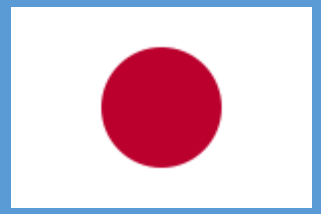
Expectation

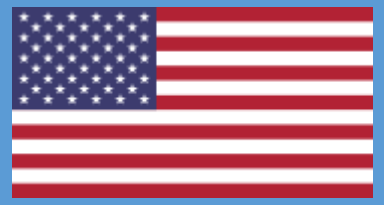


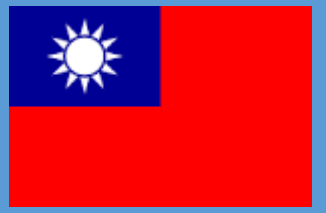
DRAFT ANNEX 1

Working Group









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DRAFT ANNEX 1

Drafting progress

DRAFT ANNEX 1

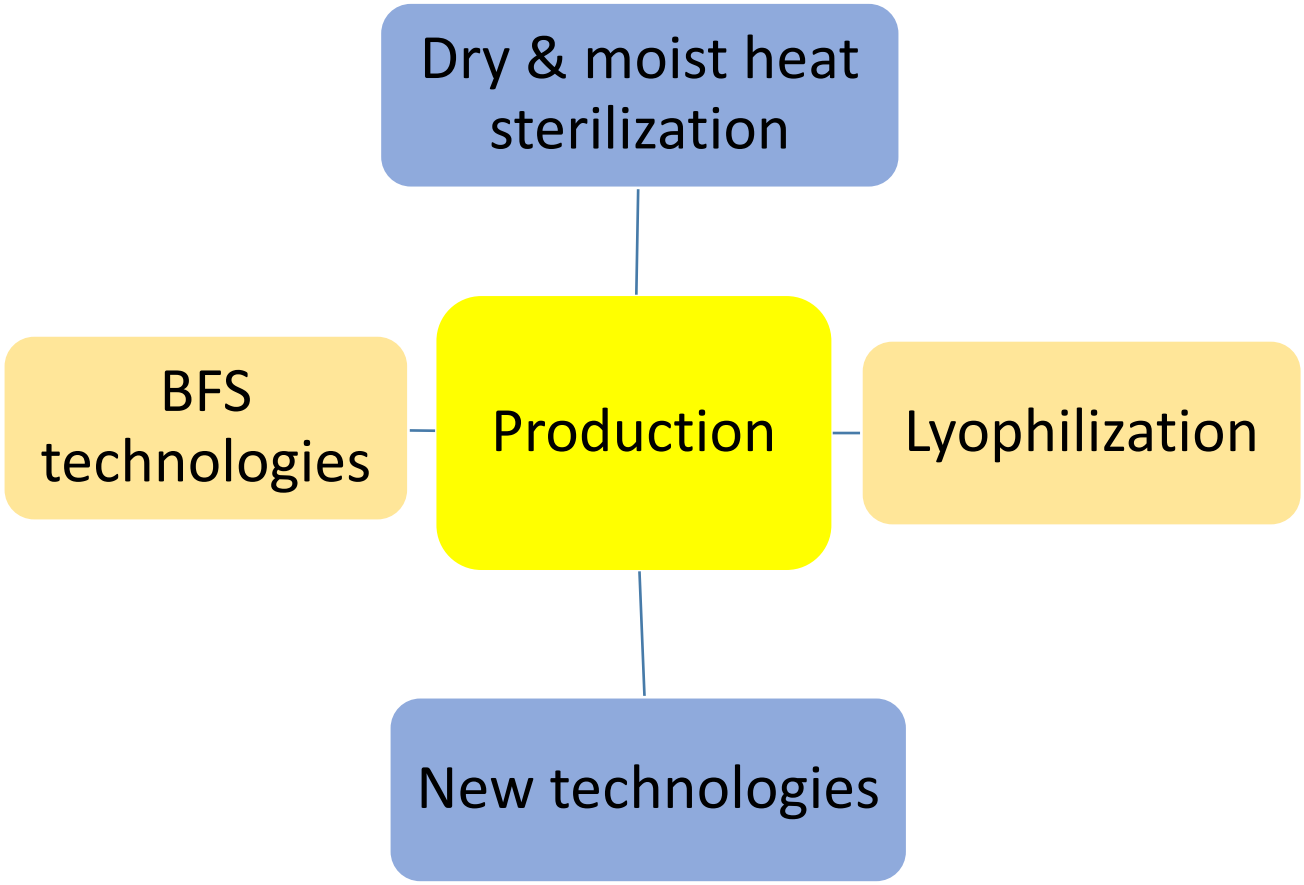
overview

10 sections
290 paragraphs

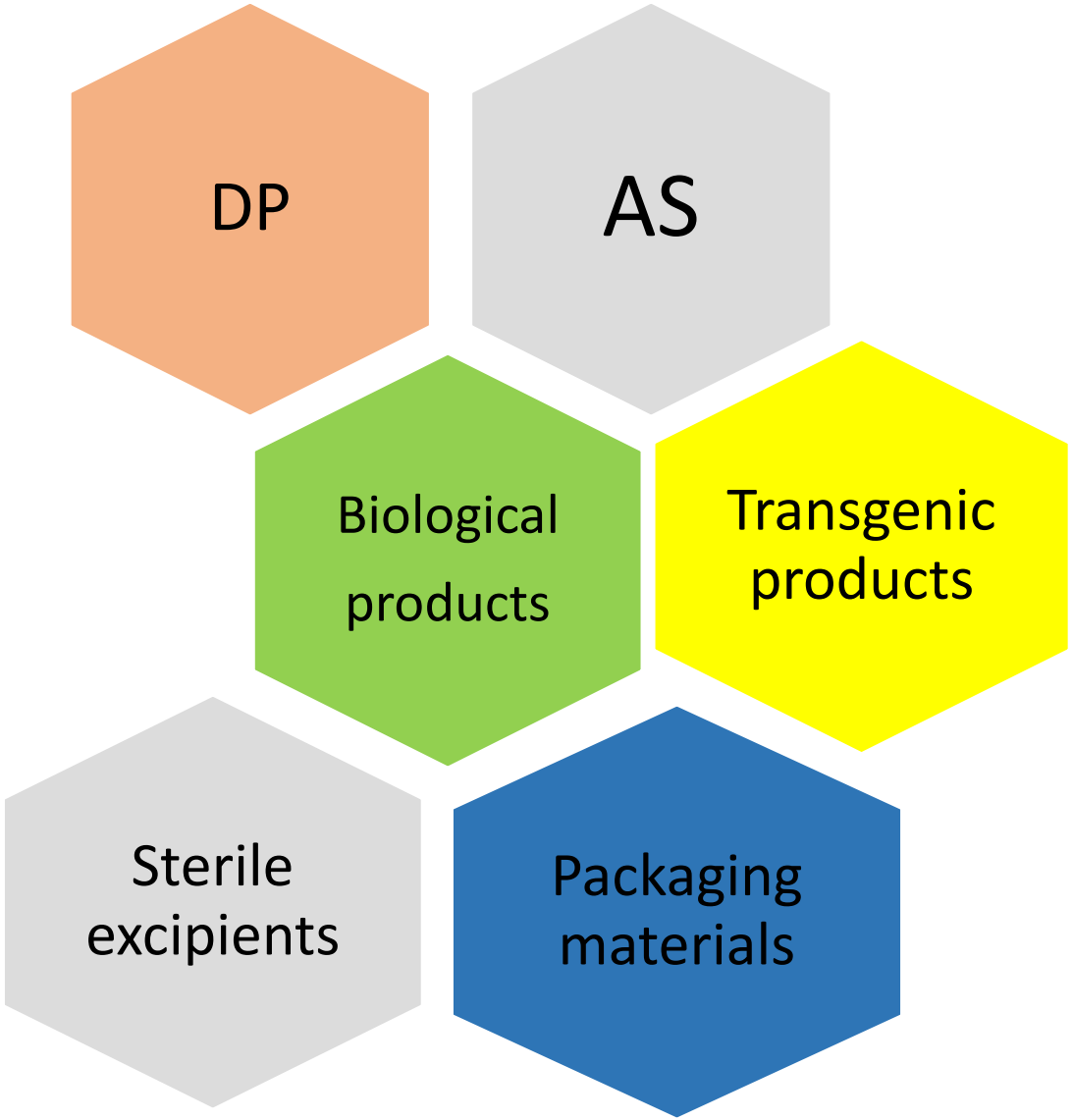
1. Scope
2. Principle
3. Pharmaceutical Quality System (PQS)
4. Premises
5. Equipment
6. Utilities
7. Personnel
8. Production and specific technologies
9. Viable and non-viable environmental and process monitoring
10. Quality control (QC)
11. Glossary

DRAFT ANNEX 1
overview

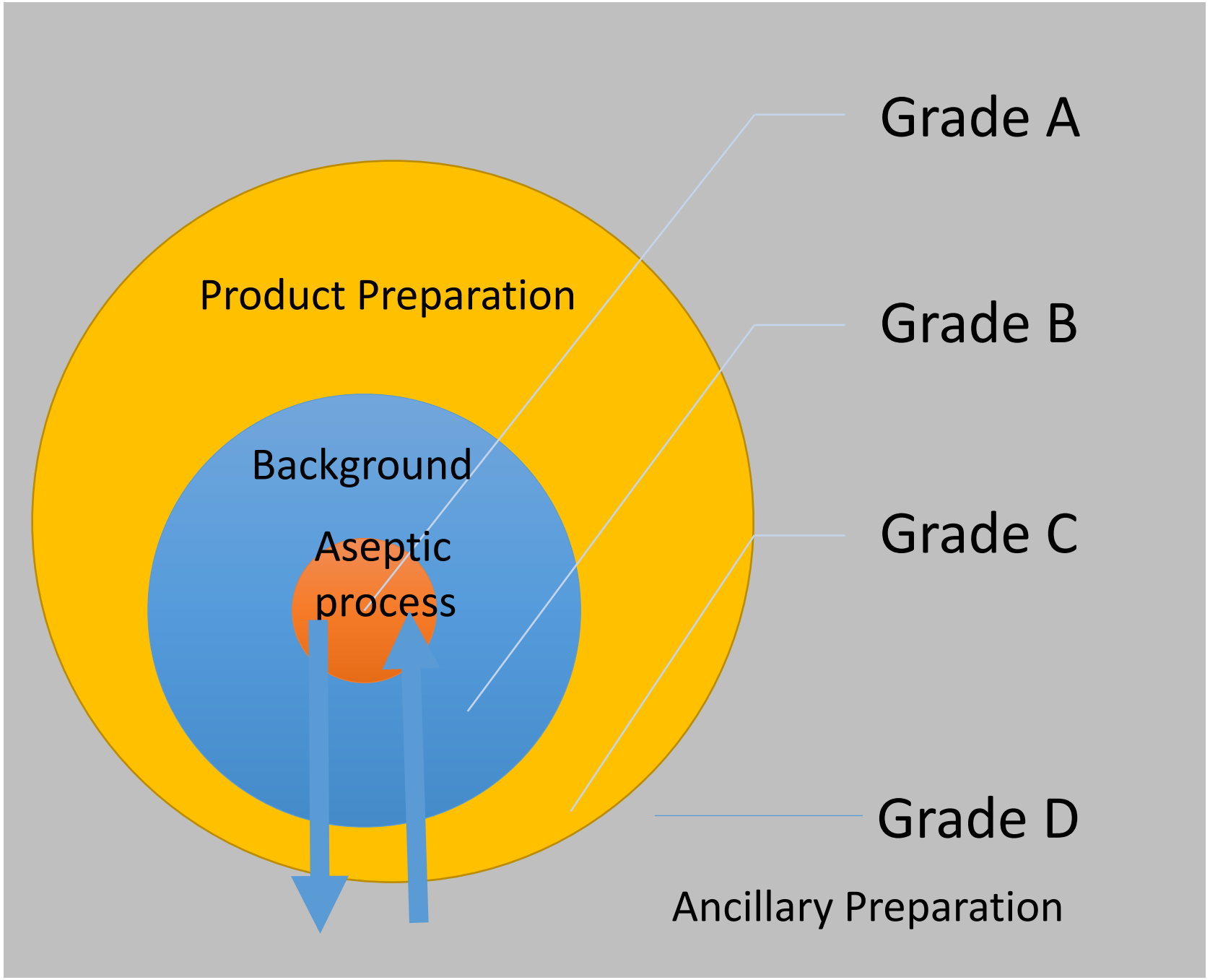
- Text reorganized with chapters by item
  - ✓ Utilities
  - ✓ Monitoring
  - ✓ Production



MANUFCATURE SCOPE



CLEANROOMS



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CLASSIFICATION

Classification is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particle concentration. Reference for the classification of the cleanrooms and clean air devices can be found in the ISO 14644 series of standards.

CLASSIFICATION

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5.0 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	Not applicable	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	To be defined	29 000	To be defined

QUALIFICATION

Qualification is a method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. This includes but is not limited to the viable airborne and surface particle concentration. The classification of a cleanroom or clean air equipment is part of its qualification.

QUALIFICATION

Test	Specification
Leak and integrity Filter test	Site's protocol and ISO 14644 part 3
Air flow measurement/ Airflow velocity	Site's protocol clean up period (15-20 min) 0.36 – 0.54 m/s (guidance value)
Microbial contamination	
Temperature	Site's protocol
Humidity	Site's protocol
Air pressure differentials	min 10 Pascals
Airflow visualization	Site's protocol (Cleanliness protected)

s

QUALIFICATION

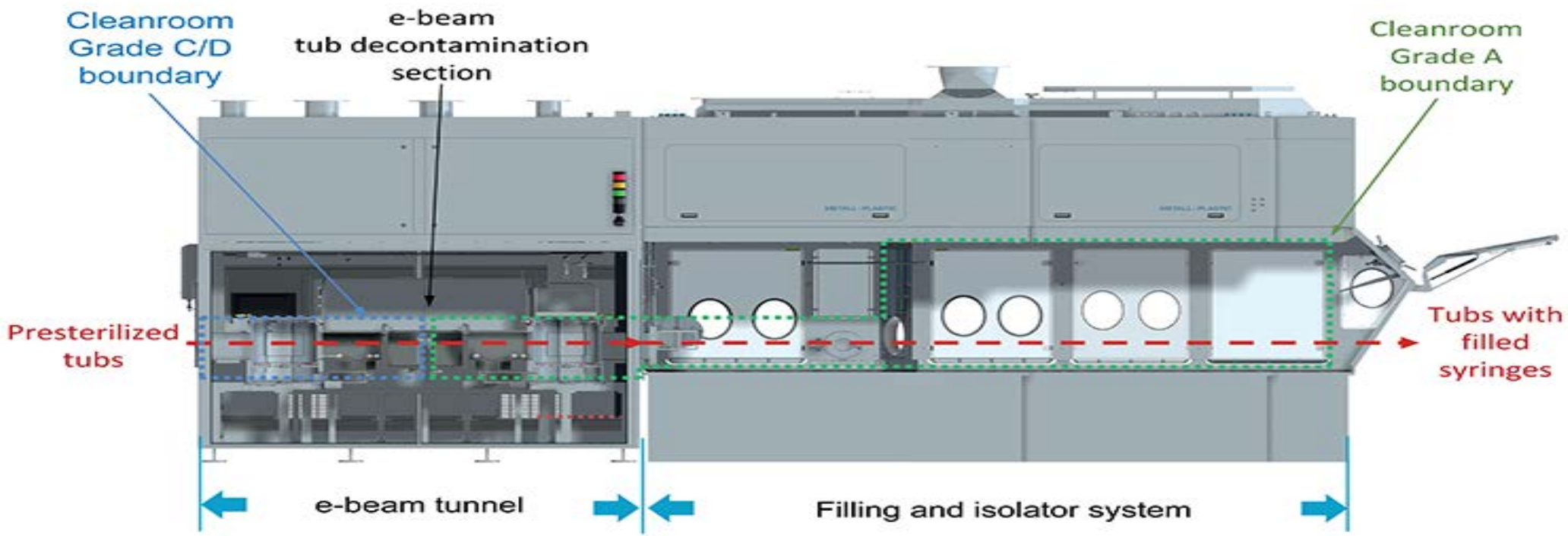
Grade	Air sample cfu/m^3	Settle plates (diameter 90 mm) cfu/4 hours [(a)]	Contact plates (diameter 55 mm) cfu/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

BARRIER TECHNOLOGIES

Franziel RABS

BARRIER TECHNOLOGIES

Open Isolators



BARRIER TECHNOLOGIES

Radioactive containment

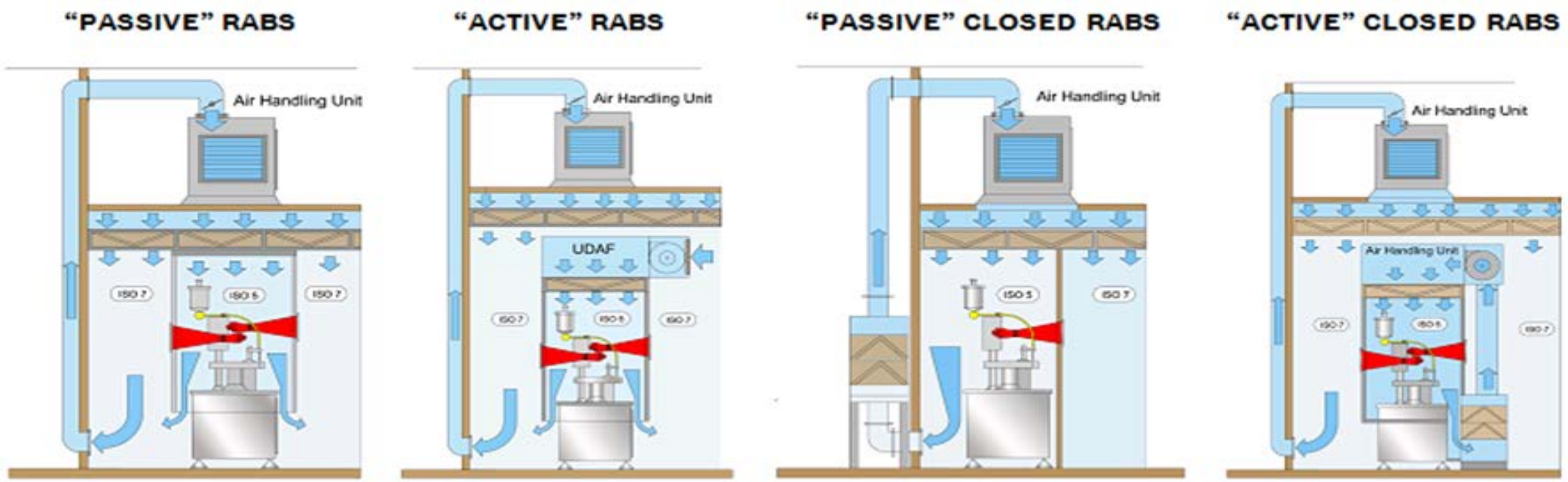
Airlock Grade B

Grade A

Filling of radiopharmaceutical

BARRIER TECHNOLOGIES

RABS



Credit image : ASEPTIC ENCLOSURES

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BARRIER TECHNOLOGIES

Qualification

❖Qualification according to Annex 15

- ✓ Design qualification (mechanical chemical, ergonomic design)
- ✓ Installation qualification (environment, accessibility to equipment…)
- ✓ Operational qualification (friendly process pressure differentials…)
- ✓ Performance qualification (cleaning/decontamination validation…)
- ✓ SOPs and operator training and qualification.

BARRIER TECHNOLOGIES

Monitoring/maintenance

- ❖ Regular leak testing and glove testing
  - ✓ At least at the beginning and end of each batch
- ❖ Systematic Visual inspection
  - ✓ Before the beginning and end of session
  - ✓ When replaced
- ❖ Maintenance
  - ✓ Description and frequencies
  - ✓ Glove replacement, inspection, testing

DECONTAMINATION

Isolator and RABS

For RABS and isolator systems, decontamination methods should be validated and controlled within defined cycle parameters. The cleaning process prior to the disinfection step is essential; any residues or particles that remain may inhibit the effectiveness of the decontamination process.

Evidence should also be available to demonstrate that the agent does not have negative effect on the sterile product produced in the RABS or the isolator, such as having an adverse impact.

DECONTAMINATION

For isolators, the decontamination process should be automated and should include a sporicidal agent in a suitable form (e.g. gaseous, aerosolized or vaporized form) to ensure thorough microbial decontamination of its interior. Decontamination methods (cleaning and sporicidal disinfection) should render the interior surfaces and critical zone of the isolator free of viable microorganisms.

For RABS systems, the disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly disinfect the interior and ensure a suitable environment for aseptic processing.

DISINFECTION

Contaminant Ingress avoidance

- 4.12 …The movement of material or equipment from lower grades or unclassified areas to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the contamination control strategy (CCS).

- 8.47… the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas…

DISINFECTION

Contaminant Ingress avoidance

- 4.12…Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring regime approved by quality assurance.

DISINFECTION

Cleaning

- Detergent
- Residue limit
- Rinsing
- Effectiveness
- SOPs

Surface disinfection

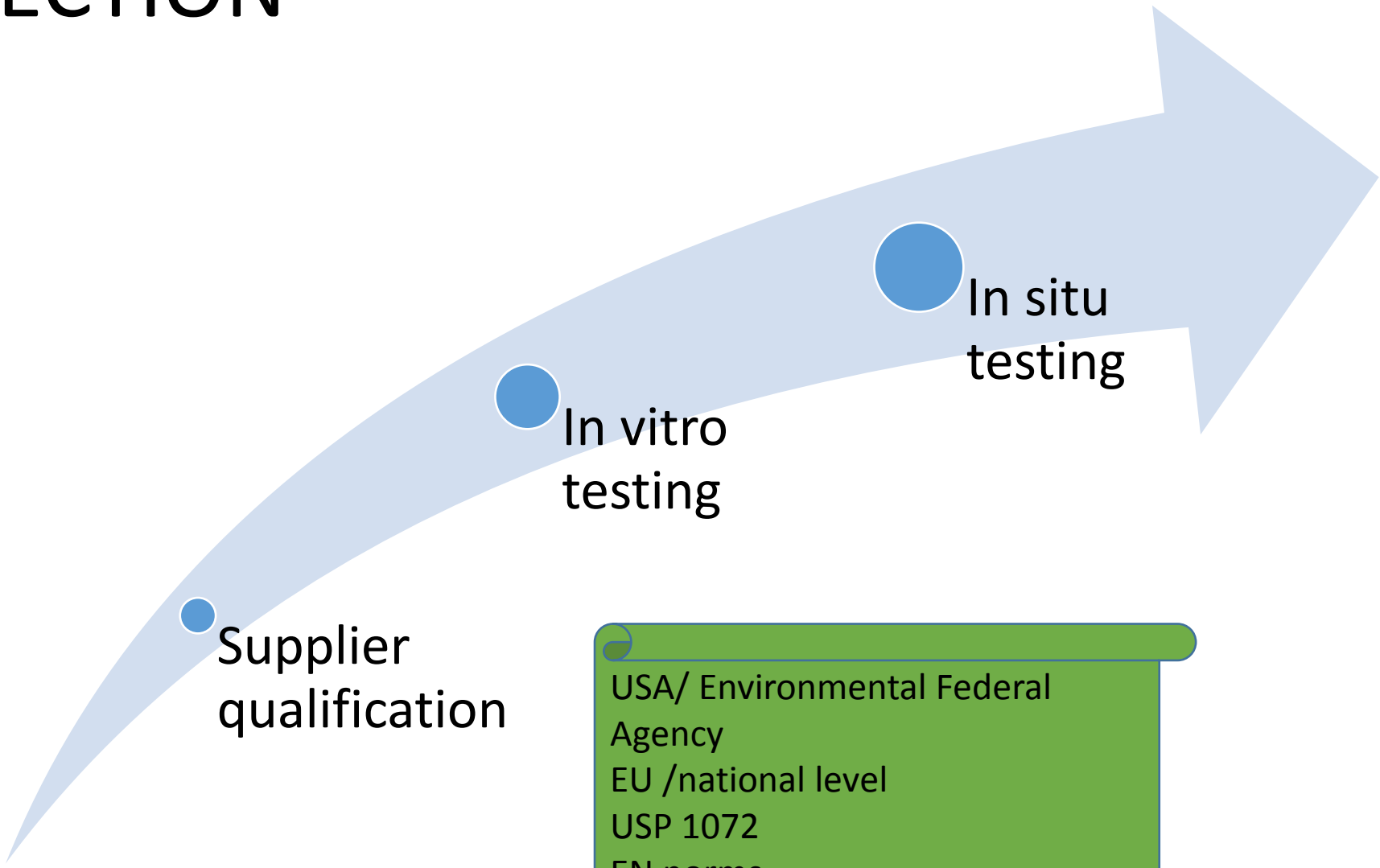
- Validation (contact time/duration)
- controlled /Sterile agent(A & B grade)
- Sporicidal agent use
- Rinsing effectiveness
- SOPs

Cleanroom disinfection

- Gassing
- Fogging
- Aerosolized
- Validation (contact time/duration)
- Sporicidal agent use
- SOPs

DISINFECTION

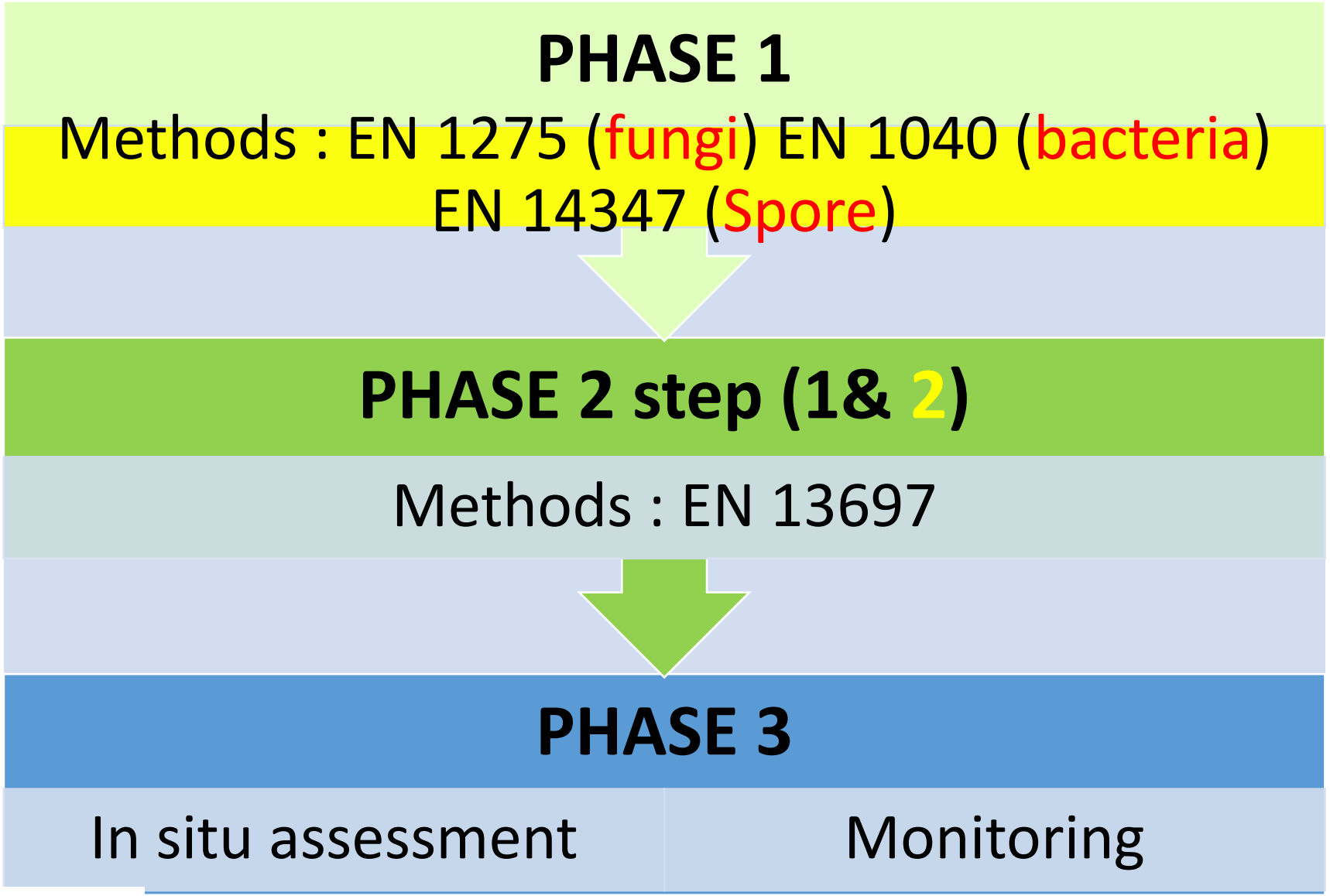
validation



USA/ Environmental Federal Agency
EU /national level
USP 1072
EN norms

DISINFECTION

validation



UTILITIES

Gas filters

- Pre-use and post use integrity testing
- Systematic integrity testing when gas in contact with sterile product
  - ✓ Critical vent filter
  - ✓ Critical gas / nitrogen filter
- Appropriate frequency for integrity testing
  - ✓ Non critical gas filter

PRODUCTION
Moist heat sterilization

Defined limits for load acceptance

Cycle validation

- Pressure/temperature
- Equilibration time
- Exposure time

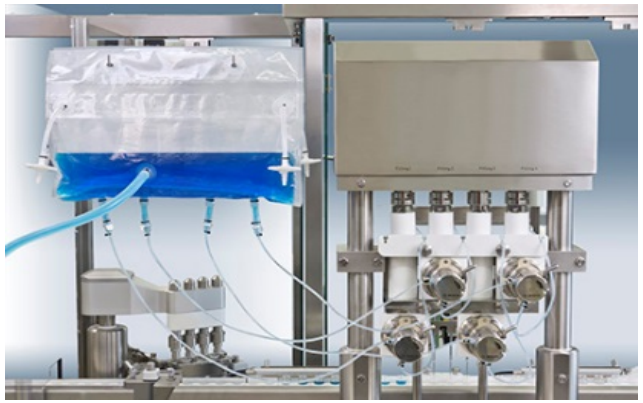
System qualification

- Steam Quality
- Additive limit
- Steam dryness
- Double probe

Regular monitoring

- Leak test in case of vacuum (weekly)
- Air removal in case of porous load (daily)

CLOSED SYSTEMS



Advantage

- ❖ Fixed tanks / reusable
- ❖ Product pathways defined
- ❖ CIP & SIP
- ❖ Fixed location defined by risk (over-pressurized)

Disadvantage

- ❖ Cross contamination issue
- ❖ Contamination issue
- ❖ Tank maintenance
- ❖ Aseptic connection
- ❖ No visual check

CLOSED SYSTEMS
Single Use System

RISKS

- Fragile bags
- Number and complexity of manual operations
- Complexity of assembly
- Risk of hole and leakage
- Risk of particulate contamination
- Extractables issue
- Potential for compromising the system integrity

MITIGATION

- Supplier qualification
- Sterilization qualification
- Checking of each unit upon reception
  - ✓ Manufacture conditions
  - ✓ Sterilization
  - ✓ Visual inspection

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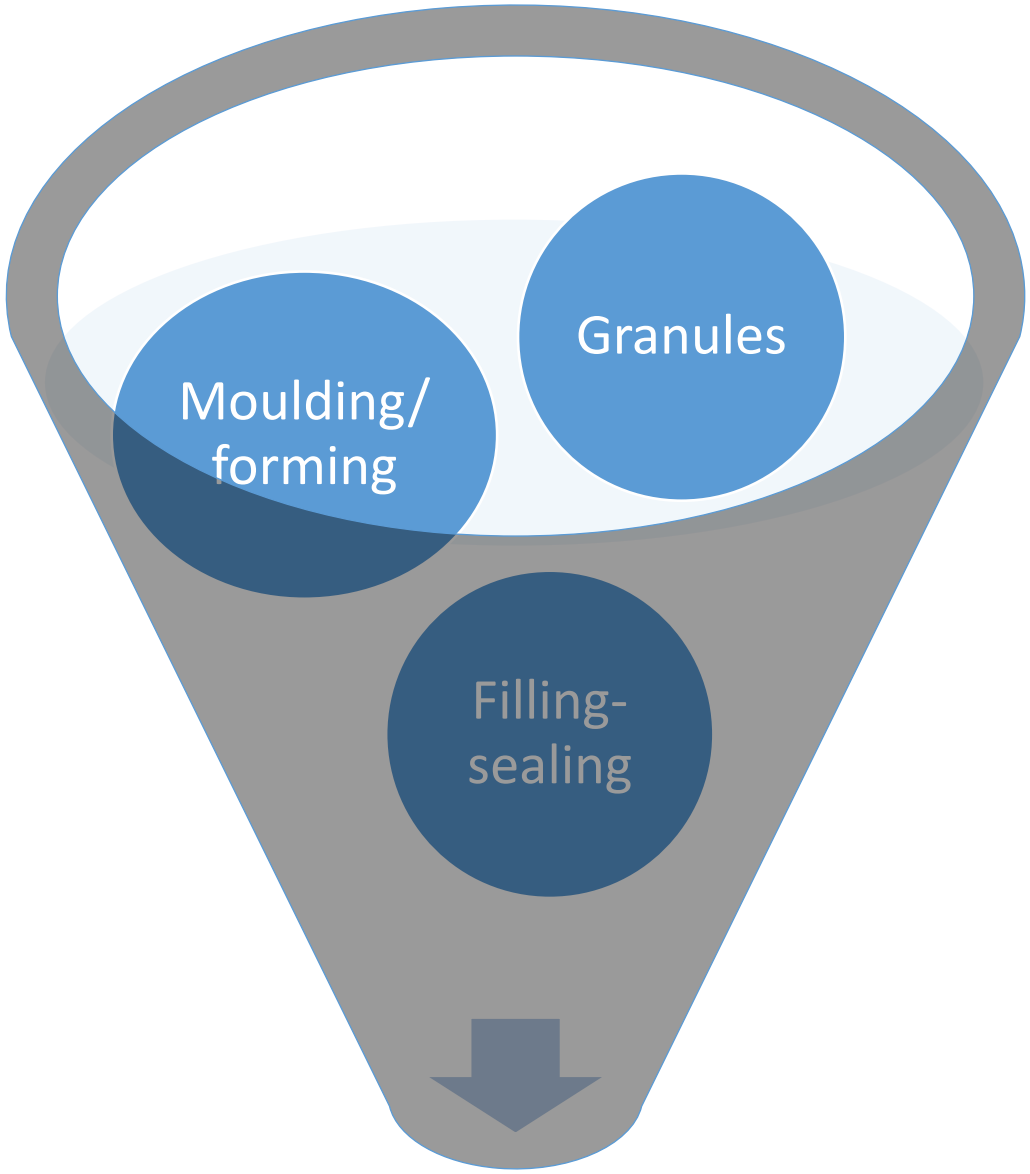
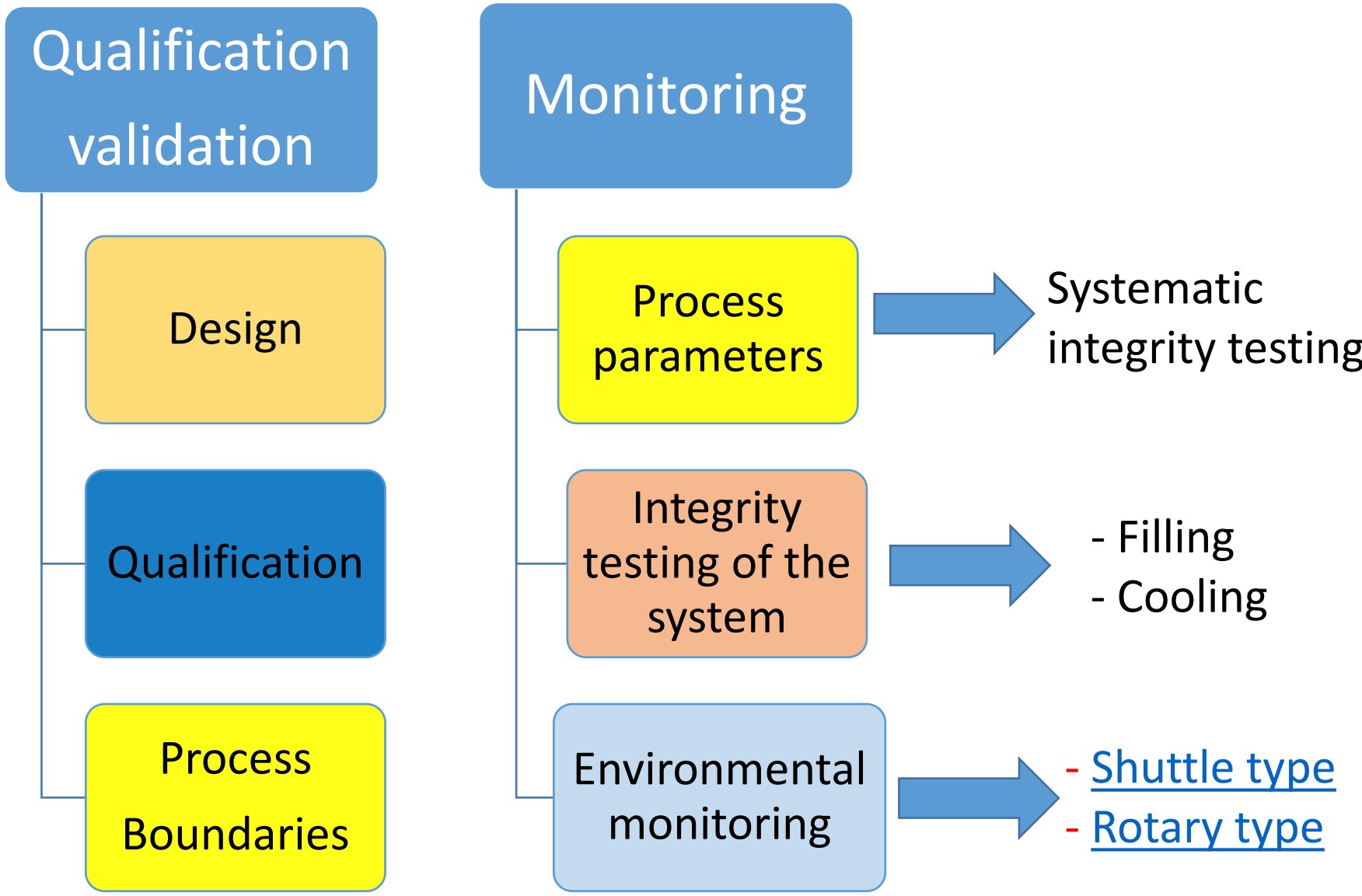
FORM-FILL-SEAL



Finished products

FORM-FILL-SEAL

Qualification



LYOPHILIZERS HANDLING

❖ In 2009 unloading improvement

- ✓ Grade A conditions vs Grade A supply
- ✓ RABS
- ✓ Displaced stopper detection

❖ In 2019 loading improvement

- ✓ Minimize direct operator intervention
- ✓ Chamber sterilization after each load
- ✓ Filter and vacuum/leak integrity testing

Contamination Control Strategy

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Contamination Control Strategy elements

Quality Risk Management

Knowledge; Continuous Improvements

Organisational and Technical Measures

Personnel

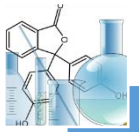
- Cultural considerations
- Appropriate education
- Suitable knowledge and experience
- Clothing considerations
- Gowning processes
- Training strategy
- Qualification for aseptic processing

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

Risk assessments; Monitoring; Data Review

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Pharmaceutical Quality System

Contamination Control Strategy elements

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Pharmaceutical Quality System

Contamination Control Strategy elements

Quality Risk Management

Knowledge; Continuous Improvements

Risk assessments; Monitoring; Data Review

Organisational and Technical Measures

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

Pharmaceutical Quality System

Contamination Control Strategy elements

Quality Risk Management

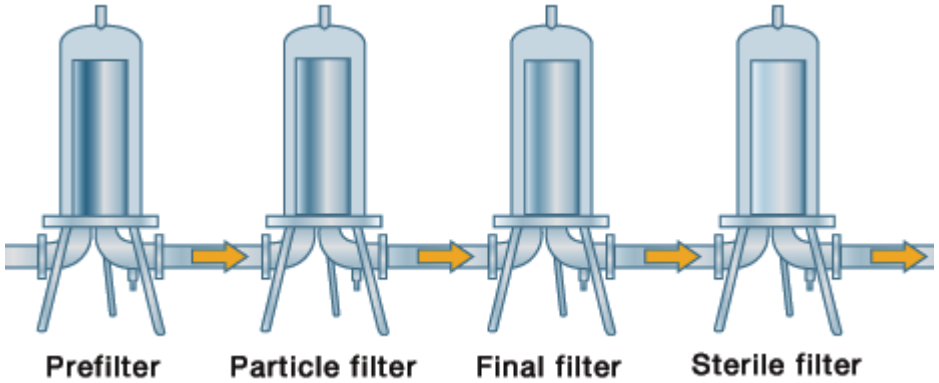
Knowledge; Continuous Improvements

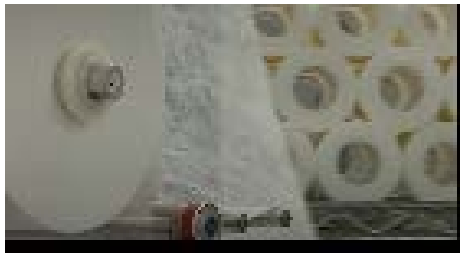
Risk assessments; Monitoring; Data Review

Organisational and Technical Measures

Production & Process

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





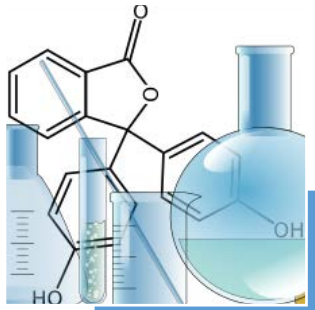
Pharmaceutical Quality System

Contamination Control Strategy elements

Quality Risk Management

Knowledge; Continuous Improvements

Organisational and Technical Measures



Materials & Quality Control

- Specifications
- Materials Management
- Parameters & attributes of
  - API
  - Excipients
  - Components
  - Process aids
  - Packaging
  - Intermediates
  - Bulk
  - Finished product
- Environmental Monitoring
- Sterility testing
- Endotoxin testing
- Biological Indicators

Pharmaceutical Quality System

Risk assessments; Monitoring; Data Review

Contamination Control Strategy elements

Quality Risk Management

Knowledge; Continuous Improvements

Risk assessments; Monitoring; Data Review

Organisational and Technical Measures

Outsourced activities

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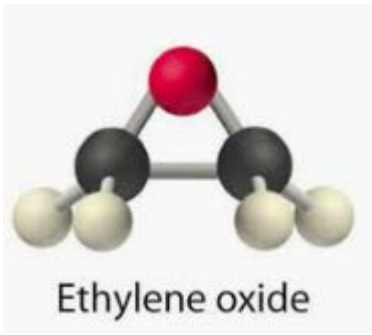

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Pharmaceutical Quality System

What would we be looking for?

Existing facilities:

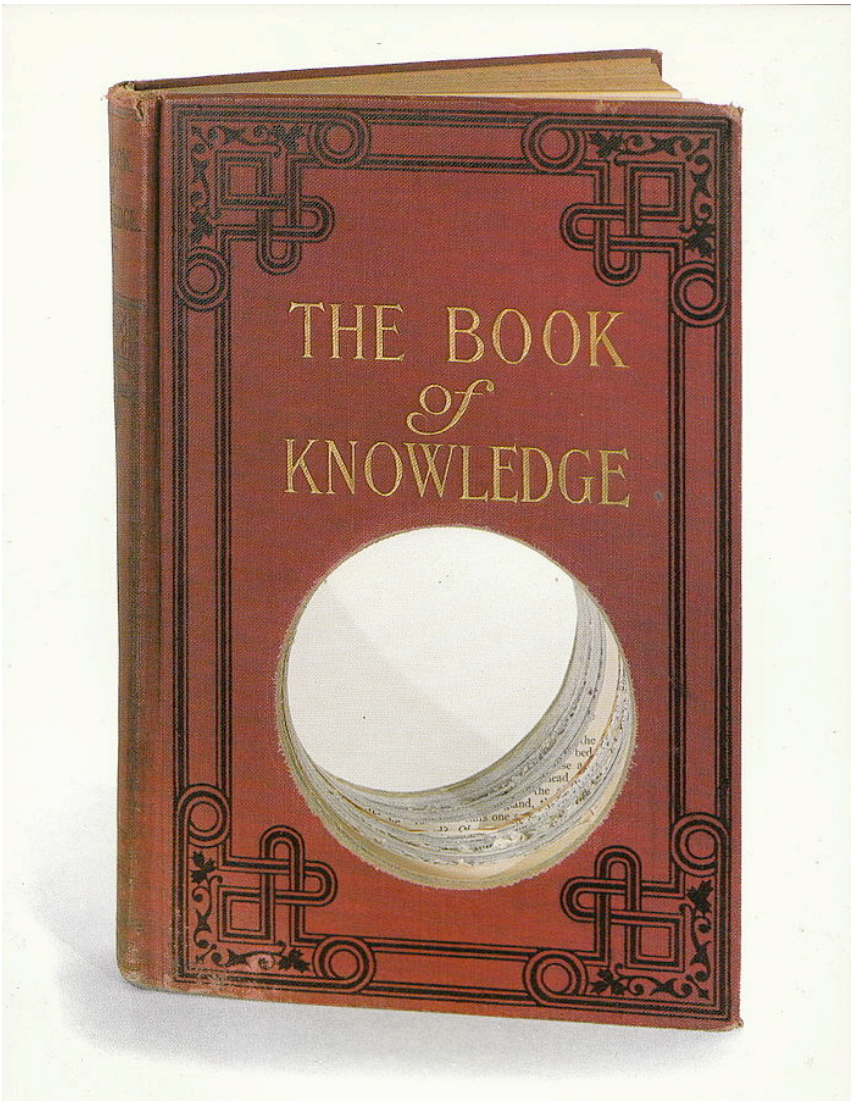
- The Contamination Control Strategy should already be in place …
  - Probably not in a ‘new’ format or called a Contamination Control Strategy!
- The process should be mapped, and the risk areas highlighted
- The interactions and process touch points should be considered.

New facilities:

- Part of the design process!
- What are the specifications – and does the strategy support this?

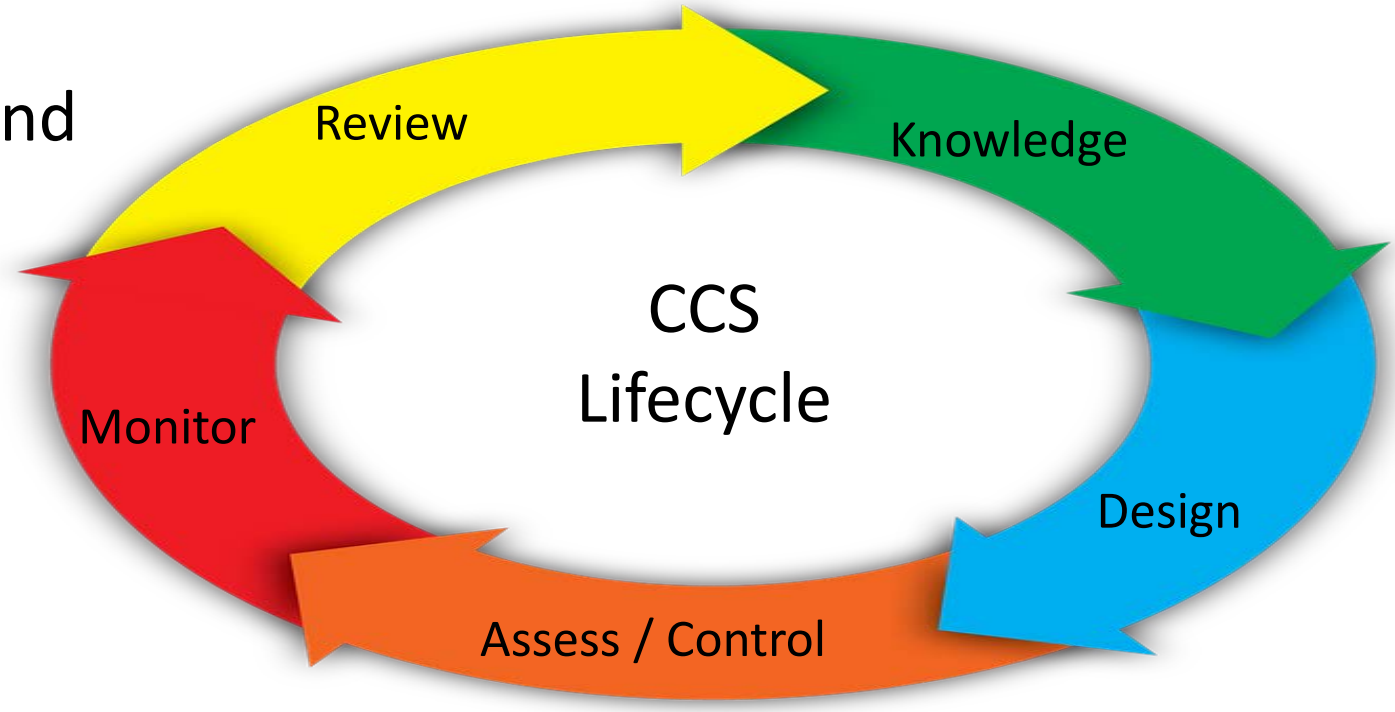
What should it look like?

- One document?
- Multiple documents with a central summary and conclusion?



What should it look like?

- The Contamination Control Strategy should be subject to regular review and update based on data and process knowledge…



Visual Inspection

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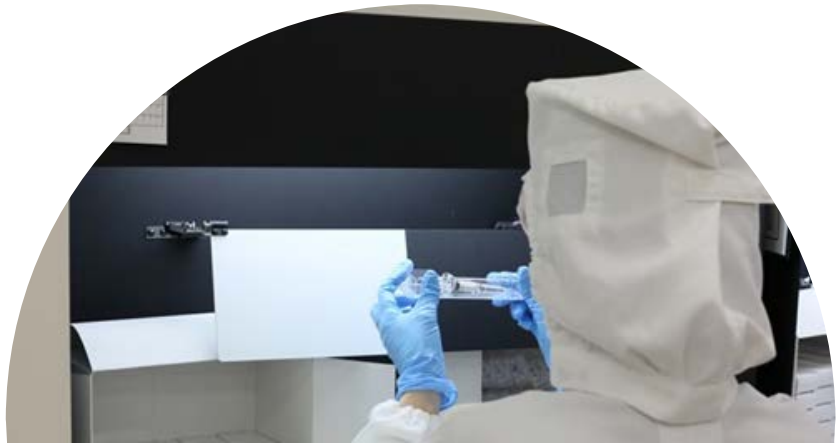
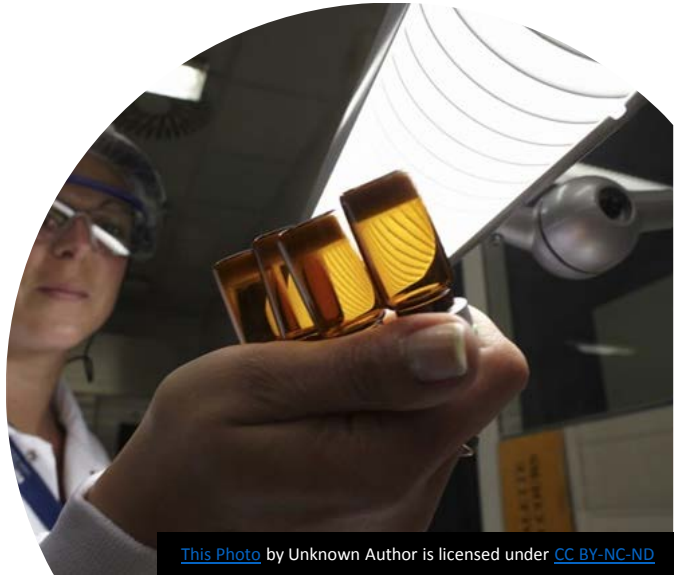
Visual Inspection of finished dosage forms





CONCLUSION

- ✓ Comprehensive document (defined chapters)
- ✓ Consideration of multiple products and new technologies
- ✓ Multiple boundaries are set along the objectives
- ✓ Contamination control strategy
- ✓ Risk management


Thank you
Any Question ?

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