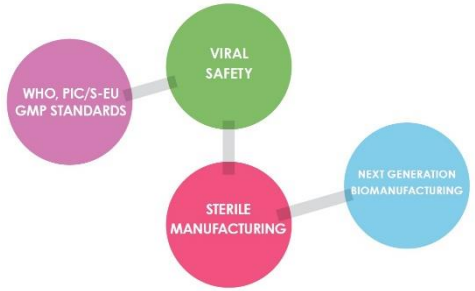
2nd ASEAN Educational Workshop on
GMP FOR BIOLOGICALS/BIOSIMILARS



Ellen Ying-Hua Chen, MBA, Taiwan ROC

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GaBI Educational Workshops

18 December 2019, Hotel Gran Mahakam, Jakarta, Indonesia

2nd ASEAN Educational Workshop on
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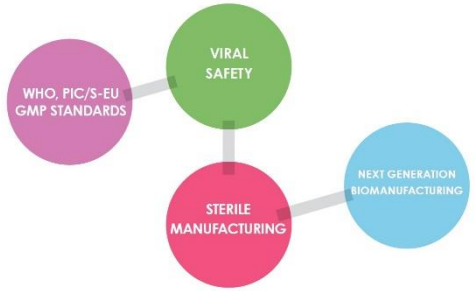


Sterile manufacturing based on Annex 1 of the PIC/S-EU GMP Guide

Ellen Ying-Hua Chen, MBA

18 December 2019

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

asean

2nd ASEAN Educational Workshop on GMP FOR BIOLOGICALS/BIOSIMILARS

Sterile manufacturing

based on **Annex 1 of the PIC/S-EU GMP Guide**

Ellen, Ying-Hua Chen

18 December 2019

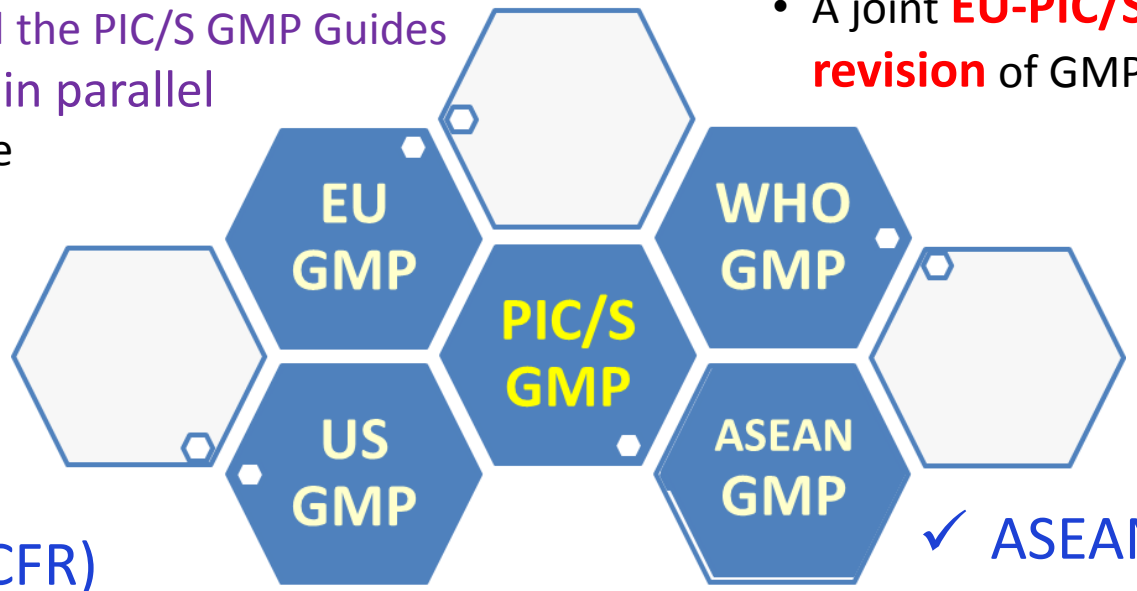
Outline

- General overview
  - PIC/S-EU GMP Guide
  - Manufacture of sterile products
- Today's focus on Aseptic Processing
  - Cleanrooms
  - Personnel
  - Monitoring system
  - Contamination Control Strategy
- Summary

PIC/S GMP Guide - Global recognized GMP standards

✓ EU GMP Guide

In 1989, the EU adopted its own GMP Guide, which was equivalent to the PIC/S GMP Guide. Since that time, EU and the PIC/S GMP Guides have been developed in parallel and whenever a change has been made to one, the other has been amended so that **both Guides are practically identical.**



✓ WHO GMP Guide

- WHO has signed co-operation agreement with PIC/S.
- A joint **EU-PIC/S-WHO Project on revision** of GMP for sterile and ATMPs

✓ US CGMP (21 CFR)

The GMP regulatory framework covers all PIC/S GMP requirements & annexes is one of the assessment items for PIC/S membership.
PIC/S presently comprises 52 Participating Authorities coming from all over the world

✓ ASEAN MRA on GMP Inspection

of Manufactures of Medicinal Products:

"Equivalent GMP Code" means any GMP standard recognised by the JSC to be equivalent to the PIC/S Guide to GMP for Medicinal Products.

Structure of PIC/S GMP Guide

PE 009-14 (1 July 2018)

Part I: Medicinal products | **Part II: APIs**

principles and general requirements

Annexes provide detail on specific areas of activity

- **Annex 1 Sterile Medicinal Products**
- Annex 2 Biological Medicinal Substances & Products for Human Use
- Annex 3 Radiopharmaceuticals
- Annex 4 Veterinary Medicinal Products other than immunologicals)
- Annex 5 Immunological veterinary medical products
- Annex 6 Medicinal Gases
- Annex 7 Herbal medicinal products
- Annex 8 Sampling of Starting and Packaging Materials
- Annex 9 Liquids, Creams and Ointments
- Annex 10 Pressurised Metered Dose Aerosol Preparations for Inhalation
- Annex 11 Computerised Systems
- Annex 12 Use of Ionising Radiation
- Annex 13 Investigational Medicinal Products
- Annex 14 Products derived from Human Blood or Human Plasma
- Annex 15 Qualification and validation
- Annex 17 Real Time Release Testing and Parametric Release
- Annex 19 Reference and Retention Samples
- Annex 20 Quality Risk Management

Revision of Annex 1

2003/9/1: Amendment of Annex 1

2009/1/15: Revision of Annex 1

current version (127 paragraph)

- 2015:
  EMA-PIC/S joint published
  Concept paper on the revision
- 2017/12/20
  parallel public consultation
  by the EC, WHO and PIC/S.
- 2018/3/20 6,200 comments recieved
- 2018~2019 Review processs
  1st & 2nd NCA reveiw (draft v10, 290)
- Dec 2019~Feb 2020 Targeted consultation
- Q2 2020 Review of the comments
- Q3 2020 Final document

Draft Annex 1 (Document map)

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

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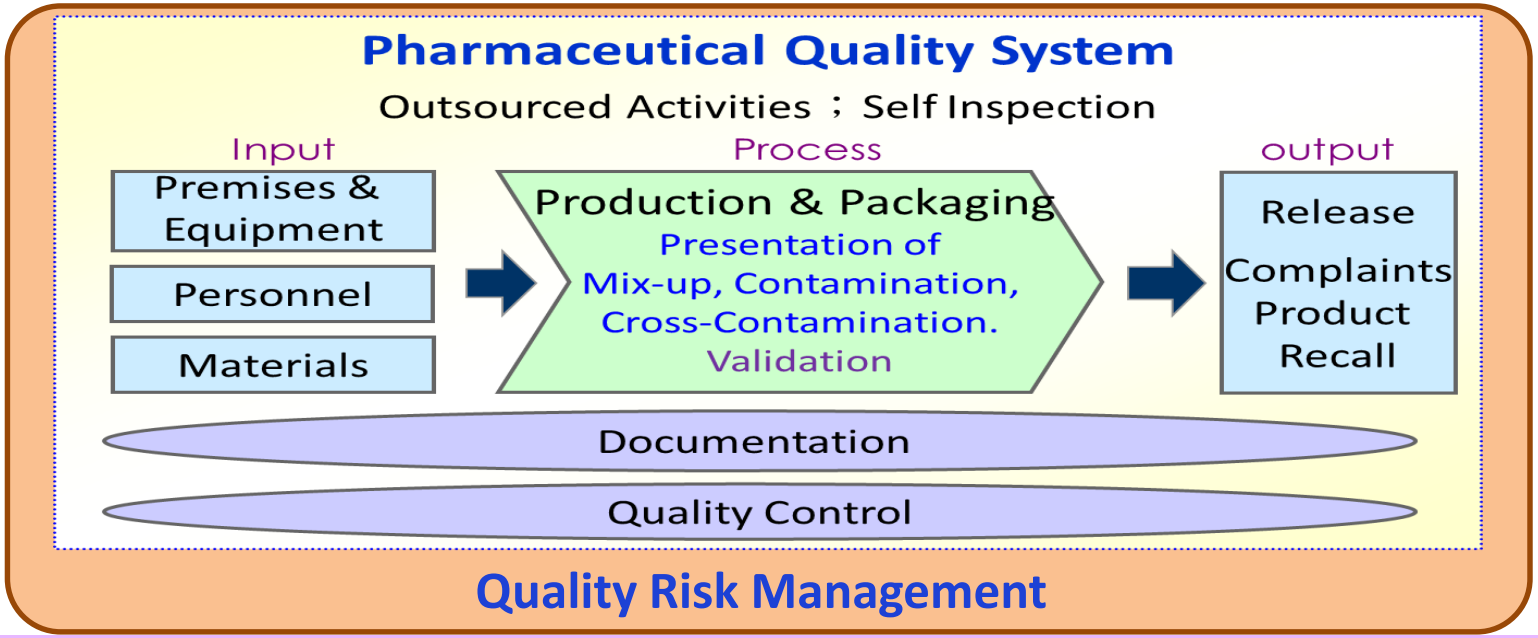
Manufacture of sterile products

- Sterile products are those products which are free from
  - viable microorganisms (product sterility),
  - pyrogens (endotoxins free) and
  - particulate matter (particulate contaminants free)
- The manufacture of sterile products is subject to special requirements in order to minimize risks of contamination



Manufacture of sterile products

- Manufacturing of sterile medicinal products

Terminal sterilization
Products filled in it final container is subject to a sterilization process.

Aseptic Processing
Drug bulk, containers and closures are subject to a sterilization separately, and then brought together.

- Biopharmaceutical are typically large moleculess and typically heat labile (temperature sensitive), cannot be terminally sterized, and should be manufacturered aseptically

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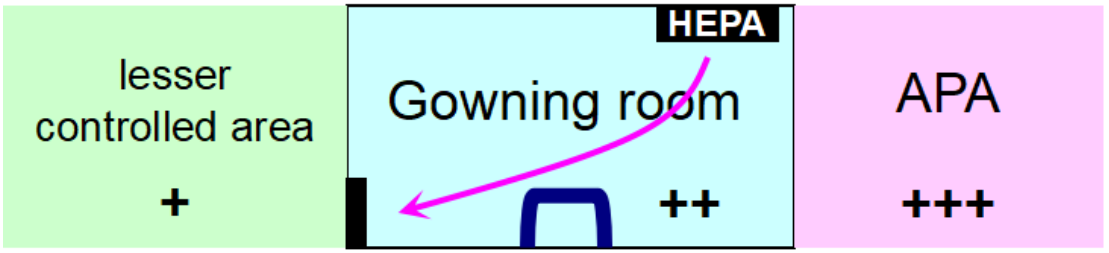
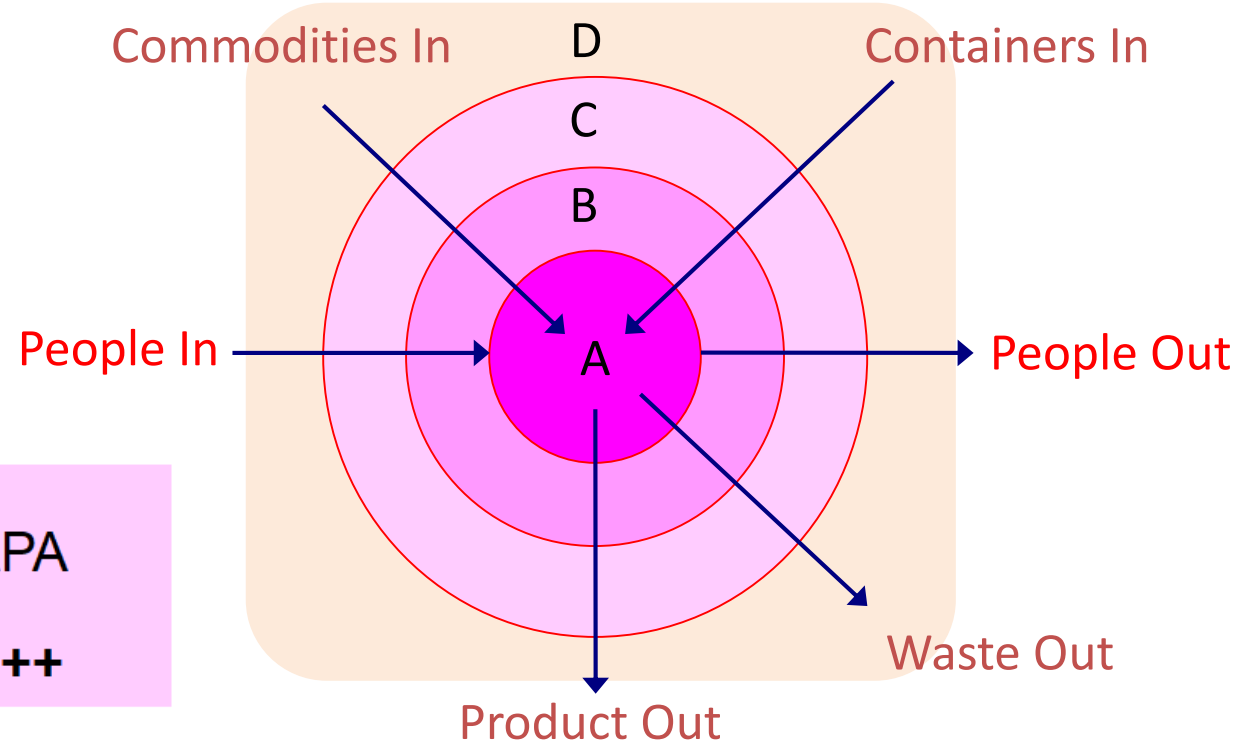
Today's focus

- **Cleanrooms** (environment quality)
  - Facility design and sterile barriers (Isolators & RABS)
  - Cleanrooms Qualification
  - Decontamination (cleaning and disinfection)
- **Personnel** (major source of contamination)
- **Monitoring system**
  - Environmental & personnel monitoring
  - Processing monitoring:
    Aseptic process simulation (known as media fills)
- **Contamination Control Strategy**

Cleanrooms - Facility Design

- Four grades (A, B, C & D) of clean rooms should be distinguished
- Entry to cleanrooms should be through personnel airlocks and Material airlocks, interlocking system
- Pressure differentials
- Airflow patterns/visualization in the critical processing areas



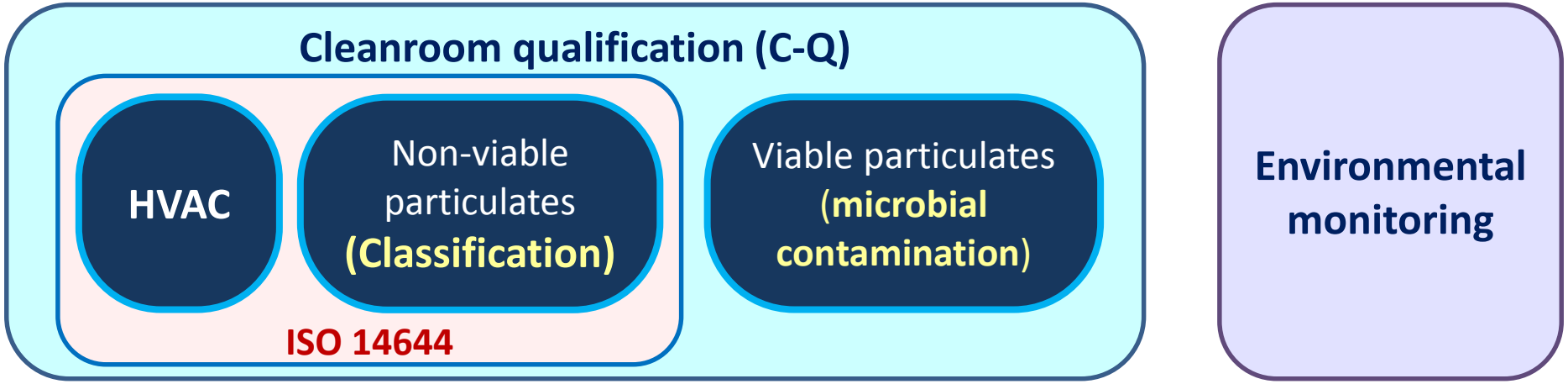


Cleanrooms - sterile barriers

- **Isolators or RABS**
  - are designed to provide protection of the grade A
  - with grade B background for RABS and open isolators used for aseptic processes
  - a minimum of grade D background environment for closed isolator
- Qualification according to Annex 15 of the PIC/S GMP Guide
- Monitoring/maintenance
- Decontamination: cleaning, disinfection, sterilization

Cleanrooms Qualification

- Cleanrooms and clean air equipment (e.g. RABS, isolators) used for the manufacture of sterile products, should be qualified and classified according to the required characteristics of the environment.
- Cleanroom classification is part of a cleanroom qualification
  - a method of assessing the level of air cleanliness by measuring the non-viable airborne particulate concentration. Reference to ISO 14644 series of standards.
- The microbial contamination of the cleanrooms should be determined as part of the cleanroom qualification.
- Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.



C-Q – HVAC

- HVAC: Heating, ventilation, and air conditioning system
  - AHU, filters, BMS (Building Management system)

Test	Specification
Leak and integrity test of Filters (HEPA filters)	ISO 14644 part 3 Site's protocol
Air flow measurement / Airflow velocity / air change rate	Site's proposal Clean up period (15-20 mins) Velocity at the filter face: 0.36-0.54 m/s
Temperature	Site's proposal
Humidity	Site's proposal
Air pressure differentials	$\Delta P > 10$ pascals
Air flow visualization	Site's proposal

C-Q – for classification

- Maximum permitted airborne particulate concentration during classification
  - the airborne particulates 0.5 µm and 5 µm should be measured.
  - both at rest and in operation should be performed
    - For grade D, in operation limits are to be defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.
  - the minimum number of sampling locations:
    ISO 14644 (Part 1), plus critical processing locations in grade A & B areas

Current version of Annex 1 of PIC/S GMP Guide

Grade	Maximum equal to or
	At rest
	0.5µm
A	3,520
B	3,520
C	352,000
D	3,520,000

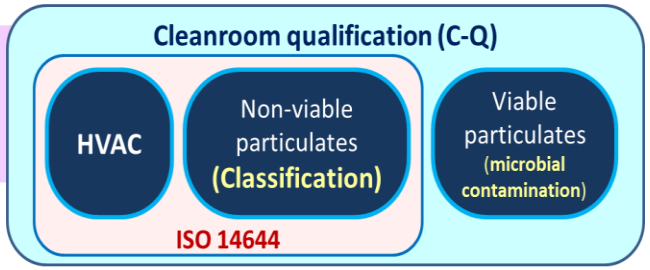
draft Annex 1 for public consultation in Dec. 2017

Grade	At rest equal to (than 0.5 µ
A	3 520
B	3 520
C	352 000
D	3 520 000

Coming draft Annex 1 for targeting consultation

Grade	Maximum limits for particulates ≥ 0,5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	29	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[(a)]	29 000	Not defined[(a)]

C-Q – Microbial contamination



- Limits for microbial contamination during qualification
  - Qualification should include both at rest and in operation states.
  - Settle plates should be exposed for the duration of operations and changed as required after 4 hours.
  - for grade A, the expected result should be no growth

Current version of Annex 1 of PIC/S GMP Guide

Recommended limits for microbiological operation:

Grade	Recommended limits fo	
	Air sample cfu/m³	Settle plates (diam. 90 mm), cfu/4 hours (b)
A	< 1	< 1
B	10	5
C	100	50
D	200	100

The draft Annex 1

Grade	Air sample cfu/m³	Settle plates (diameter 90 mm) cfu/4 hours (a)	Contact plates (diameter 55 mm) cfu/plate
A(b)	No growth(b)		
B	10	5	5
C	100	50	25
D	200	100	50

Cleanrooms re-Qualification

- Maximum time interval for requalification
  - For Grade A & B areas: 6 months.
  - For Grade C & D areas: 12 months.
- Minimum test requirements for the requalification

Grade	Determination of the conc. of airborne particles (viable and non-viable)	Integrity test of Terminal Filters	Airflow volume measurement	Verification of air pressure difference between rooms	Air Velocity test
A	Yes	Yes	Yes	Yes	Yes
B	Yes	Yes	Yes	Yes	*
C	Yes	Yes	Yes	Yes	*
D	Yes	Yes	Yes	Yes	*

* performed according to risk assessment documented as part of the CCS. However, required for filling zones and back ground to Grade A RABS.

- Requalification should be considered
  - after action to correct out of compliance equipment or facility conditions
  - after changes to equipment, facility or process

Cleanrooms - Cleaning and Disinfection

Cleaning	Disinfection
• Removal of particulate , residues and Microbes from the surface • Removal of residues and buildup that can complicate Disinfection	• Saturate & Penetrate the Cell Wall of the microorganism by a chemical agent • requires a specified contact time • Concern with particulate, residues and irregular surfaces

- Written program for cleaning and disinfection
  - More than one type of disinfecting agent should be used, and should include a sporicidal agent
    - Isopropyl & Ethyl Alc. Solution @ 70%, Phenols (high/low pH), Quaternary ammonium, Hydrogen Peroxide @ 3-6%
    - Sporicide: Sodium Hypochloride, Peracetic acid and Hydrogen peroxide, Glutaraldehyde Products
  - Fumigation or vapour disinfection (vapour phased hydrogen peroxide) of cleanrooms and associated surfaces may be useful for reducing microbial contamination in inaccessible places

Cleanrooms - Cleaning and Disinfection

- Written program for cleaning and disinfection
  - General order: Ceiling → Walls → Equipment →Floors, Top to Bottom, Back to Front (towards person)
- Qualification of Disinfectant
  - Antimicrobial Effectiveness (Lab. study)
    - Time Contact Kill Studies: 3-10 minute contact time by surface challenge test (on surface)
  - “In Situ” Field Studies
    - Using the actual cleaning procedures, method with approval disinfectants, compares EM date
  - Expiration dates shall be qualified
- Disinfectants and detergents in Grade A and B to be sterile prior to use (may also apply to Grade C and D)
- Monitoring the effectiveness and detect changes in flora type

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- **Monitoring system**
  - Environmental & personnel monitoring
  - Processing monitoring: Aseptic process simulation (media fills)
- **Contamination Control Strategy**

Personnel

- Appropriate education, suitable knowledge and experience (including basic knowledge of microbiology, hygiene, aseptic techniques-cleanroom behavior and practices)
- Clothing considerations & Gowning processes
- for entering aseptic processing areas
  - Initial (a least 3 sets) & Annual gowning qualification
  - Qualification for aseptic processing (participate in a successful aseptic process simulation once per year)
- There should be systems in place for disqualification of personnel from entry into cleanrooms

Gowning Procedures

- ↓ Sanitize hands
- ↓ Don first pair of sterile gloves
- ↓ Sanitize the gowning bench
- ↓ Sanitize each garment package
- ↓ Sanitize the gloved hands
- ↓ Don Face Mask
- ↓ Don sterile Hood
- ↓ Don sterile Gown
- ↓ Don sterile Boots (swing the booted foot over the gowning bench)
- ↓ Don sterile Goggles
- ↓ Don Second pair of sterile gloves
- ↓ Verify Proper Coverage

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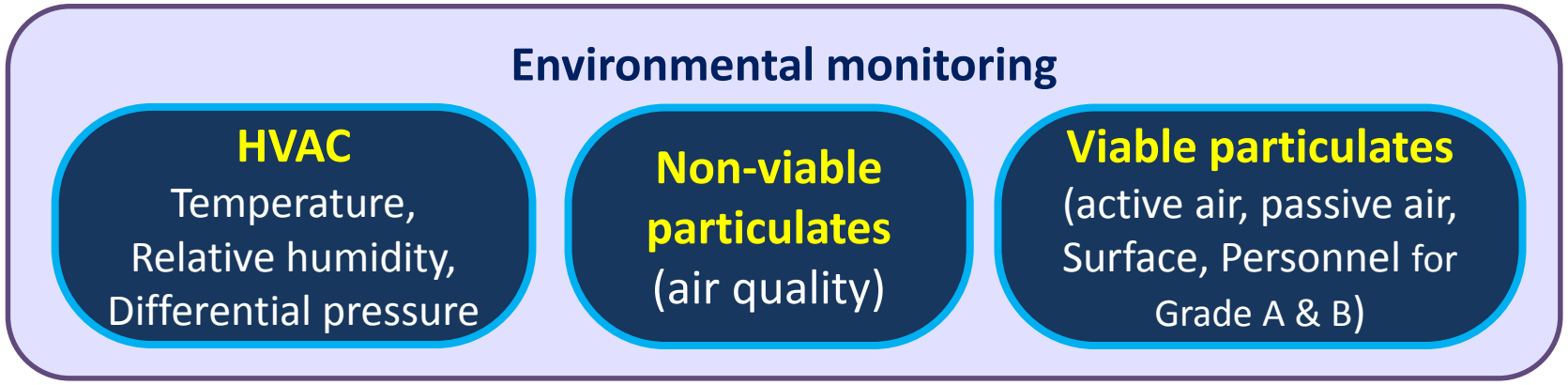
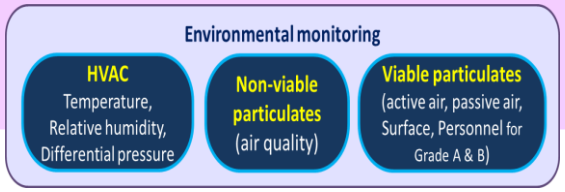
Environmental monitoring (EM)



- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program (i.e. locations, frequency of monitoring, monitoring method)
- Appropriate alert levels and action limits should be set, and should define the approach to trending.
  - If action limits are exceeded: a root-cause investigation including potential impact to product, followed by corrective and preventive action.
  - If alert levels are exceeded: scrutiny and follow-up
- Microorganisms detected in grade A & B should be identified to species level, potential impact on product quality should be evaluated.

EM - Non-viable monitoring



- Limits for airborne particulate concentration for the monitoring of non-viable contamination

Current version of Annex 1 of PIC/S GMP Guide

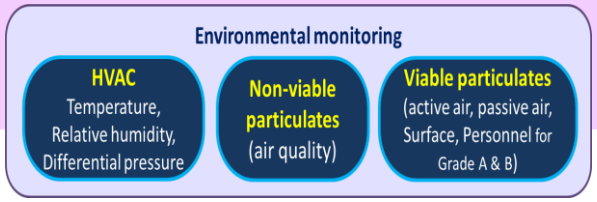
Grade	Maxi equa At re 0.5µ
A	3,52
B	3,52
C	352,
D	3,52

Coming draft Annex 1 for targeting consultation

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[(a)]	29 000	Not defined[(a)]

- For grade A: full duration of critical processing including equipment assembly, continuous monitoring
- For grade B area: similar to Grade A, frequency may be decreased
  - Filling locations: depend on the barrier between Grade A and B)
  - Entry airlock locations: beginning & end of filling operations

EM - Viable monitoring



- Maximum action limits for microbial contamination

Current version of Annex 1 of PIC/S GMP Guide

Recommended limits for operation:

Grade	Air sample cfu/m³	(c
A	< 1	
B	10	
C	100	
D	200	

Coming draft Annex 1 for targeting consultation

Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) cfu/4 hours [a]	Contact plates (diam. 55mm), cfu/ plate [c]	Glove print 5 fingers on both hands, cfu/ glove
A	No growth[b]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Methods		Frequency
Active air	A	Continuous for the full duration of critical processing
	B	similar to Grade A, frequency may be decreased
Passive air		the full duration of operations
Surface		at the end of each fill (after filling operation have been completed prior to cleaning & sanitization)
Personnel		after critical interventions and exit from the cleanroom

Processing monitoring (media fills)

- requires for initial facility PQ, significant changes to the facility/process (a minimum of 3 consecutive successful media fills) and routine re-qualification (at least twice per year, per fill configuration)
- should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps
  - Set-up operations, filling operations, hold times, lyophilization process, routine/non-routine interventions
- Count all filled media units and integral rejects
  - A 100% reconciliation is required after each media fill inspection
  - Unresolved counts must be immediately reported
- Acceptance criteria : the target should be zero growth.
- As any positive media vials found
  - Perform microbial identification
  - Filling line is not qualified for use
  - Evaluate filling line since last acceptable media fill
  - Once the cause has been identified and corrected, the media fill may be revalidated

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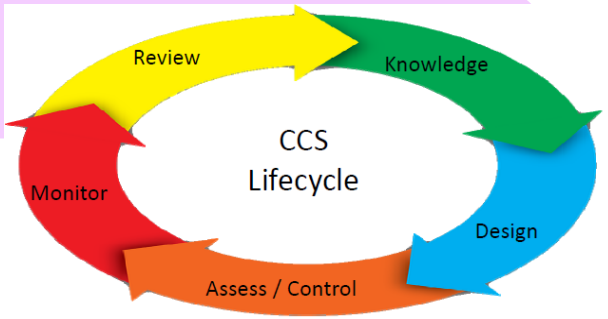
Contamination Control Strategy



- New language of Annex 1, cited 43 times

Quality Risk Management

Organisational and Technical Measures

Knowledge; Continuous Improvements

Risk assessments; Monitoring; Data Review

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

Pharmaceutical Quality System

Reference to : Tracy MOORE/MHRA, SUMMARY OF REVISING ANNEX 1 & Discussed Points During Revision, 2019 PIC/S annual seminar

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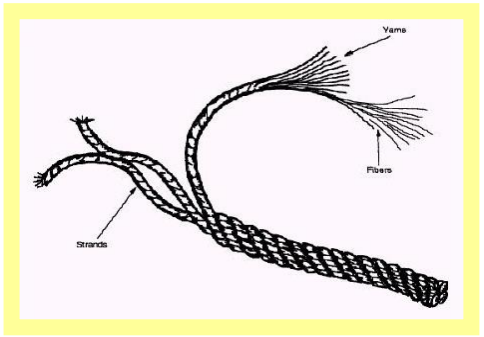
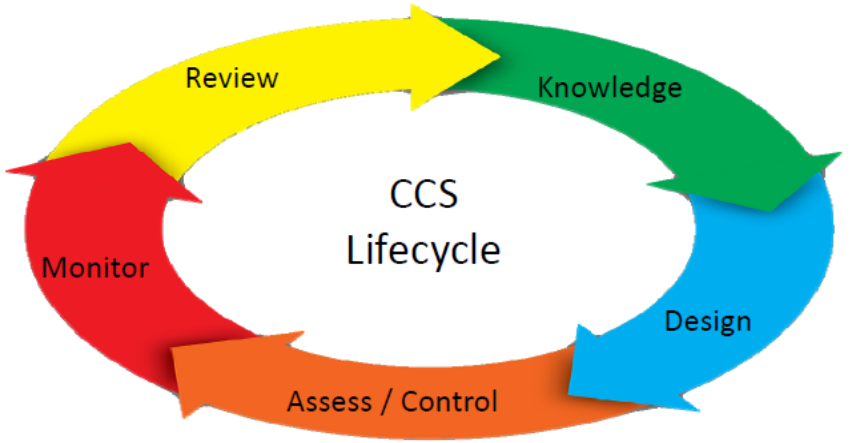


Each Unit operation of Aseptic Processing
is like a strand of a rope

The more unit operations that have issues or fail,
the higher risk to the product.



Thank you for your attention

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