# Aseptic Processing: Behaviors, Processes and Controls

Ruchir Pansuriya, Ph.D.,

International Vaccine Institute, Seoul, South Korea

International Vaccine Institute

Copyright© 2022 All rights reserved

# Contents

- Aseptic Processing Concept
- Principles and controls
- Personnel and Behavior
- What can go wrong?
- Facility, Equipment and Process
- Overview of Contamination Control Strategy: EU GMP Annex-1
- Environmental Monitoring
- Aseptic Process Simulation

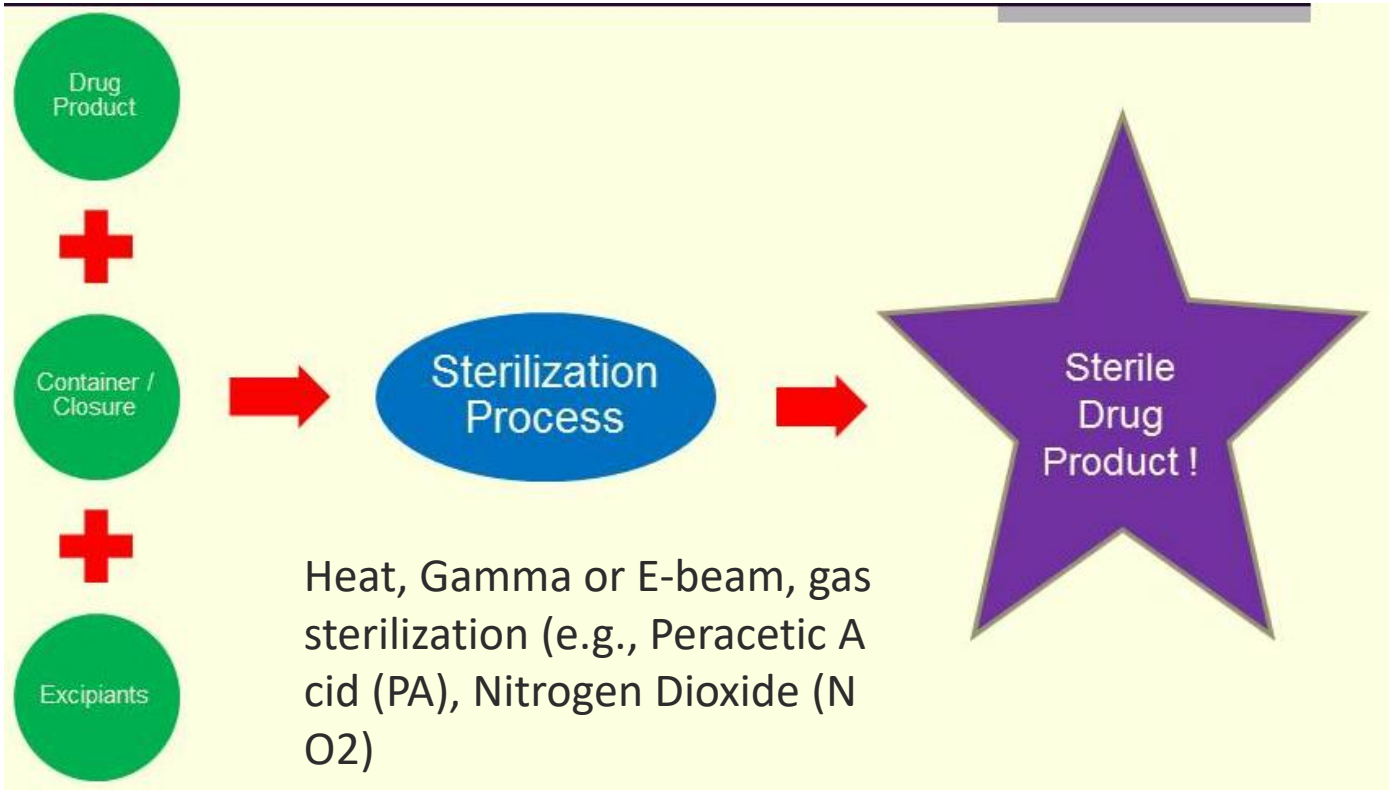


Copyright© 2022 All rights reserved

# Technical framework: Terminal sterilization Vs Aseptic Processing

- There are basic differences between the production of sterile drug products using aseptic processing and production using terminal st erilization

Terminal sterili zation





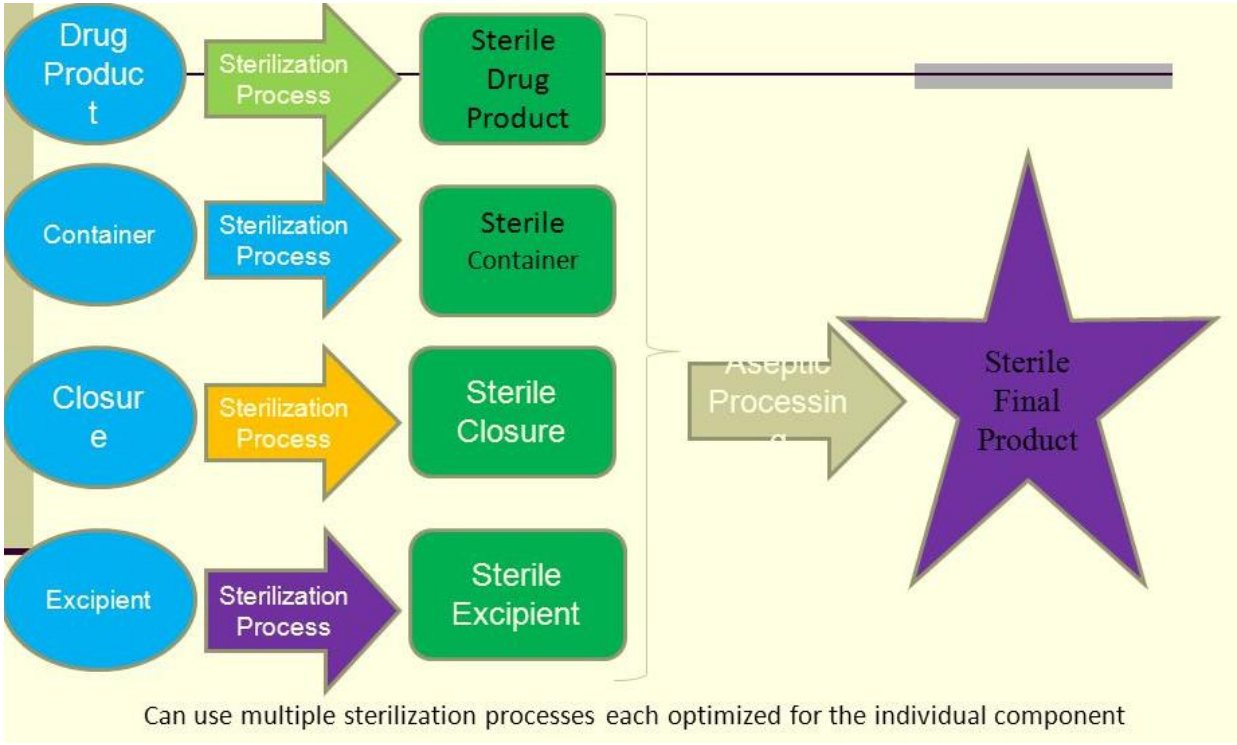

Ref: USFDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing CGMP

Copyright© 2022 All rights reserved

# Technical framework: Terminal sterilization Vs Aseptic Processing

- In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together. it is critical that containers be filled and sealed in an extremely high-quality environment.

Aseptic processing






Ref: USFDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing CGMP

Copyright© 2022 All rights reserved

# Technical framework: Terminal sterilization Vs Aseptic Processing

- **Decision making:**

  - Terminal sterilization is preferred to sterilization by aseptic proc essing for pharmaceutical products because it provides a SAL th at is possible to calculate, validate and control, and thus incorp orates a safety margin.
  - Aseptic processing is the last possibility as stated in all major st andards (European Medicines Agency (EMA), US Food and Drug Administration (FDA))

However, all most all biologics, vaccine & injectables requires the use of Aseptic processing due to nature of API.



Ref: USFDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing CGMP

Copyright© 2022 All rights reserved

# Aseptic Processing

International Vaccine Institute

Copyright© 2022 All rights reserved

# Aseptic Processing

## DEFINITION

Handling sterile materials in a controlled environment, in which the air supply, materials, equipment, and personnel are regulated to control microbial and particulate contamination to acceptable levels

Simply put, “Operating in a manner that prevents contamination of the process”.



Ref: PDA TR22, ISPE glossary

Copyright© 2022 All rights reserved

# Aseptic Processing: Where it is applicable

## Considerations

- Grade A/B operations
  - Seed/cell inoculation, DS sterile filtration, DP (blend, fill finish)
- However, principle of Aseptic processing, cGMP for sterile medicinal product is applicable to entire processes such as cell bank, DS and DP manufacturing.



Ref: USFDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing CGMP

Copyright© 2022 All rights reserved

# Principles and Controls

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin / pyrogen contamination.

- Facility, Equipment and Process
- Personnel
- Processes and monitoring systems
- Raw material and packaging materials



Copyright© 2022 All rights reserved

# What can go wrong? Implication: Meningitis case study

NEW ENGLAND COMPOUNDING CENTER

Proper sterilization procedure

Exposure to high-pressure saturated steam for at least 20 min

**September 2012:**
Steroid batch exposed just 15 min

RESULTS

**Meningitis outbreak**

Hundreds sick

60 killed

While the **risk of a contamination can never be entirely eliminated**, it can be brought to a minimum by following the proper aseptic practices and sterilization procedures

**Note: Underexposure was actually common practice (not just a one-time error)**



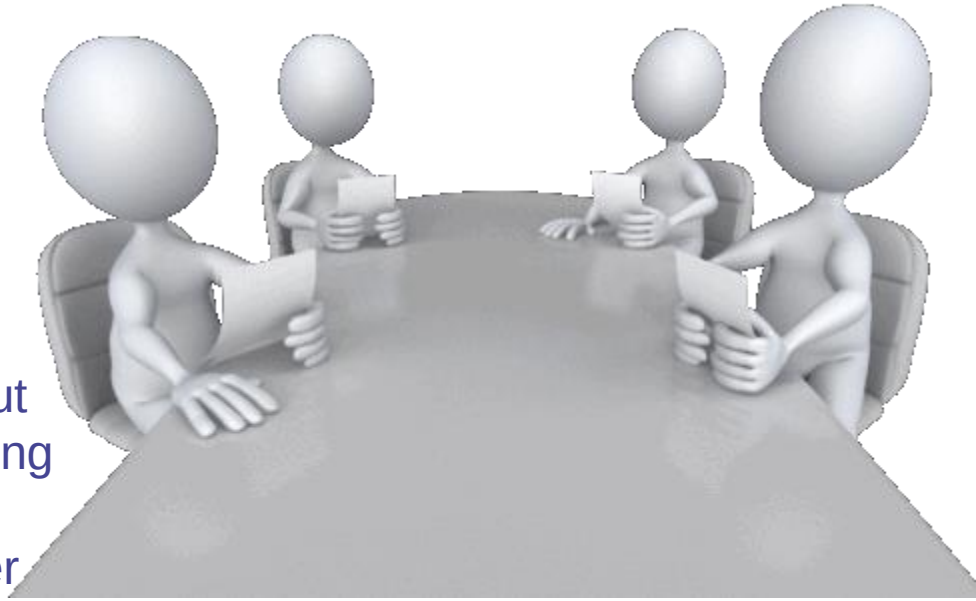
Copyright© 2022 All rights reserved

# What can go wrong? Implication: Meningitis case study

Think about the case study we just reviewed.

Let's think as a group:

- What went wrong?
- Not only did they not follow their validated sterilization procedure, but they were also cited for poor cleaning and poor environmental control. They even had a garbage dumpster located immediately next to the intake of their air handler for the clean space.



**There were many safeguards that should have prevented this tragedy, But all failed in this example … and it cost people their lives!**

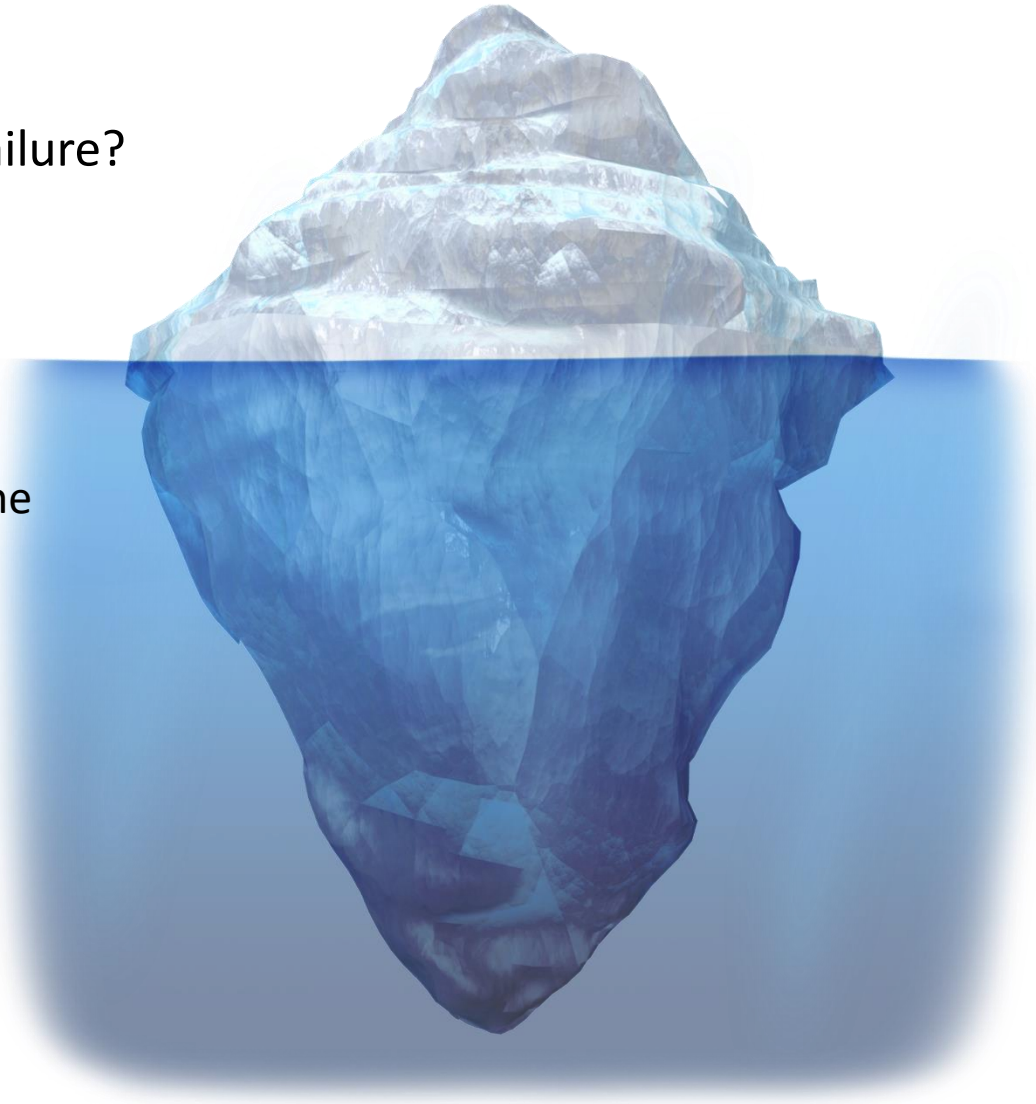


Copyright© 2022 All rights reserved

# What can go wrong? implication

What's the impact of a Sterility Failure?

- Over 50,000 Euros per Investigation
- Multiple batches thrown away
- 30+ days of production line downtime
- Millions of doses unavailable
- Millions of patients impacted





Copyright© 2022 All rights reserved

# Principles and Controls

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin / pyrogen contamination.

- Facility, Equipment and Process
- Personnel
- Processes and monitoring systems
- Raw material and packaging materials



Copyright© 2022 All rights reserved

# Aseptic Processing: Personnel & Behavior

International Vaccine Institute

Copyright© 2022 All rights reserved

# Personnel Behavior

People are the most important element in Aseptic Processing and in defining fate of the product

**Positive impact**

If we have the appropriate level of knowledge and follows Good Aseptic Behaviors

**Negative impact**

Without the appropriate controls and behaviors, we can introduce contamination



Copyright© 2022 All rights reserved

# Personnel Behavior

## Why is Hygiene Important
## People - The Walking Culture

- Microbes are found everywhere ; all around you and on you.
- Microbes are extremely resilient and adaptive at surviving and thriving in the world.
- Humans play a large part in supporting the growth and transportation of microbes.

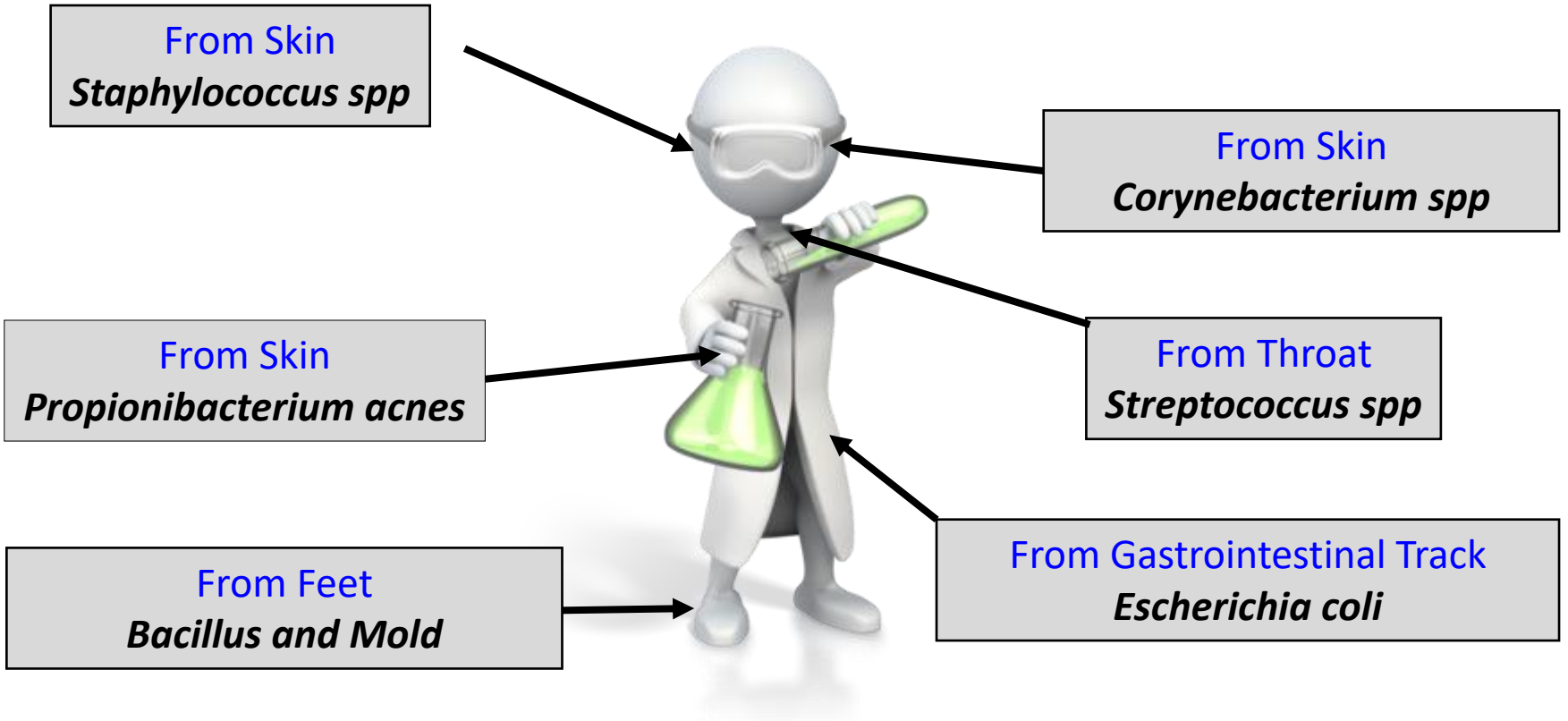


Copyright© 2022 All rights reserved

# Personnel Behavior

## Why is Hygiene Important People - The Walking Culture

- Garden soil - 5 billion in 1 teaspoon
- Human skin - 2.5 million on 1 square inch of skin
- Human saliva - 1 billion per milliliter
- Sneeze - 200,000
- Human feces - 100 billion per gram






Copyright© 2022 All rights reserved

# Personnel Behavior

## Daily Life Mindset

## Aseptic Area Mindset

**Rules Change!**



Copyright© 2022 All rights reserved

# Personnel Behavior

## What can go wrong?

If any gowning component need change or adjustment:

- **Operator must exit to the gowning room**
- **Change/adjust, using aseptic technique.**

- **For hole in gloves, exit to Grade B, plate, and re-glove**

If Communication is needed due to safety or quality reasons/risk

- **Communicate away from the exposed product or components**



Copyright© 2022 All rights reserved

# Personnel Behavior

## What can go wrong?

You talk, sneeze or cough into the mask?

- **Return to the gowning room and change the mask**

In the event of an emergency, when the operators need to evacuate

- **Then the cleanroom gowning is changed upon reentry and shoe covers must be worn until dedicated shoes are disinfected.**

Gloved hands contacted any part of gowning apparel.

- **If contact occurs, gloves must be sanitized with Sterile 70% Isopropyl Alcohol/changed.**



Copyright© 2022 All rights reserved

# Personnel Behavior

## Why do we need Cleanroom Clothing? (Gowning)

**Remember we are the Walking Culture!**

We need gowning/cleanroom clothing as a barrier between our body/skin/clothes/shoes and the aseptic manufacturing environment to contain dispersion of particles and the contaminants they carry

| Average Skin Cells Shed by an adult/day = $10^{9*}$ | | |
|---|---|---|
| Type of garment | Average # of Particles ≥ 0.5µm Shed/ Minute | Average # of Micro be Carrying Particle s (MCP) /minute |
| Personal Indoor Clothing | 2,130,000* | 2400* |
| Cleanroom garments | 1,020,000* | 177* |

Reference: W. Whyte and M. Hejab; Eur. J. Parenteral & Pharm Sci, 12 (2), 39, 2007



Copyright© 2022 All rights reserved

# Personnel

## Clothing requirements for each grade

### Grade A/B

- Headgear to totally enclose hair.
- One piece jumpsuit, gathered at wrist & high neck.
- Headgear to tuck in neck of suit.
- Facemask
- Sterile non powdered gloves
- Sterilized footwear
- Trouser bottom to be tucked in footwear & garment sleeve in to gloves

### Grade C

- Hair should be covered
- Once piece jump suit gathered at wrist & high neck.
- Appropriate shoes and overshoes should be worn
- Clothing  should release no fiber or particulate matter

### Grade D

- Hair should be covered
- Protective clothing and appropriate shoes or overshoes should be worn.
- Appropriate measures should be taken to avoid any contamination from outside the clean area.



Reference: WHO TRS 961 Annex6

Copyright© 2022 All rights reserved

# Personnel

Ensure availability of sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products

Only the minimum number of personnel required should be present in aseptic areas. As far as possible, inspections and controls should be conducted from outside such areas.

All personnel including cleaning and maintenance staff should receive training on:

- Correct manufacturing of sterile products
- Hygiene
- Basic elements of microbiology
- Cleanroom practices

Copyright© 2022 All rights reserved

# Personnel

The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviors.

Outside staff who are not trained, should be specifically instructed and supervised.

Staff engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas.

If unavoidable, rigorous and clearly defined decontamination procedures should be followed

High standards of personal hygiene and cleanliness are essential.

Personnel should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants



Copyright© 2022 All rights reserved

# Personnel

Monitoring of Health condition and action taken with regards to the personnel who may introduce undue microbial hazards should be documented.

Cleanroom gowning and washing should follow a written procedure designed to minimize contamination of clean area clothing.

Clothing and its quality should be appropriate to the process and grade of working area and should be worn in a way to protect the product from contamination.

Outdoor clothing should not be allowed in changing rooms leading to Grade B and C rooms.

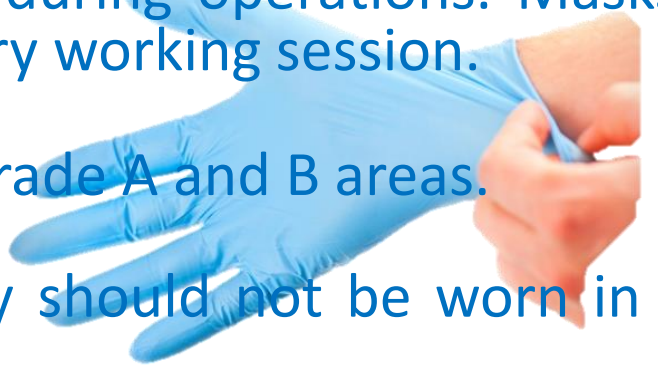
For every worker in a Grade A/B area, clean, sterile protective garments should be provided for each work session.



Copyright© 2022 All rights reserved

# Personnel

Gloves should be regularly sanitized during operations. Masks and gloves should be changed at least every working session.



Sanitized goggles should be worn in Grade A and B areas.

Wrist watches, cosmetics and jewelry should not be worn in clean areas.

Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed.

Separate laundry facilities for such clothing are desirable.

If fibers are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles.

Washing and sterilization operations should follow SOPs



Copyright© 2022 All rights reserved

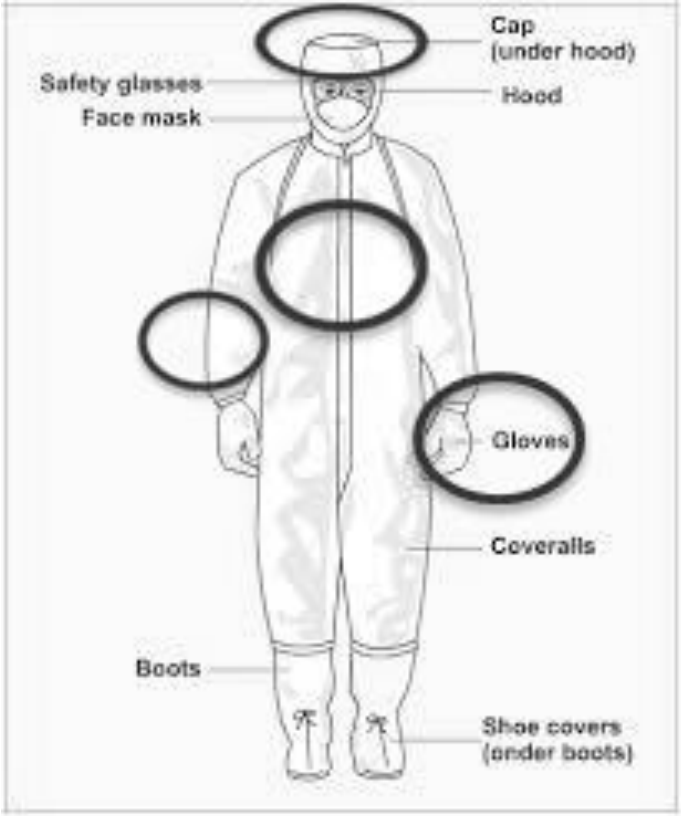
# Personnel

Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually and should involve both visual and microbial assessment

Monitoring locations such as

- Gloved fingers - all
- Forearms – underside of each sleeve
- Chest – Zipper
- Hood (facemask / forehead).

Usually more sampling points are included for gowning qualification than for routine



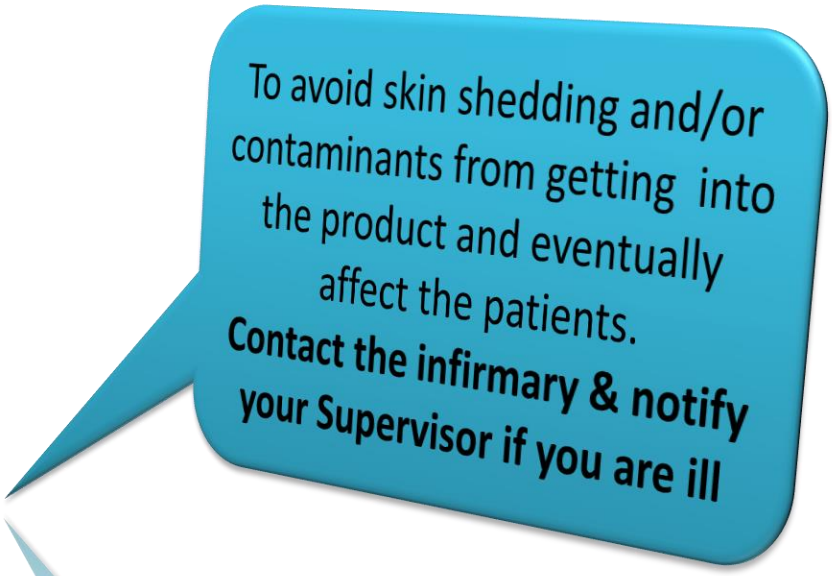



Copyright© 2022 All rights reserved

# Personnel Behavior

**Be Trained & Qualified**

- Basic Microbiology
- Contamination Control
- Personal Hygiene
- Gowning
- Area Procedures




**Be Medically Qualified**

- Absence of Skin Conditions that may represent risk to aseptic processing (e.g., eczema, psoriasis, sun burn).
- No illness that may affect the environment (including but not limited to cough or sneezing, respiratory infections, gastrointestinal infections)

**Follow the Good Aseptic Behaviors in a consistent manner**



Copyright© 2022 All rights reserved

# Facility, Equipment and Process

International Vaccine Institute

Copyright© 2022 All rights reserved

# Facility, Equipment and Process

Sources of contaminants like endotoxin / pyrogen, particulate matter or Microorganisms may come from:

- Personnel
- Material
- Surrounding environment

Facility, Equipment and process should be Designed, Qualified or validated subjected to ongoing verification as applicable according to relevant cGMP requirements.

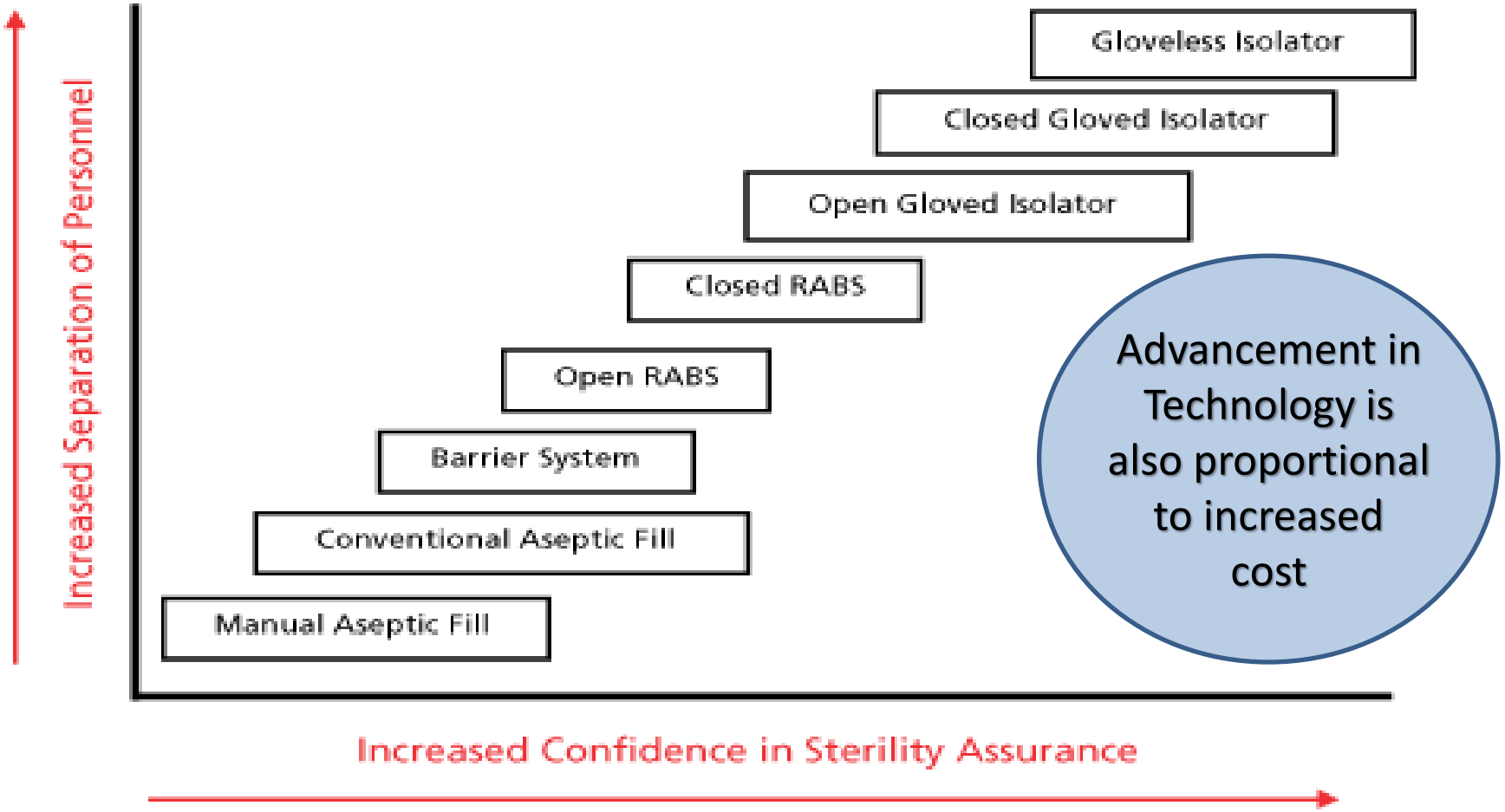
In order to enhance protection of product from any extraneous sources of contamination, appropriate technologies may be used like

- RABS,
- Isolators,
- Robotic systems,
- Rapid / alternative methods and
- Continuous monitoring systems

Copyright© 2022 All rights reserved

# Facility, Equipment and Process

## Use of Technology for Increased Sterility Assurance with increased separation of personnel




Source: Achieving Balance in Sterile Product Manufacturing, December 2, 2015,James E. Akers, James P. Agalloco, Pharmaceutical Technology ,' Pharmaceutical Technology-12-02-2015, Volume 39, Issue 12, Pages: 36–41



Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

EUROPEAN
COMMISSION

Brussels, 22.8.2022
C(2022) 5938 final

**GUIDELINES**

**The Rules Governing Medicinal Products in the European Union**
**Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use**

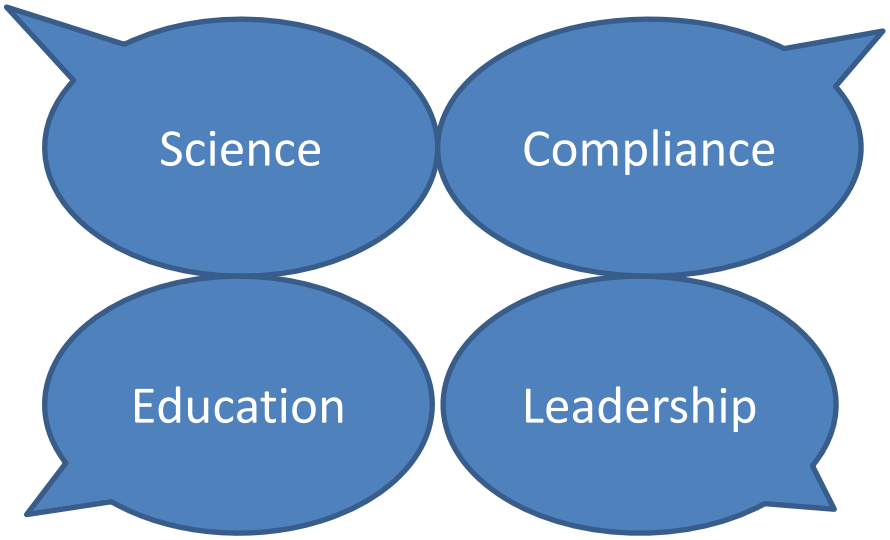


Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

**New Technology,**
First major review since inception




**Regulatory and Industry pe rception of risk**

- Global supply chain
- Clarification on expectati on
- Concern on noted GMP deficiencies
- Alignment on ICH Q9 & Q10

**Internal Education program not linked to risk**

- Lack of details
- Lack practice
- Lack of understanding and know how
- Lack of proficiency testing

**Regulatory and Industry pe rception of risk**

Turnover of expertise
Commercial imperative



Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Science vs standardization: justification vs blindly following rules

Citation data

| | Current version of Annex1 | Draft rev12 of Annex1 |
|---|---|---|
| RISK | 20 | 100 |
| JUSTIFY | 1 | 32 |
| STRATEGY | 0 | 48* |

* Including 42 specific citations of Contamination Control Strategy (CCS)

Contamination Control Strategy: *Risk, Justification, Strategy*



Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## What are the Key Messages..?

1. Quality Risk Management to ICH Q9
2. Effective Root Cause Analysis and scientifically justifiable product impact assessment
3. Education, not training
4. Criticality of staff behaviours, habits and attitudes
5. Separation of staff from open or critical stages in the process
6. Special considerations for non-mainstream processes



Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Risk identification

### 3 Key Steps

- See it..?
  - Are you seeing it for what it is..?
- Say it..?
  - Does your company culture allow you to articulate the concerns..?
- Sort it..?
  - Are you able to take the appropriate action for long term, sustainable reduction in risk?

**Historical EMP trend, personal qualification, batch failure, APS failure**



Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Consideration for CCS

Use ICH Q9 (RPN=S x O x D) and rank it

Use process flow and map the risk

Access unit against

- Risk of contamination
- Risk of misbranding
- Compliance to guideline

Seek insight and scientific rational/data so that you s ee brutal reality of your un it

Target the priorities & put in place CAPA to reduce RPN

- 1st priority: redesign
- 2nd priority: Better control
- 3nd priority: Better monitoring

Use multidisciplinary team to generate CCS



Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Structure of CCS

| Section | Owner (leading a multi-disciplinary team) | Risk identification methods | Risk Description | Risk Score (RPN = S x O x D) | Proposed SMART CAPA |
|---|---|---|---|---|---|
| a) Plant and Process Design | Engineering Head | Eg Audit, Gemba, OEE, QRM, FMEA, HACCP | Individual description of key risks.<br><br>Individual description of current precautions, checks and tests<br><br>Individual description of the key concerns | Scoring of each concern (Score 1,3,7,or 10) | Each priority concern allocated a **Specific, Measurable, Achievable, Realistic and Target oriented CAPA** with owner identified and charter required if needed. |
| b) Equipment and Facilities | Engineering Head | Eg Audit, Gemba, OEE, QRM, FMEA | | | |
| c) Personnel | Production Head | Eg Audit, appraisal, EM, OD | | | |
| d) Utilities | Engineering Head | Eg Audit, Gemba, OEE, QRM, FMEA | | | |
| e) Raw Materials & IPCs | QA Head | Eg Supplier maps, SQM, VMP | | | |
| f) Containers & Closures | Technical Services Head | Eg CCI, validation, design, testing | | | |



Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Structure of CCS

| Section | Owner (leading a multi-disciplinary team) | Risk identification methods | Risk Description | Risk Score (RPN = S x O x D) | Proposed SMART CAPA |
|---|---|---|---|---|---|
| g) Vendor Approval | Purchasing | Eg Audit, SQM, business continuity | Individual description of key risks.<br><br>Individual description of current precautions, checks and tests<br><br>Individual description of the key concerns | Scoring of each concern (Score 1,3,7,or 10) | Each priority concern allocated a **Specific, Measurable, Achievable, Realistic and Target oriented CAPA** with owner identified and charter required if needed. |
| h) Outsourcing | QA Head | Eg Audit, SQM, supplier appraisal | | | |
| i) Process Risk Assessment | Technical Services Head | Eg, HACCP, FMEA, periodic quality review | | | |
| j) Process Validation | Technical Services Head | Eg VMP, Audit, CPP review, CPV | | | |
| k) Planned Preventive Maintenance | Engineering Head | Eg OEE, PPM records, reliability analysis, backups | | | |
| l) Cleaning & Disinfection | QC Microbiology | Eg EM, periodic reviews, QRM | | | |



Copyright© 2022 All rights reserved

# EU GMP Annex 1 (Draft)

## Structure of CCS

| Section | Owner (leading a multi-disciplinary team) | Risk identification methods | Risk Description | Risk Score (RPN = S x O x D) | Proposed SMART CAPA |
|---|---|---|---|---|---|
| m) Monitoring | QC Microbiology | Eg Audit, periodic reviews, recurring concerns | Individual description of key risks.<br><br>Individual description of current precautions, checks and tests<br><br>Individual description of the key concerns | Scoring of each concern (Score 1,3,7,or 10) | Each priority concern allocated a **Specific, Measurable, Achievable, Realistic and Target oriented CAPA** with owner identified and charter required if needed. |
| n) Prevention, trending, investigation, root cause analysis and CAPA | QA Head | Eg Tools, periodic quality review, analysis of GMP deviations, human error, recurring deviations, CAPA effectiveness checks | | | |
| o) Continuous improvement | QA Head | Eg Technology advances, changes to cGMP, regulatory surveillance | | | |



Copyright© 2022 All rights reserved

# Facility, Equipment and Process

Principles of Quality Risk Management should be used to manage Process, Equipment, Facility and manufacturing activities in order to proactively identify and manage risks

QRM priorities should include:

1. Design of facility, Equipment and Process
2. Implementation of well designed procedures
3. Application of monitoring systems to verify that design and procedures are correctly implemented

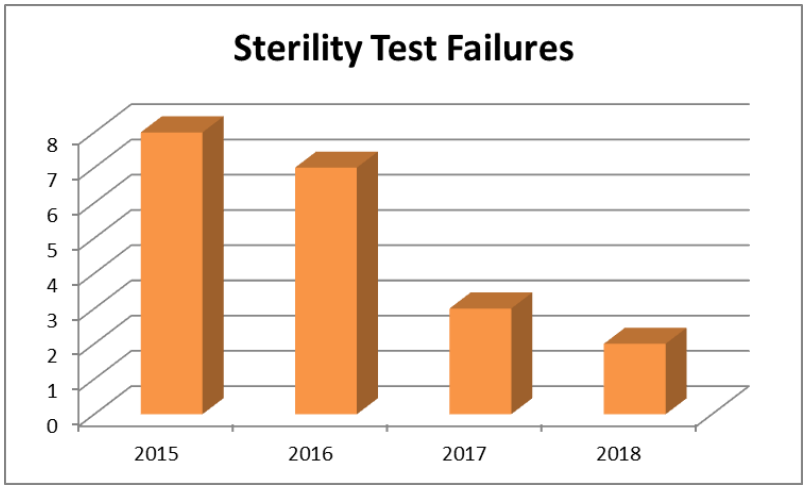
CCS- Contamination control strategy should be implemented across the facility to define all critical control points and to assess effectiveness of controls – Design, procedural, technical and organizational.

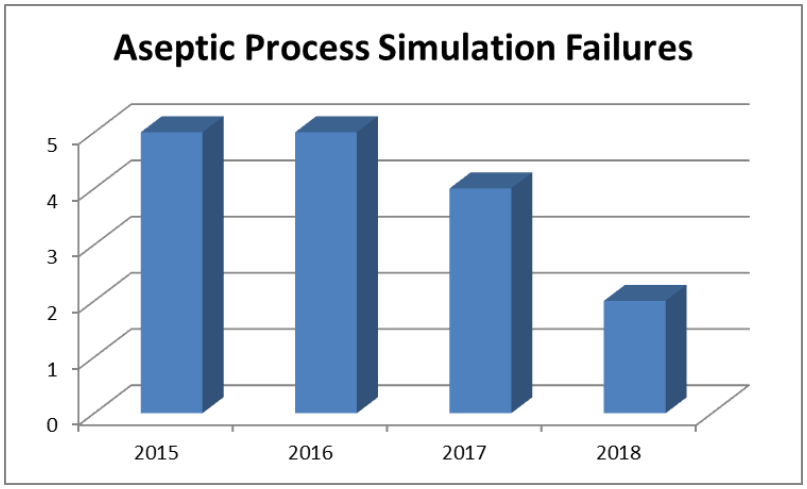


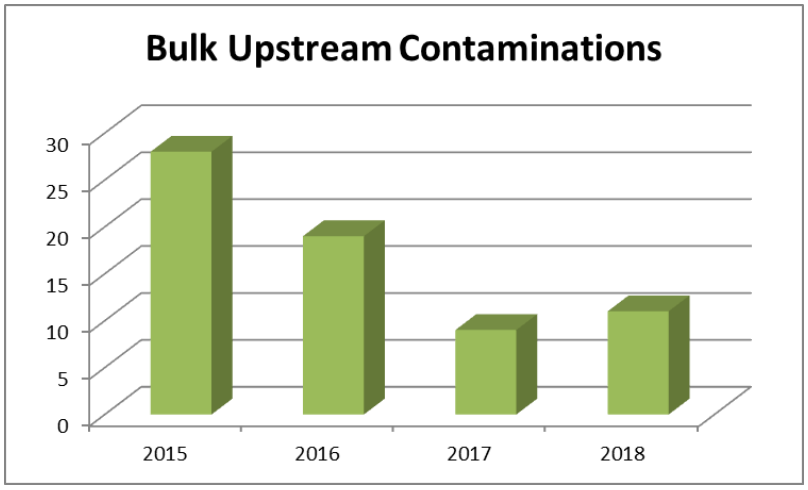
Ref: EU Guidelines for GMP Annex1

Copyright© 2022 All rights reserved

# Final target consideration




Getting better – but the target for all three should be ZERO

Ref: EU Guidelines for GMP Annex1





Copyright© 2022 All rights reserved

# Facility, Equipment and Process

- Assess capability of the process to produce sterile products reproducibly.
- Assess vulnerability to microbial contamination
- Demonstrate that the aseptic operating practice and procedures are appropriate
- Evaluate aseptic processing personnel practices
- Qualify/requalify or disqualify personnel
- Compliance with cGMPs and regulatory expectations



Reference Link -https://www.pda.org/docs/default-source/website-document-library/chapters/presentations

Copyright© 2022 All rights reserved

# Facility, Equipment and Process

## Aseptic Process Simulation

Process simulation tests should be performed as part of validation by running "3" consecutive satisfactory simulation tests

These tests should be repeated at defined intervals and after any significant modification to the HVAC system, equipment or process.

Process simulation tests should incorporate activities and interventions known to occur during normal production as well as the worst-case situation.

The process simulation tests should be representative of each shift and shift changeover to address any time-related and operational features.

Reference: WHO TRS 961 Annex6

Copyright© 2022 All rights reserved

# Facility, Equipment and Process

The number of containers used for media fills should be sufficient to enable a valid evaluation.

| Small Batches | Filling 5000 to 10000 units | Filling >10000 units |
| --- | --- | --- |
| Fill Number of containers equal to batch size | One Contaminated unit results in investigation<br>Consider repeat | One contaminated unit results in investigation |
| Zero growth | Two contaminated units -Revalidation | Two contaminated units -Revalidation |



Reference: WHO TRS 961 Annex6

Copyright© 2022 All rights reserved

# References


- Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 1 Manufacture of Sterile Medicinal Products
- World Health Organization WHO Technical Report Series, No. 961, 2011
- Technical Report No.22, (Revised 2011) Process Simulation for Aseptically Filled Products
- ISPE Glossary
- Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- PDA Letter: Contamination Control Strategies: A Path for Quality & Safety, Aseptic Processing & Sterilization, May 18, 2022 by Subrata Chakraborty, Gxpfont Consulting Group and Hal Baseman, ValSource, Inc.
- Achieving Balance in Sterile Product Manufacturing, December 2, 2015 James E. Akers, James P. Agalloco, Pharmaceutical Technology, Pharmaceutical Technology-12-02-2015, Volume 39, Issue 12, Pages: 36–41




Copyright© 2022 All rights reserved

# Q&A



International Vaccine Institute

Copyright© 2022 All rights reserved

# Personnel Behavior

***Identify the wrong behaviors in the pictures provided***

***&***

***Identify what can be the impact to the product and the patient***

Copyright© 2022 All rights reserved

# Personnel Behavior

**What is wrong here? What  can the impact to product & Patients be? What is the Good behavior?**

Copyright© 2022 All rights reserved

# Personnel Behavior

**What is wrong practice here? What is impact? What is good behavior?**

Copyright© 2022 All rights reserved

# Personnel Behavior

**What is wrong practice here? What is impact? What is good behavior?**

Copyright© 2022 All rights reserved