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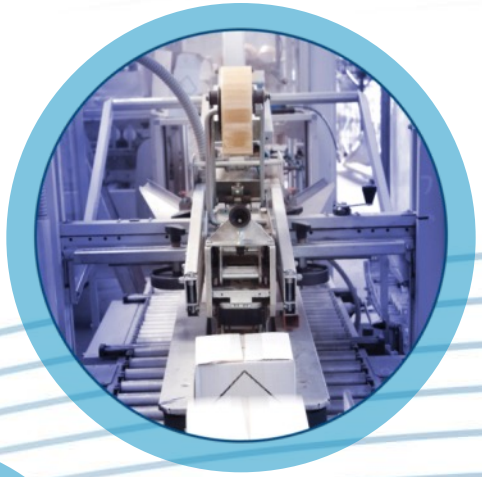
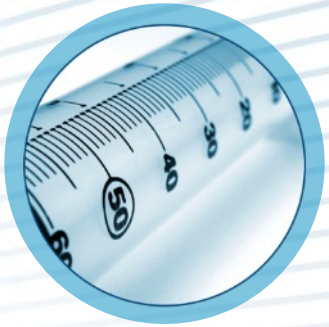
Aspects of Clean Room Concepts and Good Aseptic Working Practices



By Guenther Gapp

14 September 2023



Selected Aspects about

- Aseptic Processing vs. Terminal Sterilization
- Conventional Cleanroom concepts/ Aseptic Filling
  - First Air Concept
- RABS systems and Isolators
  - The difference
  - What´s important to consider
- Good Aseptic Working Practices
  - General Rules
  - Golden Rules & Pictures and Videos

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Terminal ST <-> Aseptic Processing

Ways to produce sterile products

Not stable against heat/ irradiation sterilization

Terminal sterilization

Product containers are filled and sealed under high-quality environmental conditions designed to minimize contamination, but not to guarantee sterility.

Product in its final container is subject to a sterilization process such as heat or irradiation.

Aseptic processing

- Drug product, container, and closure are subject to sterilization separately, and then brought together.
- Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high –quality environment.

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Definition

Aseptic Processing

WIKIPEDIA: Aseptic processing is the process by which a sterile (aseptic) product (typically food or pharmaceutical) is packaged in a sterile container in a way that maintains sterility.

The objective of aseptic processing methods is to assemble previously sterilized product, containers and closures within specially designed and controlled environments intended to minimize the potential of microbiological or particulate contamination.

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Explain in classroom

- What do we require …

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Cleanroom Classes

Source:
PDA TR 62

ISO 14644	US FDA (Aseptic Processing Guidance)	USP <1116>	EU Annex 1 and WHO	Japan (Aseptic Processing Guidance)	JP XVI
ISO 5 ≥0.5 μm 3520 ≥5 μm 29	**ISO 5 /Class 100**[1] 3520[2] not specified	**ISO 5/Class 100** 3520 not specified	**Grade A** **Grade B (at rest)** 3520 20[3]	**Grade A** **Grade B (at rest)** 3520 20[3]	**Grade A** **Grade B (at rest)** 3520 not specified
ISO 7 ≥0.5 μm 352,000 ≥5μm 2,900	**ISO 7/Class 10,000** 352,000 not specified	**Class 10,000** 352,000 not specified	**Grade B (operation)** **Grade C (at rest)** 352,000 2,900	**Grade B (operation)** **Grade C (at rest)** 352,000 2,900	**Grade B (operation)** **Grade C (at rest)** 352,000 not specified
ISO 8 ≥0.5 μm 3,520,000 ≥5μm 29,000	**Class 100,000** 3,520,000 not specified	**Class 100,000** 3,520,000 not specified	**Grade C (operation)** **Grade D (at rest)**[4] 3,520,000 29,000	**Grade C (operation)** **Grade D (at rest)**[4] 3,520,000 29,000	**Grade C (operation)** **Grade D (at rest)**[4] 3,520,000 not specified

1. Class 100 and Grade A are defined as requiring unidirectional flow by all applicable guidelines
2. Class titles for US FDA and USP indicate equivalent particle counts per ft^3
3. ISO 4.8 based upon reduced limit for particles ≥5 µm
4. Grade D operational particulate counts are dependent upon the operation and are not defined by any guideline

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EU Cleanroom Classes

For Classification: EU Annex 1

4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 µm should be measured. This measurement should be performed both at rest and in simulated operations in accordance with the limits specified in Table 1.

Table 1: Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

[a] Classification including 5µm particles may be considered where indicated by the CCS or historical trends.
[b] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

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EU Cleanroom Classes

Routine Monitoring : EU Annex 1

9.15 The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5.

Table 5: Maximum permitted total particle concentration for monitoring.

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

[a] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

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EU Cleanroom Classes and Operations

Table 4: Examples of operations and grades for aseptic preparation and processing operations

Grade A	- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	- Preparation of solutions to be filtered including sampling and dispensing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

EU Annex 1

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Critical Area/ Grade A

Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.

EU Annex 1, 2022

Critical Area - An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas such as the grade A area or a closed system.

FDA Guide, 2004

Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area.

EU Annex 1, 2022

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Definitions

Unidirectional Airflow (First Air)

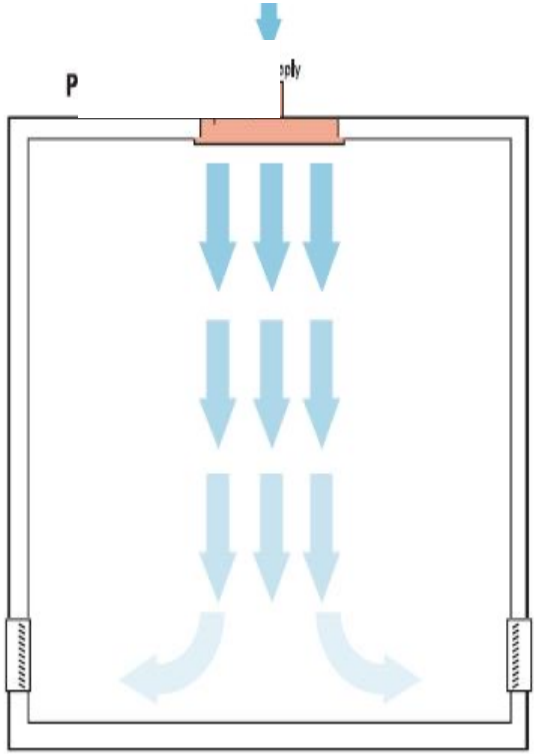

Image source: Price Industries Limited, 2014, http://pricecriticalcontrols.com/content/uploads/assets/literature/catalogs/catalog-pages/section%20e/lfdc.pdf

Annex 1:

First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

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First Air (First Work Location)

The work location first in the path of HEPA filtered air (8).

The first air concept refers to what the air touches “first”. There are objects or persons in the air flow path between the HEPA filter diffuser and the product or product contact surfaces, including equipment frames, sensors, light fixtures (M. Polen)

8. NASA-TM-X-66397, NHB-5340.2; *NASA Standards for Clean Rooms and Work Stations for the Microbially Controlled Environment*; National Aeronautics and Space Administration: 1967. ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/19700078206_1970078206.pdf (accessed Jan. 25, 2013).

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EU Annex 1

First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

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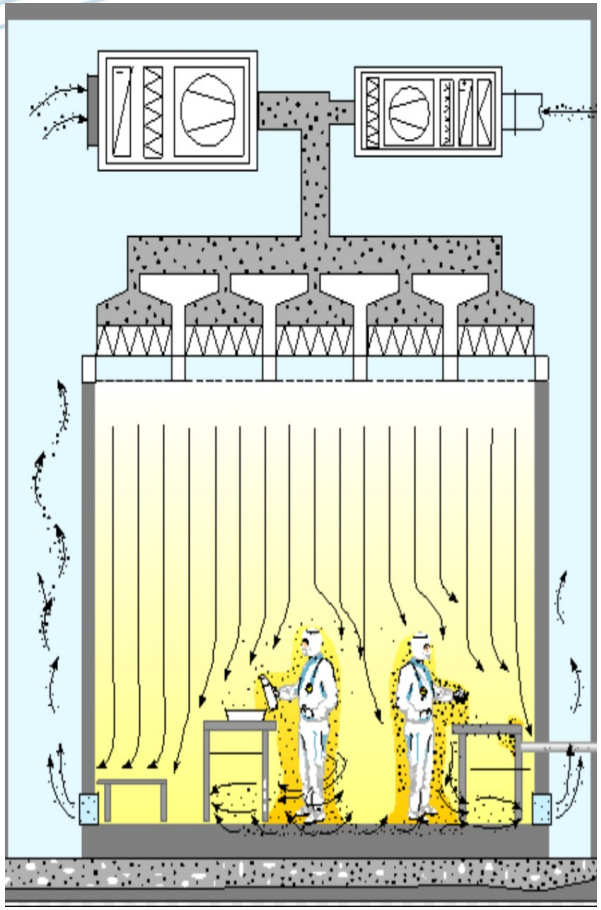
Unidirectional Cleanroom and Cabinet



Source: Wikipedia

Note: UDF can also be horizontal

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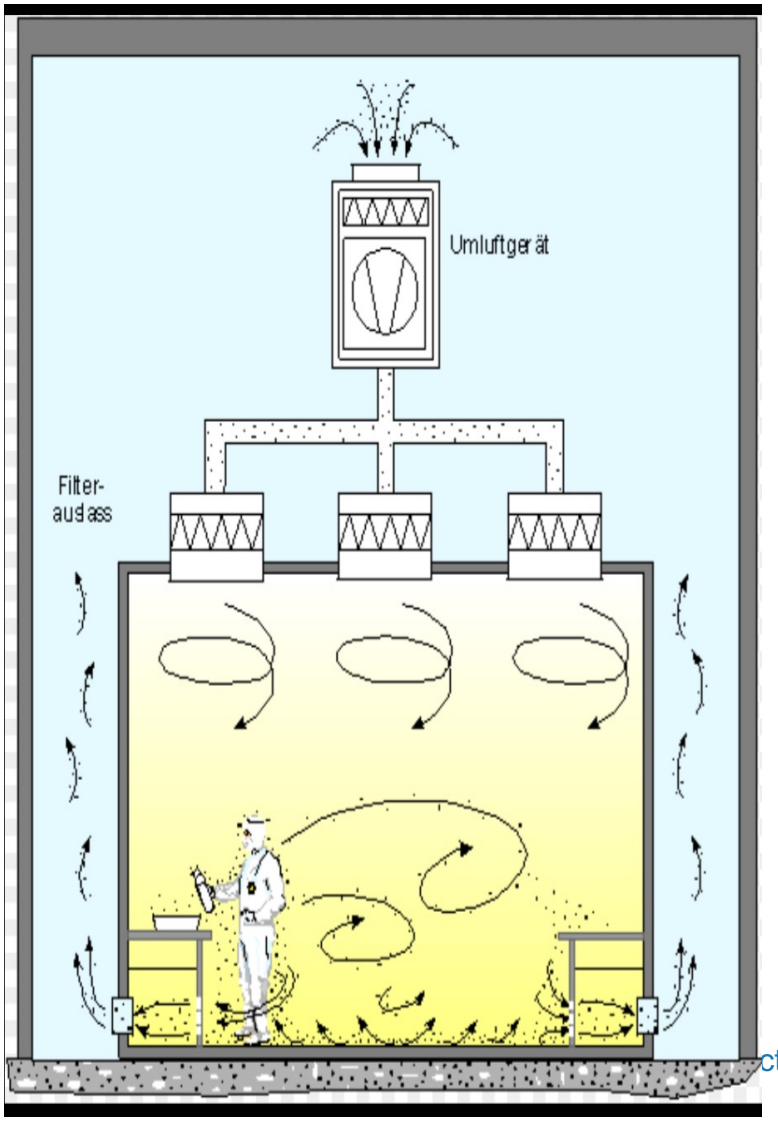
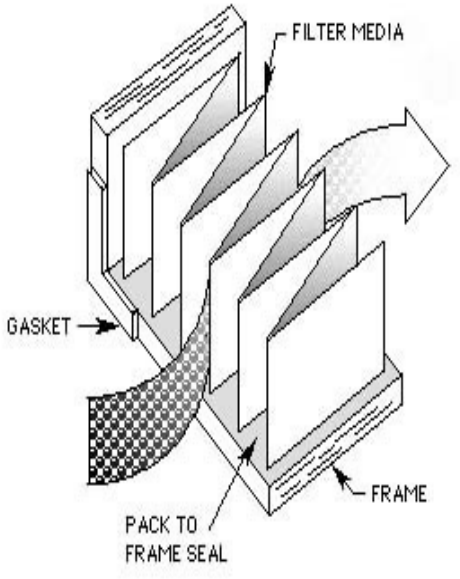
Turbulent Cleanroom: Grade C or D

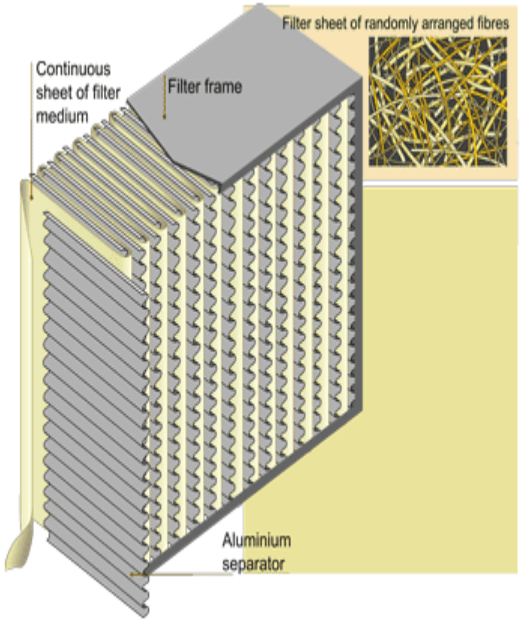


Source: Wikipedia

HEPA Filters (Cont'd)



- Rigid frame with filter pack
- Continuous pleated sheet filter media
- All-glass paper which is composed of an e number of randomly oriented micro-fibers
- Retains 99.97% particles greater than 0.3 microns



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Airflow Visualization (Smoke) Studies

- Static and dynamic
- Protocol and Document Cover
  - Set- Up , Interventions, equipment, operator movement, opening barriers, doors, pass-throughs, grade B smoke profile
- Used to design/ assess ISO 5 interventions
- Used as a training tool
- Review and draw conclusions
- Is a regulatory requirement to do

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Smoke Study Video
(FDA requires now more angles)

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Understanding the Types of Aseptic Processing

- **Filing Technologies**
  - Conventional Filling Lines with curtains/ doors / glove ports
  - Barrier Systems: RABS
  - Isolator systems

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Barriers : CURTAINS – Problems ☹

Curtains

- Flexible
- Separate filling line from operators
- Preserve laminar flow

Consider:

- Length
- Cleanliness

Image source: Terra Universal, Inc., https://m.terrauniversal.com/cleanrooms/clean-rooms-curtains.php, web accessed May 16, 2018

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Barriers (continued)

Restricted Access Barrier Systems (RABS)

- Rigid
- Separate filling line from personnel

Consider:

- Airflow
- Glove ports

Image courtesy of Howorth Air Technology

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Definition RABS (Restricted Access Barrier System) EU GMP Annex 1

Restricted Access Barrier System (RABS) – System that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined conditions.

Active RABS: Integral HEPA – filtered air supply

Passive RABS: Air suppy by ceiling mounted HEPA – filters

Open RABS: Where there are vents in the barrier that allow air move from grade A to the grade B area

(Note: The area inside the RABS is classified as "Class A," and the surrounding is classified as "Class B".)

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Passive Restricted Access Barrier System

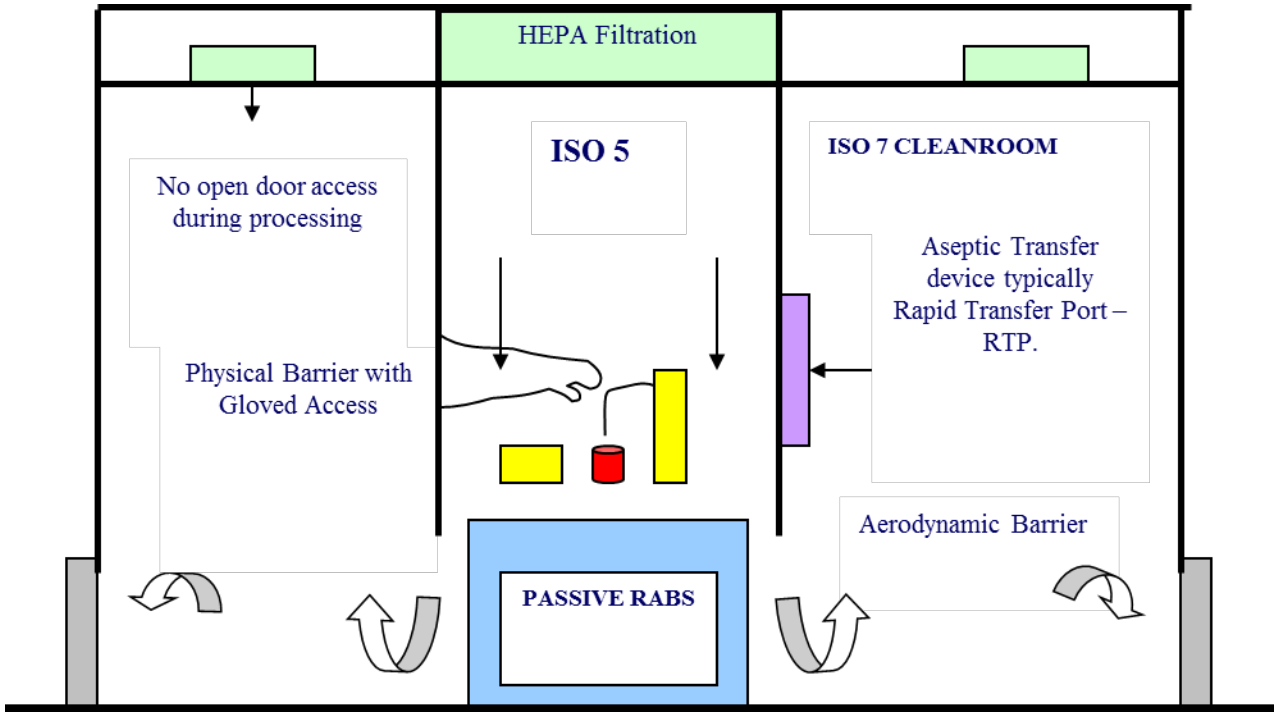

Image Courtesy Bioquell, Inc.

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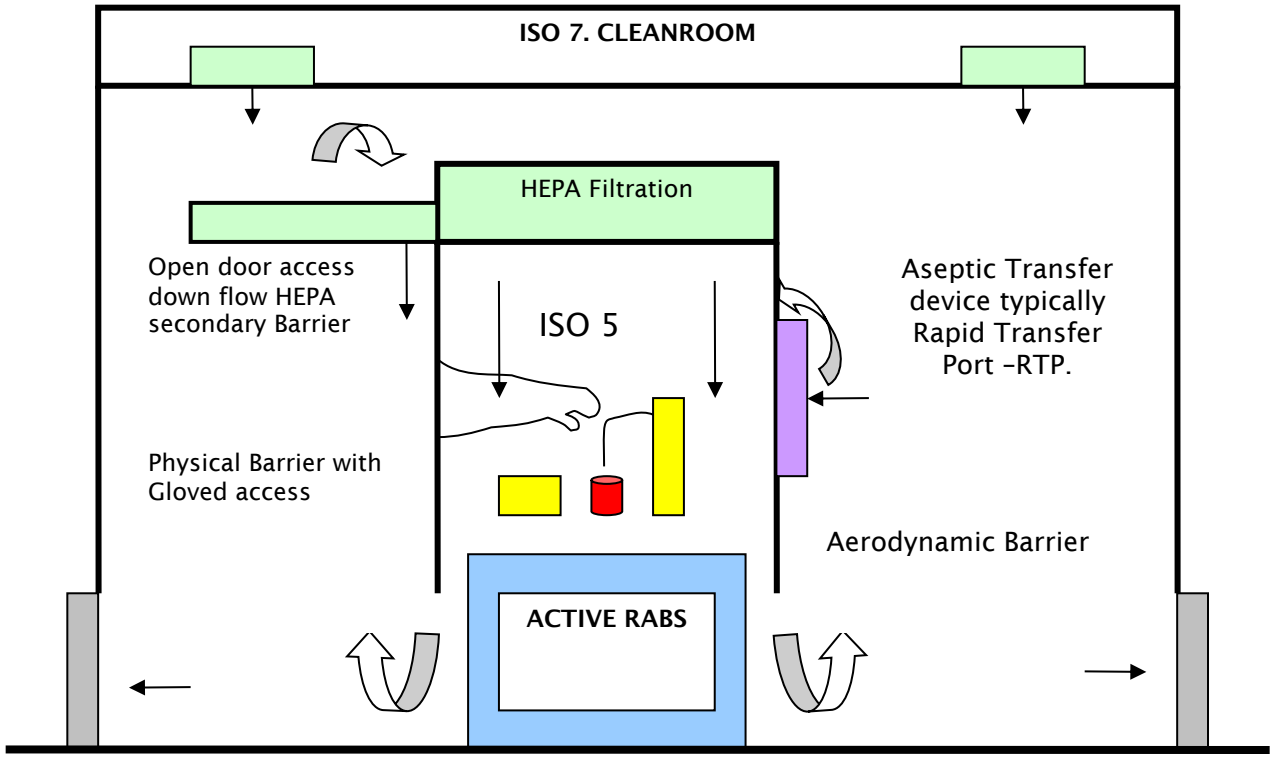
Active Restricted Access Barrier System



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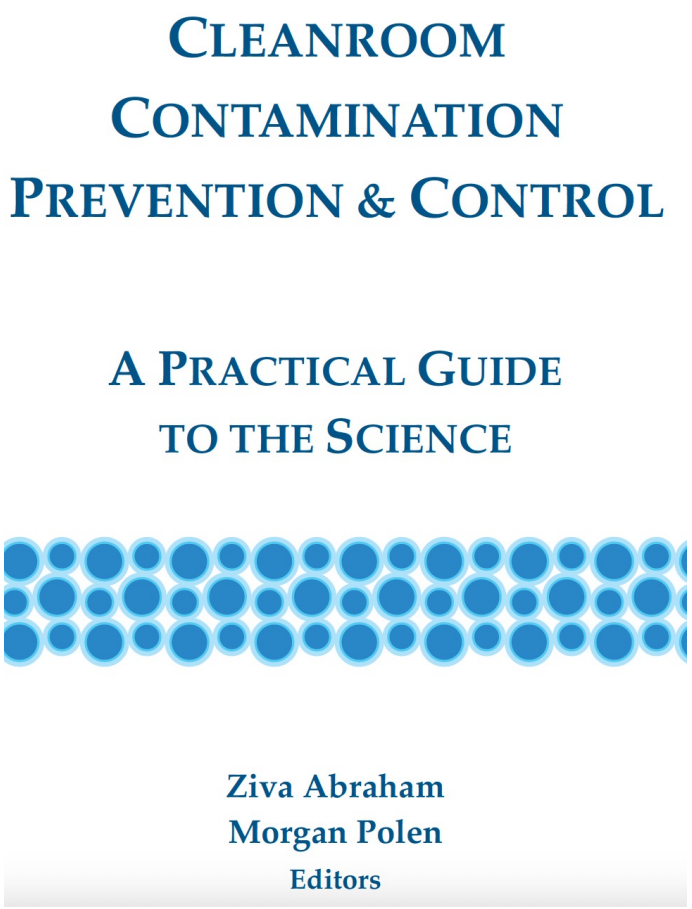
Good Book :



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Open RABS

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Open RABS

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Open RABS

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Air Flow at work bench

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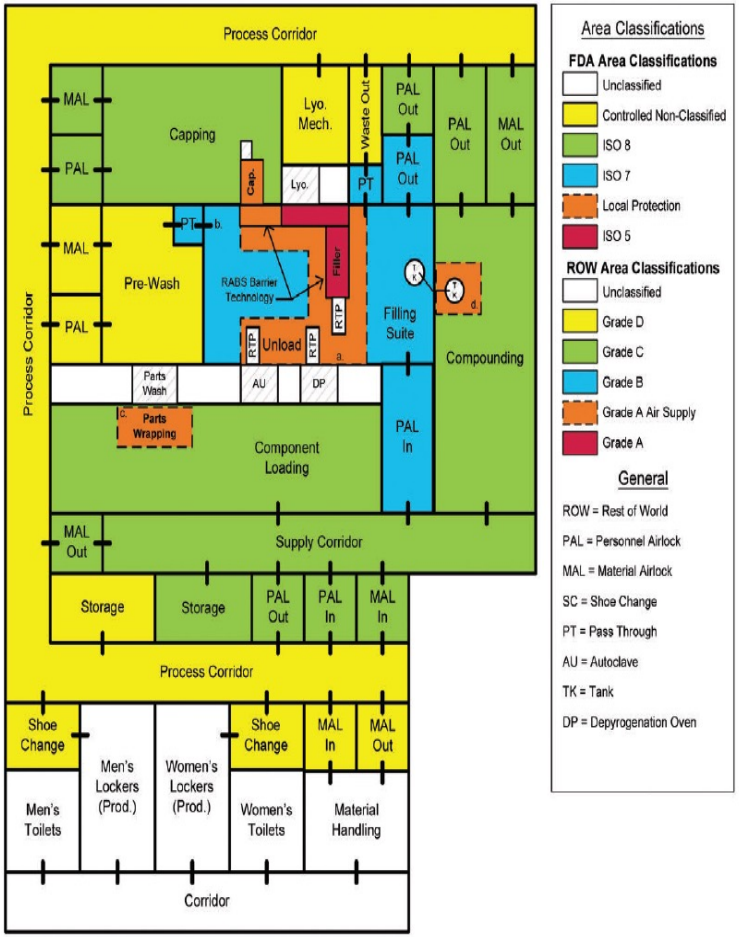
Example Layout RABS

Figure 4.4: Diagram of a Small Scale Open System Aseptic Fill with RABS



What are common layout mistakes ?

Source: ISPE 2018

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Pharmaceutical Isolators

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Question: What are the differences between

Isolator

and

RABS ?

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Isolator: Annex 1 Definition

Isolator – An enclosure capable of being subject to reproducible interior bio-decontamination, with an internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators:

i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

ii. Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.

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Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators

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Extracts from my PDA Presentation / 2021

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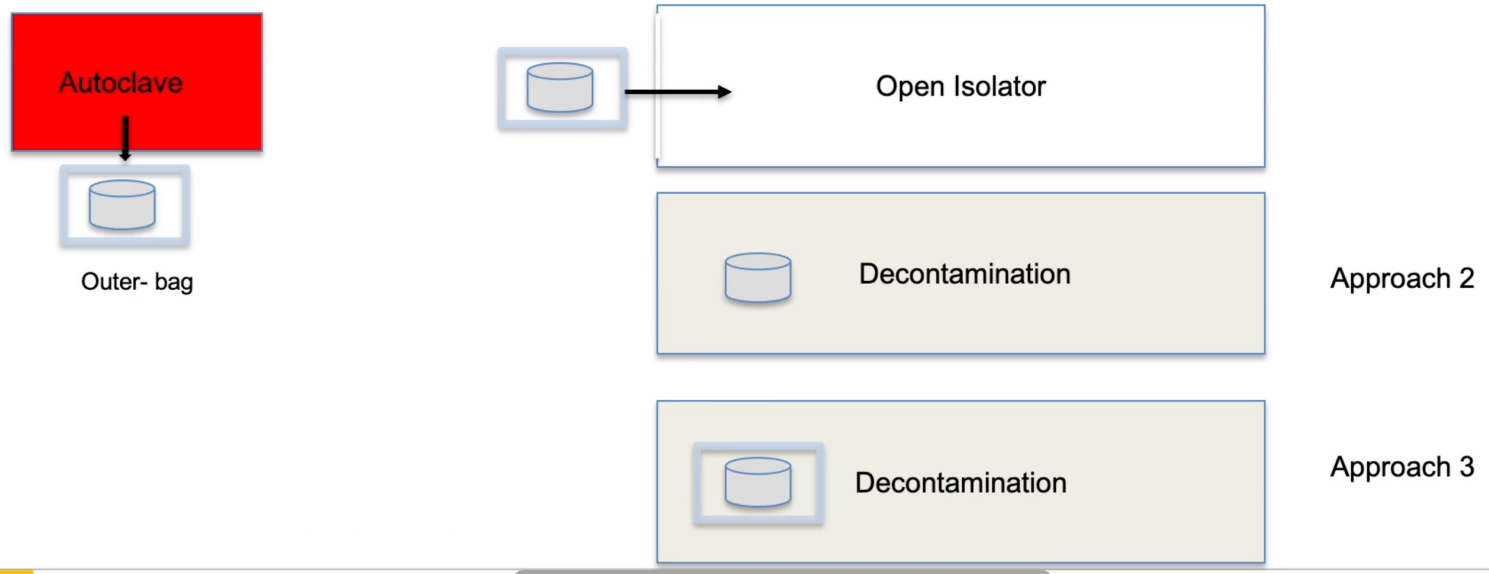
TOPIC 6: MATERIAL TRANSPORT AND LOADING OF ISOLATORS

***Approach 2**: Equipment is sterilized and transferred into isolator through a classified environment, assembled, decontaminated*
***Approach 3:** Equipment sterilized and transferred into isolator through non-Grade A/ISO 5 environment, decontaminated, assembl*



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TOPIC 6: MATERIAL TRANSPORT AND LOADING OF ISOLATORS

***Approach 4**: Equipment is periodically sterilized and decontaminated during the isolator decontamination cycle*

Approach 4: Equipment is periodically sterilized and decontaminated during the isolator decontamination cycle

- Where it is not possible or practical to remove, sterilize, and transfer equipment into the isolator (e.g., large equipment), the equipment should remain assembled, be cleaned using a validated cleaning process,* and be decontaminated in place inside the isolator using a validated decontamination process (e.g., VHP). The frequency for large equipment sterilization should be risk based.
- The validation of the decontamination process should include assurance that the indirect product contact surfaces have been rendered incapable of contaminating sterile surfaces or components.
- Additional precautions should be taken as part of the cleaning and handling process to ensure that oily residues or other substances that can reduce the effectiveness of the decontamination process are removed prior to or not present during the decontamination process.
- The bioburden of the equipment indirect product contact surfaces should be controlled, and precautions should be taken to limit their exposure to potential sources of microbiological contamination during maintenance, handling, and use.

* The cleaning process should be qualified to remove substances that inhibit the effectiveness of the decontamination process, i.e., silicone, oily residues, and fingerprints.

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TOPIC 7: CLEANING, DISINFECTION, DECONTAMINATION: CYCLE DEVELOPMENT AND VALIDATION : 7 Questions

- Q7-7: How should multiple biological indicators (BIs) be used and evaluated during VHP decontamination cycle development and validation?

The exposure of multiple, usually three, BIs at given locations may be used to evaluate and quali the effectiveness of the decontamination cycle.

The logarithmic reduction of surface contamination may be determined through empirical evide mathematical formula, experiment, most probable number (MPN) of surviving spores, and/or d evaluation.

Where all BIs at a location are deactivated or killed, a more efficient decontamination effect and reduction level may be assumed. Where one or more of the BIs are not deactivated, a less effectiv decontaminating cycle or log reduction level may be assumed.

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TOPIC 9: BEST PRACTICES IN ASEPTIC OPERATIONS :

- Q9-1: Is it necessary to use the same aseptic technique and practices when performing interventions in isolators and conventional fill lines?

Proper aseptic technique and good working principles and practices, as applied in conventional Grade A/ISO 5 cleanrooms, should also be followed in isolator operations where possible. Risk assessments should be used to provide information for making decisions related to the performance and control of interventions and procedures in the isolator.

The isolator equipment and processes should be designed to allow for proper aseptic technique and practices, where reasonably possible. Where equipment and processes cannot be designed in such a way, additional controls should be considered to mitigate risk of contamination, e.g., use of sterile devices.

pda.org

TOPIC 9: BEST PRACTICES IN ASEPTIC OPERATIONS :

- Q9-2: Should interventions that disrupt unidirectional airflow in the isolator in proximity to or above exposed sterile product, product contact surfaces and indirect product contact surfaces be permitted ?

The isolator, the placement of isolator glove positions, and the aseptic operation should be designed to avoid or minimize the disruption of unidirectional air flow above or in the proximity of exposed sterile product or product contact surfaces.

A risk assessment should be performed to determine the level of risk for each specific intervention with regard to a potential contamination created by interventions, e.g., adjusting of filling nozzles or assembling stopper bowls.

If the risk assessment shows that there is low or no risk of contamination added by the intervention, then disrupted or turbulent airflow resulting from the intervention within a properly designed and maintained isolator may be acceptable.

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Best Practices in Aseptic Operations

Note: are applicable also for RABS and Isolators !

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What can go wrong with isolators ?

- Cleaning of isolator inside surfaces not done properly
- VHP – decontamination
- Inaccessible surfaces inside
- Loading if Material intro isolator (operators/ integrity of bags)
- RTP´s and alpha/beta ports
- Integrity of isolators and gloves
- Non- sterile materials introduced
- Pressure drops
- Aseptic Working Practices
- ….

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Aseptic Processing: it´s a lot about People !

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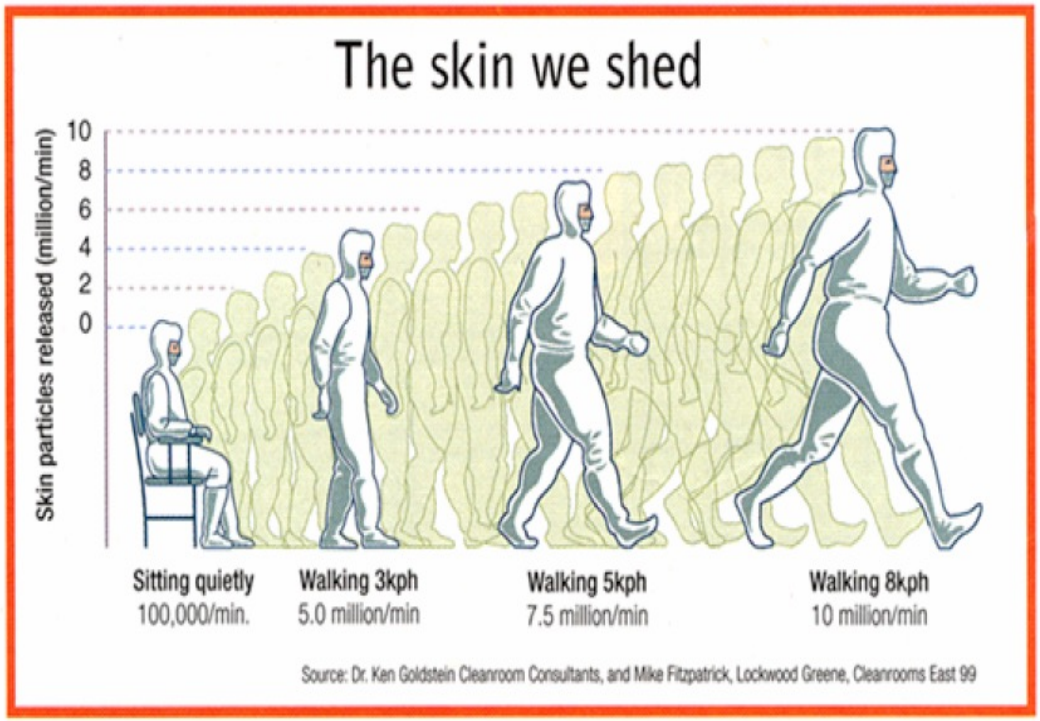
Personnel … WE SHED SKIN FLAKES (and therefore also BACTERIA)



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Video: Walking in cleanroms

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Movement

- Impact of movement
  - Flaking skin cells
  - Expelled with gown bellowing
  - Microorganisms “wicked” through saturated gown/mask
- Move slowly
  - Walking, turning, limit gesturing
  - Be conscious of airflow

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Video:

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Some potential routes for Transfer of Contamination

- **Airborne**
  - Sourced from personnel and machines
  - Small particles are dispersed (e.g. skin cells)
- **Contact**
  - Contaminated gloves, machinery, clothing, packaging
  - Direct and indirect product contact surfaces by contaminated surfaces

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Aseptic Operations – Personnel Practices

- FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (2004):

  "Some of the techniques aimed at maintaining sterility of sterile items and surfaces include:

  Contact sterile materials only with sterile instruments.

  - Sterile instruments should always be used in the handling of sterilized materials. Between uses, sterile instruments should be held under Class 100 (ISO 5) conditions and maintained in a manner that prevents contamination (e.g., placed in sterilized containers). Instruments should be replaced as necessary throughout an operation.

  - After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces with any part of their gown or gloves."

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Aseptic Operations – Personnel Practices (Cont'd)

- FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (2004) :

  - Move slowly and deliberately: Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended cleanroom design and control parameters.

  - Keep the entire body out of the path of unidirectional airflow: Unidirectional airflow design is used to protect sterile equipment surfaces, container-closures, and product. Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility.

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Aseptic Operations – Personnel Practices (Cont'd)

- FDA Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (2004):
  - *Approach a necessary manipulation in a manner that does not compromise sterility of the product.*
  - A proper aseptic manipulation should be approached from the side and not above the product (in vertical unidirectional flow operations).
  - Operators should refrain from speaking when in direct proximity to the critical area.

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Operator Impact

"A well designed, maintained, and operated aseptic process *minimizes personnel intervention*. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases."

… refer to design limitations on the next slide !

FDA Guidance "Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice" 2004.

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Short demonstration in Classroom

- Some Key Principles

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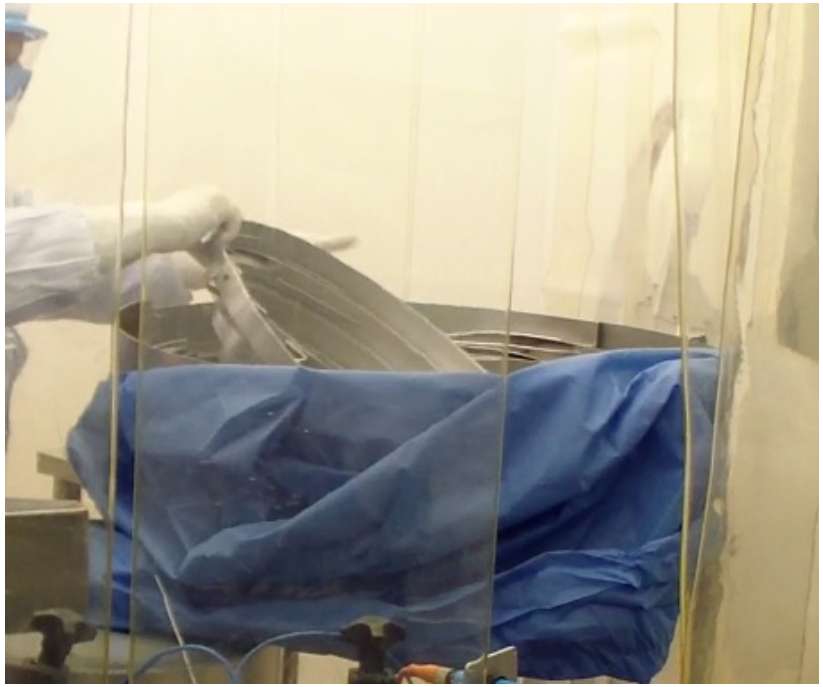
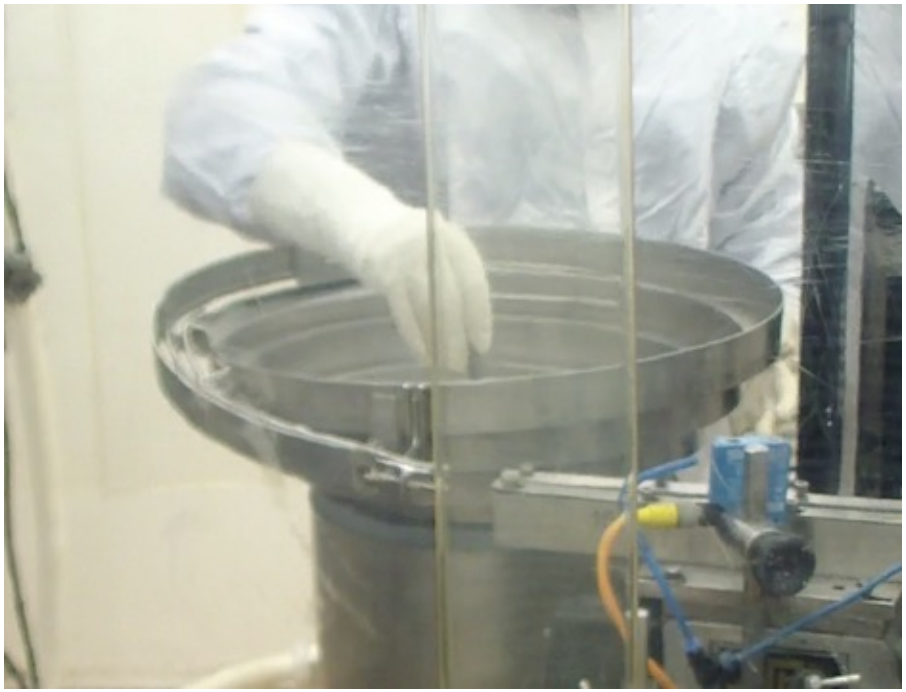
- What´s wrong ?





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Interventions : the „differences …“

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Transfer into grade A

- "Aseptic" and "Support" Operator
- Doctor/ Nurse principle or A/B Operator
- Frequent glove sanitization or change-out
- Double bag method

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Example of: Correct behaviour – no need to have „Hand Up“

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Airflow : Working in UDF

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Video: example how / not to handle filling needles

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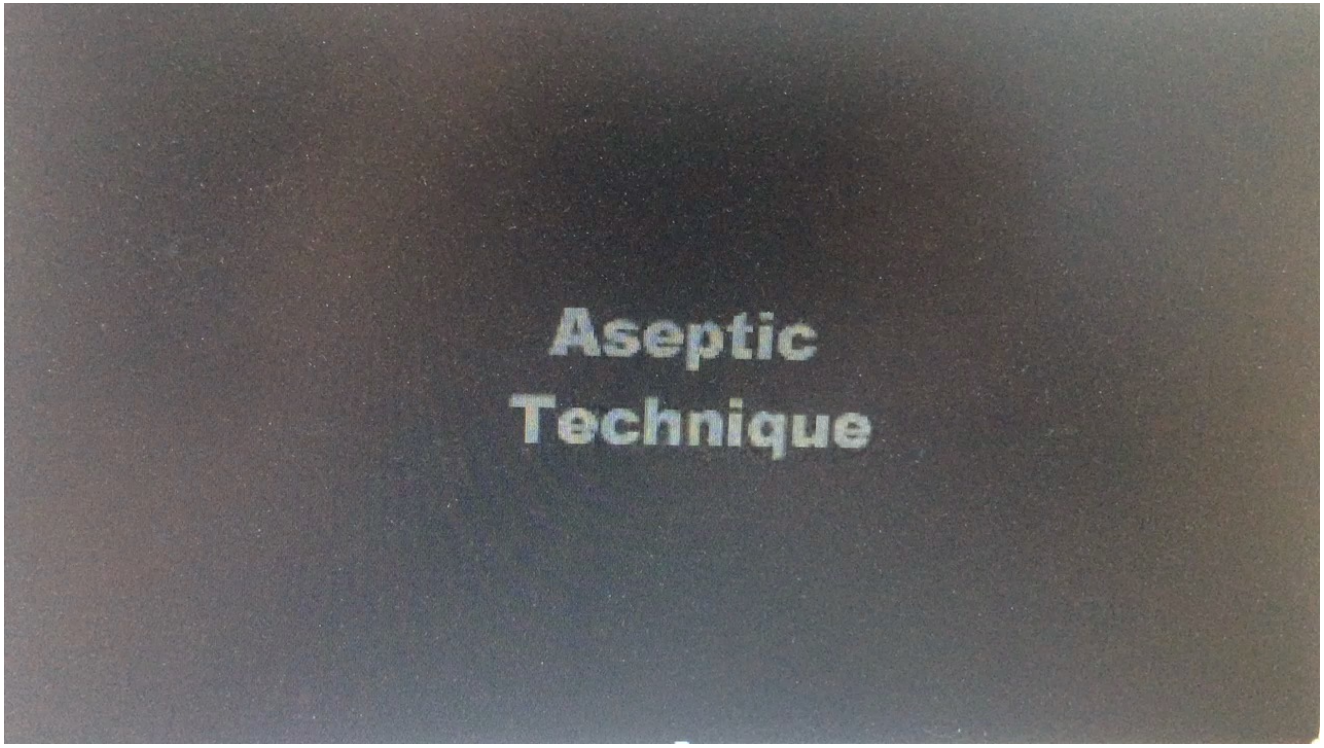
Aseptic Techniques



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Too fast:

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OK ? ….

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OK ?

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OK ?

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OK ?

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OK ?

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OK ?

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OK ?

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WL issues

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MIP Training

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Open Door : No Go !

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Double bag method

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Fingerprint

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Stopper addition

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Stopper addition

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Stopper addition

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Turntable

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Open Door / UDF / Disruption

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Storage of scissors

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RABS door santization before closing

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RABS & Turntable

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Training Video at UF / 2021

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Good Aseptic Technique – Golden Rules !

- Do not reach over or do not disrupt the unidirectional air flow with your body or your gloves (also applicable for RABS gloves): sterile product, and direct product contact parts (e.g. filling needles, open syringes and vials) and indirect product contact surface (e.g. stopper bowl)
- Do not touch Critical Surfaces
- Disinfect gloved hands prior to accessing Grade A area
- Always move slowly and make slow motions (including RABS/ Isolator Gloves)
- Transfer of material into grade A: A/B operator and 2 bag method/ or disinfection of transferred material prior to introduction
- Perform set -up operations from top to bottom, inside to outside
- Do not lean against walls, tables, equipment, doors, carts
- Do not touch the floor or any component that has touched the floor

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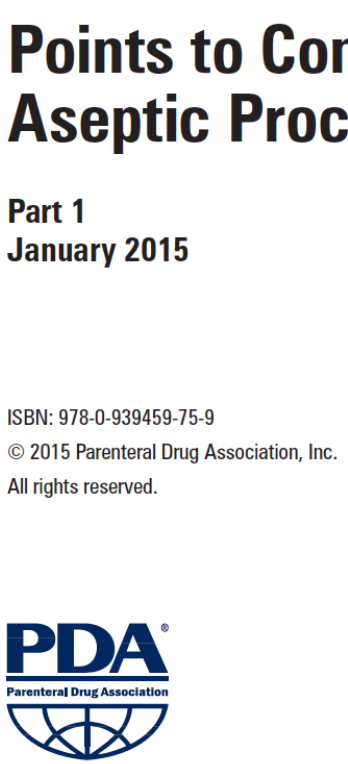
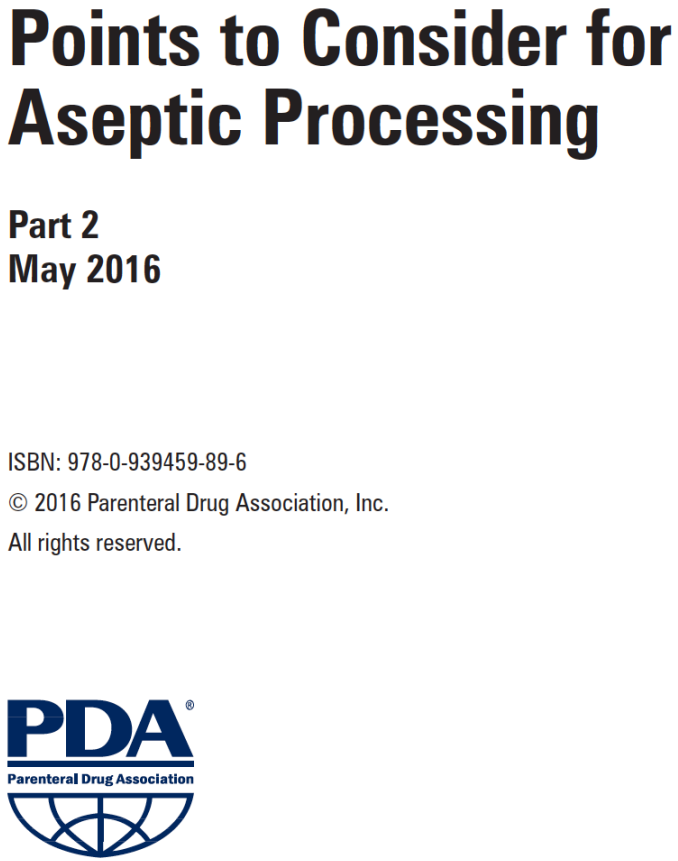
Points to Consider for Aseptic Processing. Part 1 and 2 : highly recommended to read .- under revision !





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Revision

Points to Consider for Aseptic Processing (Revised 2023)

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Do Not Distribute—PDA

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WARNING LETTER Examples

Aseptic Operations – Behaviors

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FDA

"Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b))."

January 26, 2018 Warning Letter cited poor aseptic behavior, such as reaching over open vials and disrupting unidirectional airflow, without removing affected units; failure to include set-up and routine aseptic manipulations and interventions in smoke studies; rejection of integral vials during a media fill that would not have otherwise been removed during production; not all personnel authorized to enter aseptic processing were required to participate in a media fill at least once a year; no procedures for training and qualification of personnel performing examination of media fill units; and lack of active air monitoring in ISO 5 areas.

Also described failure to thoroughly investigate 140 complaints of a particular defect.

www.fda.gov https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm594395.htm 18

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FDA

"Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv))."

May 31, 2018 Warning Letter cited several environmental monitoring plates from ISO 5 and ISO 8 areas which exceeded action limits, and for which no investigations were initiated (and "your firm had reported no results outside limits for over a year prior to the inspection date"); inadequate collection of surface samples, which "had been occurring for approximately 1–2 years"; late and missed stability pulls, for which no investigation was raised; failure to include 15 investigations of product yield failure in annual product reviews.

www.fda.gov https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm609829.htm 21

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"Lack of sterility assurance"

July 10, 2018, FDA alerted health care professionals, patients, veterinarians, and animal owners of a voluntary recall following our observation of insanitary conditions and poor sterile production practices at a particular firm.

Our **follow-up inspection** to a **March, 2017 Warning Letter** found personnel touching non-sterile surfaces without sanitizing their hands or changing gloves prior to returning to the ISO 5 hood; handling components with bare hands while disinfecting those items, prior to placement in the pass through; failure to use a sporicidal disinfectant at the appropriate concentration and contact time; use of non-sterile cleaning wipes in ISO 5; and white residue on the face panel of the HEPA filter supplying air to the ISO 5 area, as well as dirt and residue on the floor of the ISO 7 area. On **June 7, 2018, the firm informed FDA it was ceasing sterile operations**.

www.fda.gov https://www.fda.gov/Drugs/DrugSafety/ucm612911.htm 27

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Common Warning Letter(s) from FDA

- A comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  - All human interactions within the ISO 5 area
  - Equipment placement and ergonomics
  - Air quality in the ISO 5 area and surrounding rooms
  - Facility layout
  - Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)

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Recent Findings from FDA to RABS

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Recent Findings from FDA to RABS

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Recent Findings from FDA to RABS

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Recent Findings from FDA to RABS

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END

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