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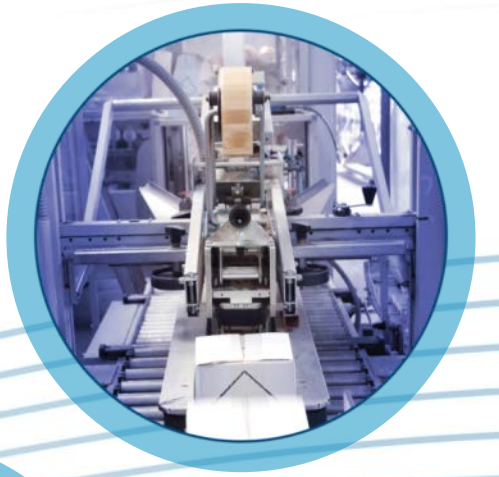
Aspects of Clean Room Concepts and Good Aseptic Working Practices



By Guenther Gapp

Online

18 October 2021

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

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.

Terminal ST ←>. Aseptic Processing

Ways to produce sterile products

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.

Cleanroom

A cleanroom or clean room is a facility ordinarily utilized as a part of specialized industrial production or scientific research, including the manufacture of pharmaceutical items and microprocessors. Cleanrooms are designed to maintain extremely low levels of particulates, such as dust, airborne organisms, or vaporized particles. Cleanrooms typically have an cleanliness level quantified by the number of particles per cubic meter at a predetermined molecule measure.

Source: WIKIPEDIA

Overall Cleanroom Design

- HEPA filters in ceiling
- Exhaust pulls from the floor
- No drains are allowed, no porous materials
- Limited number of flat, surfaces so that particulates have no place to settle
- Seamless and rounded floor to wall junctions
- Floors, walls, and ceilings constructed of smooth hard surfaces that can be easily cleaned
- Limited amount of equipment, fixtures and personnel
- Equipment layout to minimize risk from personnel

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

EU Cleanroom Classes

Table 1: Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates ≥ 0.5 $\mu m/m^3$		Maximum limits for particulates ≥ 5 $\mu m/m^3$	
	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	Not defined[(a)]	29 000	Not defined[(a)]

[(a)] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.

Source:
EU Annex 1, Rev 2020

EU Cleanroom Classes

Table 6: Limits for airborne particulate concentration for the monitoring of non-viable contamination.

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)]

[(a)] For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and on historical data, where applicable.

Source:
EU Annex 1, Rev 2020

Overview about Cleanroom Classes/ Source PDA Global Sterile Guidance/ 2016

Table 3.3.1-1: Clean Room Standards - Airborne Particulate Levels (particles/m^3)

Particle Size	ISO 14644	US FDA (Aseptic Processing Guidance)[a]	EU Annex 1	WHO Annex 4[b]
	ISO 5	ISO 5 /Class 100[c,d]	Grade A Grade B (at rest)	Grade A Grade B (at rest)
≥0.5 µm	3520	3520[e]	3,500	3,500
≥5 µm	29	Not specified	20[f]	20[5]
	ISO 6	ISO 6/Class 1000	NA	NA
≥0.5 µm	35,200	35,200	NA	NA
≥5 µm	290	Not specified	NA	NA
	ISO 7	ISO 7/Class 10,000	Grade B (operation) Grade C (at rest)	Grade B (operation) Grade C (at rest)
≥0.5 µm	352,000	352,000	350,000	350,000
≥5 µm	2,900	Not specified	2,900	2,900
	ISO 8	Class 100,000	Grade C (operation) Grade D (at rest)[g]	Grade C (operation) Grade D (at rest)[g]
0.5 µm	3,520,000	3,520,000	3,500,000	3,500,000
≥5 µm	29,000	Not specified	29,000	29,000

a Measurements always taken during operation

b The PDA TR 13 revision refers to WHO Annex 4 as it was published prior to the WHO Annex 6 adoption. The limits stated in the WHO Annex 4 are the same as those stated in Annex 6

c Class 100 and Grade A are defined as requiring unidirectional flow by all applicable guidelines

d Obsolete U.S. Federal Standard 209E classification added for continuity

e Class titles for US FDA and USP indicate equivalent particle counts per ft3

f ISO 4.8 based upon reduced limit for particles ≥5 µm

g Grade D operational particulate counts are dependent upon the operation and are not defined by any guideline

EU Cleanroom Classes and O

935 **Table 5: Examples of operations and grades for aseptic preparation and processing operations**
936

Grade A	Critical zone for - Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing filter. These connections should be sterilized by steam-in-place whenever feasible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers. - Staging and conveying of sterile primary packaging components. - 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 the Grade A zone (when not in an isolator). - Transport, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into the Grade A zone.
Grade C	- Preparation of solutions to be filtered including weighing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after washing. - Assembly of cleaned components, equipment and accessories prior to sterilization. - Assembly of closed and sterilized SUS using intrinsic aseptic connectors.

937

Source:
EU Annex,
Rev 2020

Critical Area/ Grade A

2435 Critical zone – A location within the aseptic processing area in which product and critical surfaces are
2436 exposed to the environment.
2437

EU Annex 1, rev 2020

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

UDF

2591 Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and
2592 at sufficient speed, to reproducibly sweep particulates away from the critical processing or testing
2593 area.

EU, Annex 1 ,Rev 2020

Definitions

Unidirectional Airflow (First Air)

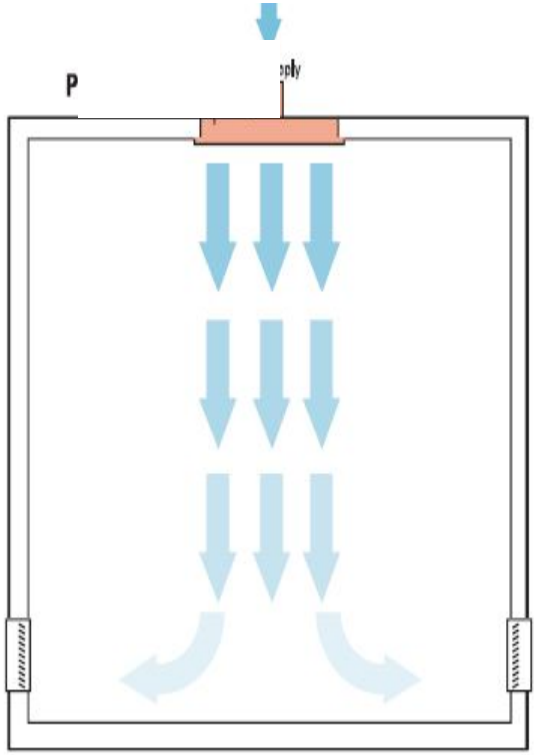
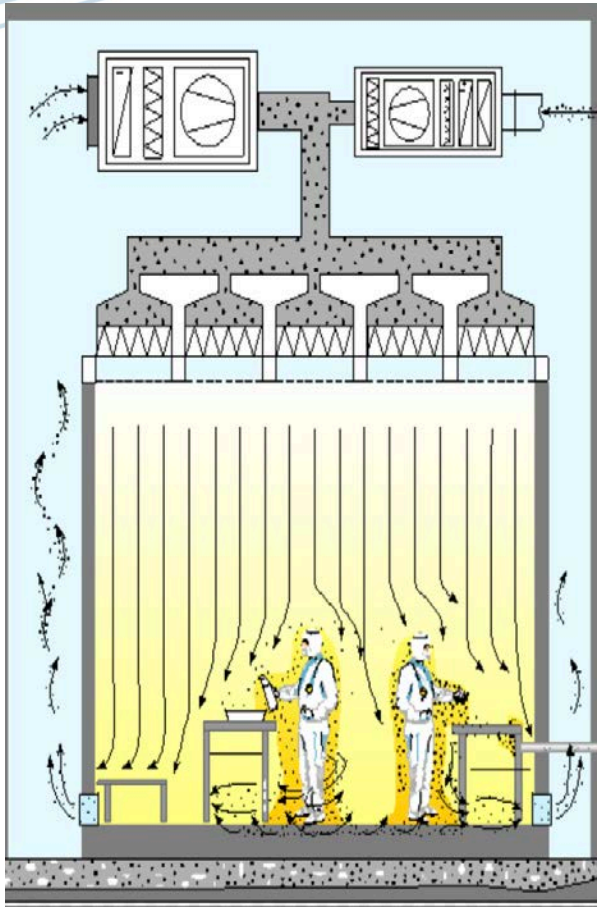


Image source: Price Industries Limited, 2014, http://pricecriticalcontrols.com/content/uploads/assets/literature/catalogs/catalog-pages/section%20e/lfdc.pdf

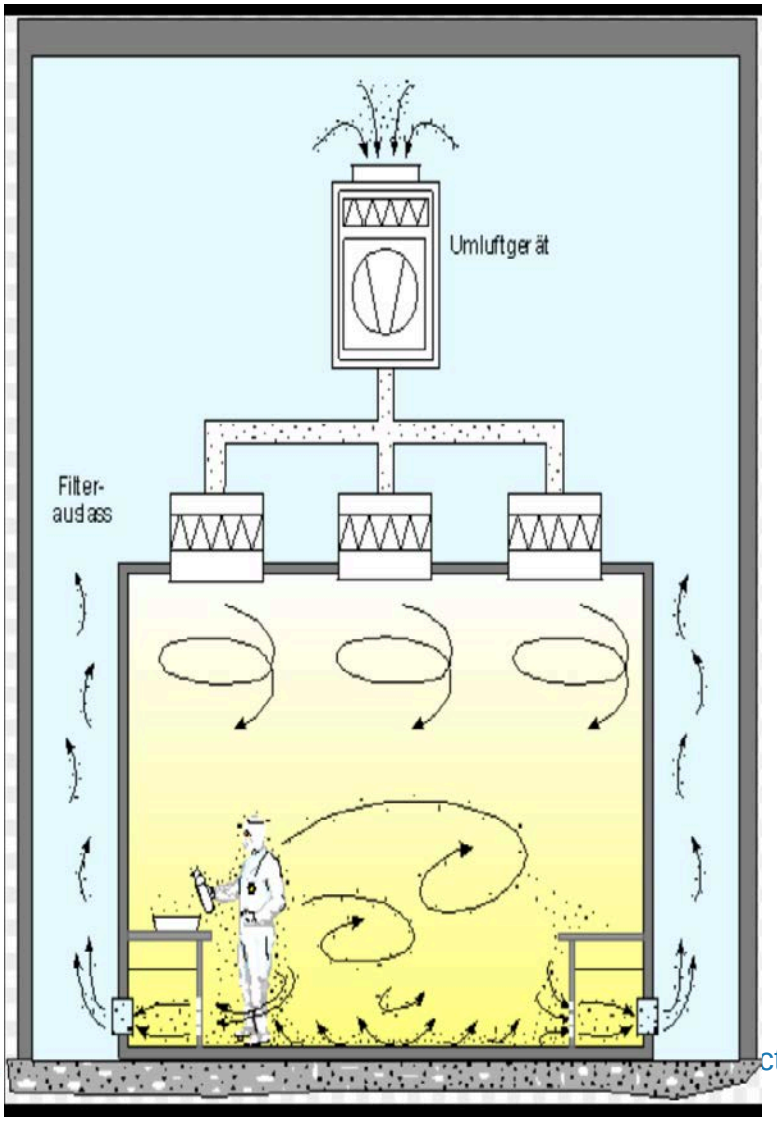
Unidirectional Cleanroom and Cabinet



Source: Wikipedia

Note: UDF can also be horizontal !

Turbulent Cleanroom



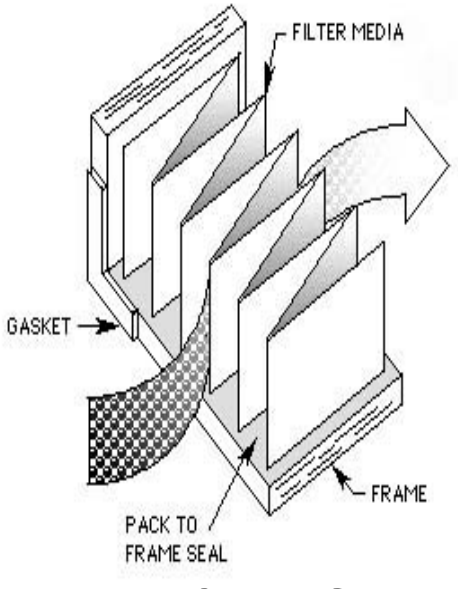
Source: Wikipedia

Definition – HEPA Filter
PDA Technical Report No. 62 “Recommended Practices for Manual Aseptic Processes”, 2013 (TR 62)

HEPA filter

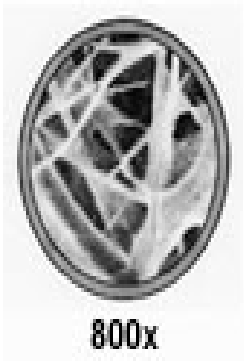
High efficiency particulate air filter with minimum 0.3 µm particle retaining efficiency of 99.97 percent *(1)*.

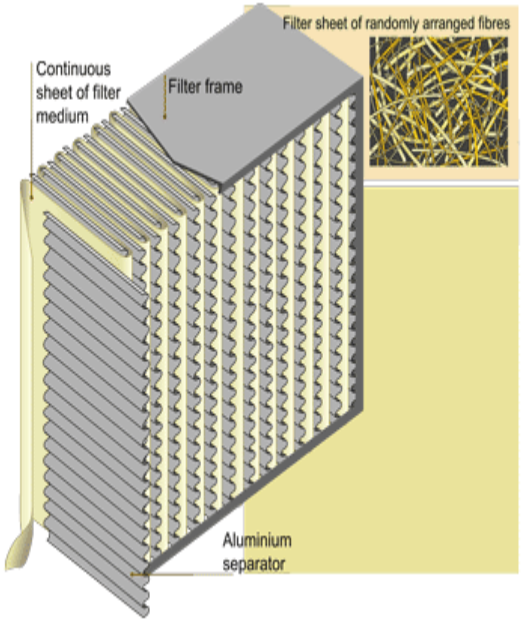
HEPA Filters (Cont'd)



- 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 tha





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
- Use as a training tool
- Review and draw conclusions

PDA TR 62

Recommended Practices for Manual Aseptic Processes

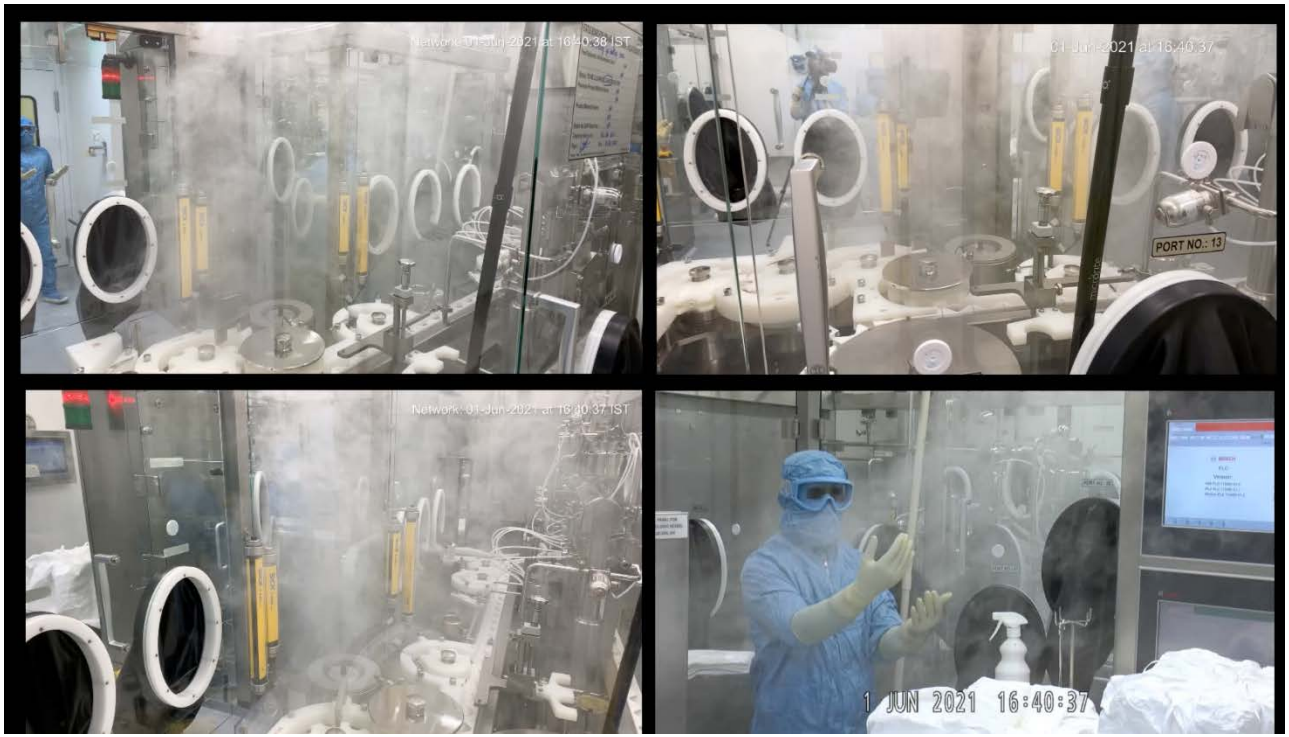
Technical Report No. 62

ISBN: 978-0-939459-57-5

Smoke Study Video (Source: Youtube)

Video

Recent FDA Requirements: different angles required



First Air (First Work Location)

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

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).

Definitions – First Air

Video

Airflow

Airflow Visualization (Smoke) Studies

- Static and dynamic
- Document (videos)
- Include
  - Interventions, equipment, operator movement, opening barriers, doors, pass-throughs
- Use as a training tool
- Review and draw conclusions

Understanding the Types of Aseptic Processing

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

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

Barriers (continued)

Restricted Access Barrier Systems (RABS)

- Rigid
- Separate filling line from personnel

Consider:

- Airflow
- Glove ports

Image courtesy of Howorth Air Technology

Passive Restricted Access Barrier System

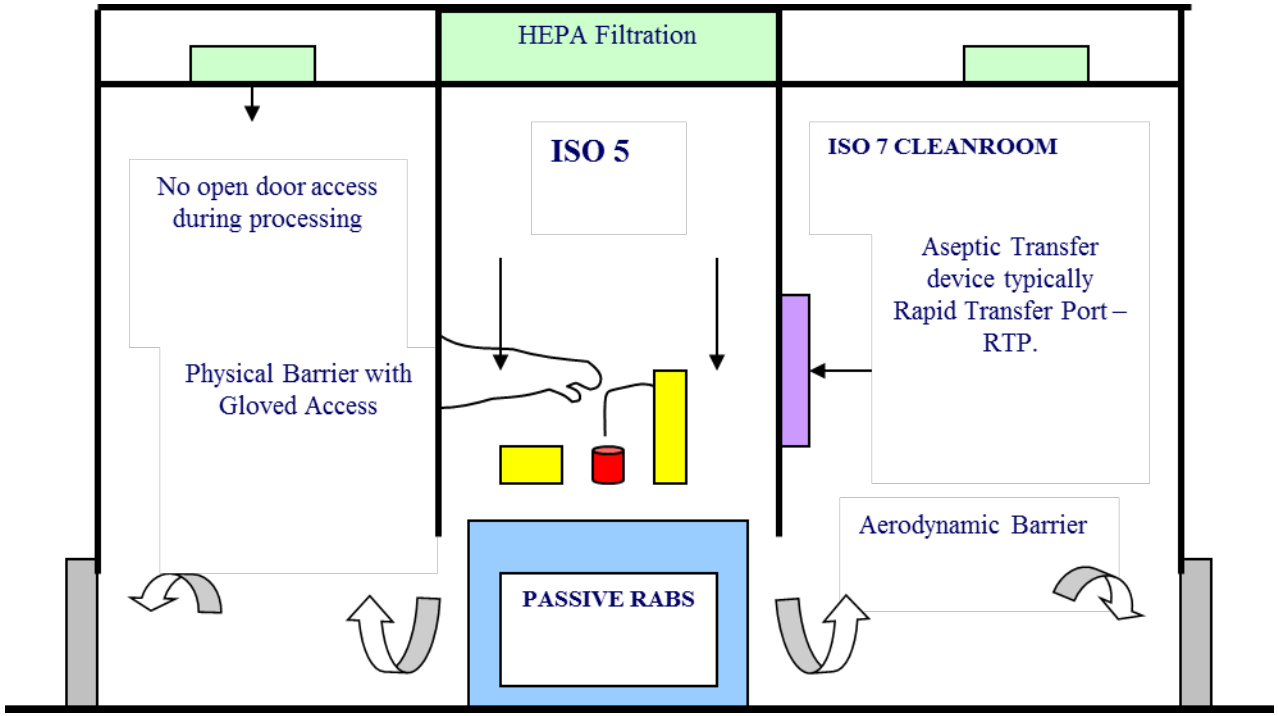


Image Courtesy Bioquell, Inc.

Active Restricted Access Barrier System

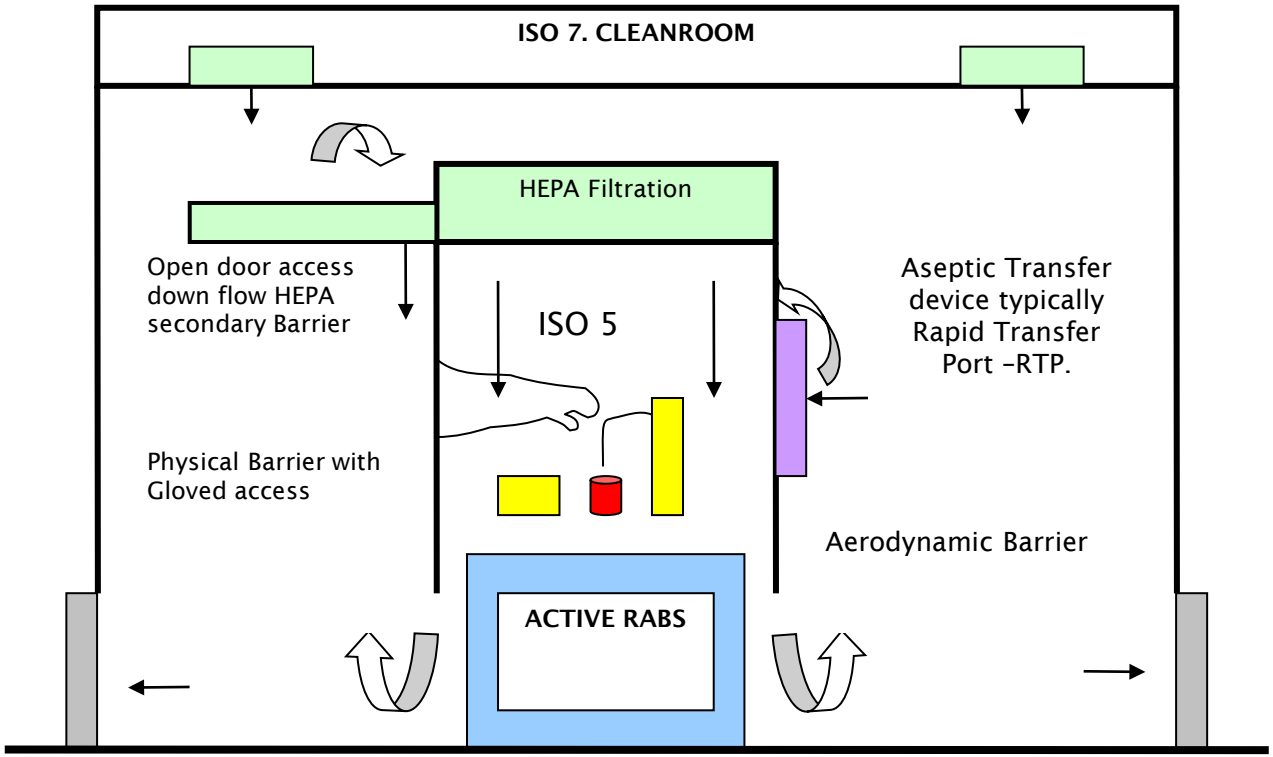


Image Courtesy Bioquell, Inc.

Definition RABS (Restricted Access Barrier System) EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft), December 2017

RABS: A restricted access barrier system (RABS) provides an enclosed, but not closed, environment meeting defined cleanroom conditions using rigid-wall enclosure and air overspill to separate its interior from the surrounding environment.

Active RABS: **I**ntegral HEPA – filtered air supply

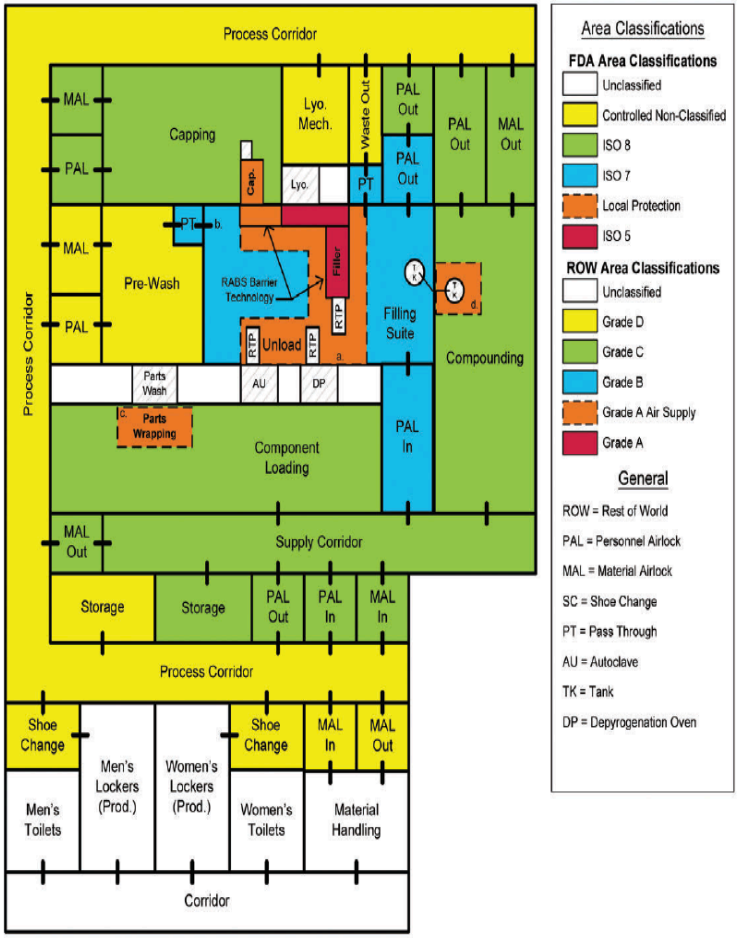
Passive RABS: Air suppy by ceiling mounted HEPA – filters

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".)

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

Isolator Systems

What is the difference between

Isolator

and

RABS ?

Isolators: FDA Guidance Definitions

Isolator- A decontaminated unit, supplied with Class 100 (ISO 5) or higher air quality, 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:

Closed isolator systems exclude external contamination from 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.

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 contamination into the isolator.

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

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Scope of PTC document for Isolators

- Initiated 2017, started 2018, finalized 2020
- Parenteral Drug Association. Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products; Bethesda, Md, 2001(accessed 2018)
- New Publications of Guidelines: FDA (2004), PIC/S (2007), scientific articles released and new technologies available
- Intention of PTC to assess, if a Revision of TR 34 required
- PTC document is designed to communicate best practices and considerations
- PTC strongly proposes and supports the usage of Isolators

Contents and Topics and number of Questions

- **Glossary**
- **Topic 1** Isolator Design: 3 questions
- **Topic 2** Physical Environment: 5 questions
- **Topic 3** Personnel: 2 questions
- **Topic 4** Integrity Testing of Isolator and Gloves: 3 questions
- **Topic 5** Environmental Monitoring: 5 questions
- **Topic 6** Material Transport and Loading of Isolators: 4 questions
- **Topic 7** Cleaning, Disinfection, Decontamination: Cycle develop. & Validation: 9 questions
- **Topic 8** Aseptic Process Simulation (APS): 12 questions
- **Topic 9** Best Practices in Aseptic Operations: 5 questions

Glossary in PTC : 12 terms defined, may be different outside of this document

Intervention

Activities, manipulations, and tasks performed in Grade A/ISO 5, or other critical processing areas during aseptic operations.

Decontamination

An action taken to render the surface of an item, environment, material, or component in the isolator incapable of microbiologically contaminating sterile product, product contact surfaces, or materials (also referred to as bio-decontamination).

"Isolator" Definition: Annex 1 and extended PTC definition

Isolator – A decontaminated unit, 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

Isolator

A contained, decontaminated environment meeting Grade A/ISO 5 conditions used for aseptic process manufacturing that provides an uncompromised, continuous isolation of its interior from the external environment. Once decontaminated by a validated cycle, an isolator prevents the microbiological contamination of sterile products and product contact surfaces of the interior by enclosures and the supply of continuous, controlled overpressure of HEPA-filtered air ***(1)***.

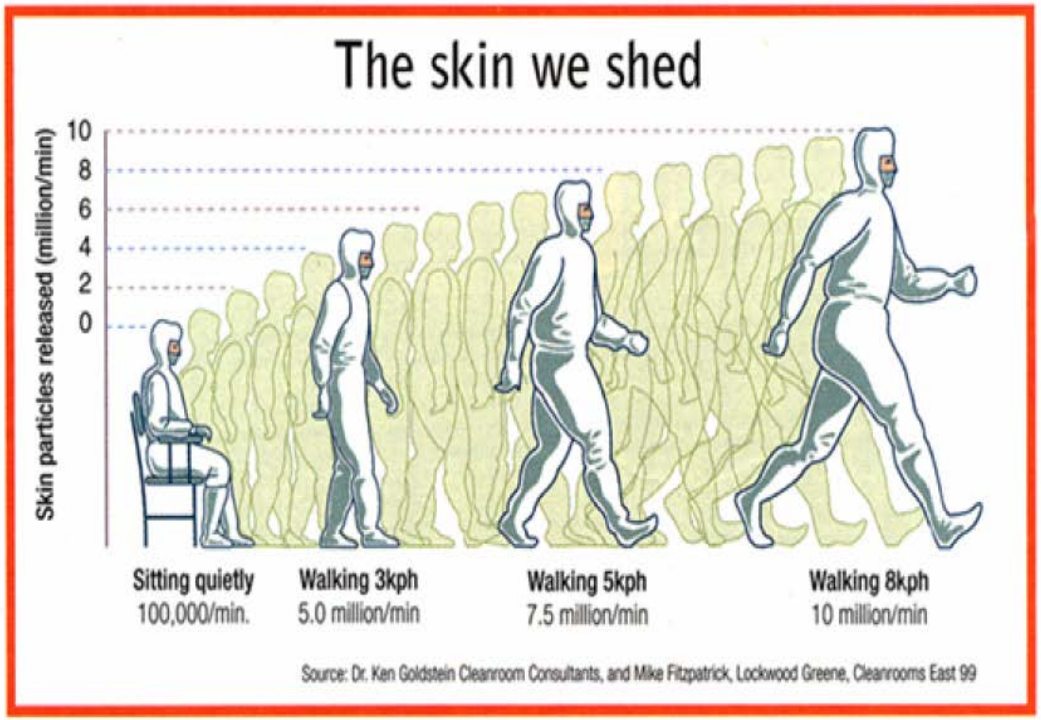
What can go wrong with isolators ?

- 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
- ….

Best Practices in Aseptic Operations

Are applicable also for RABS and Isolators !

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

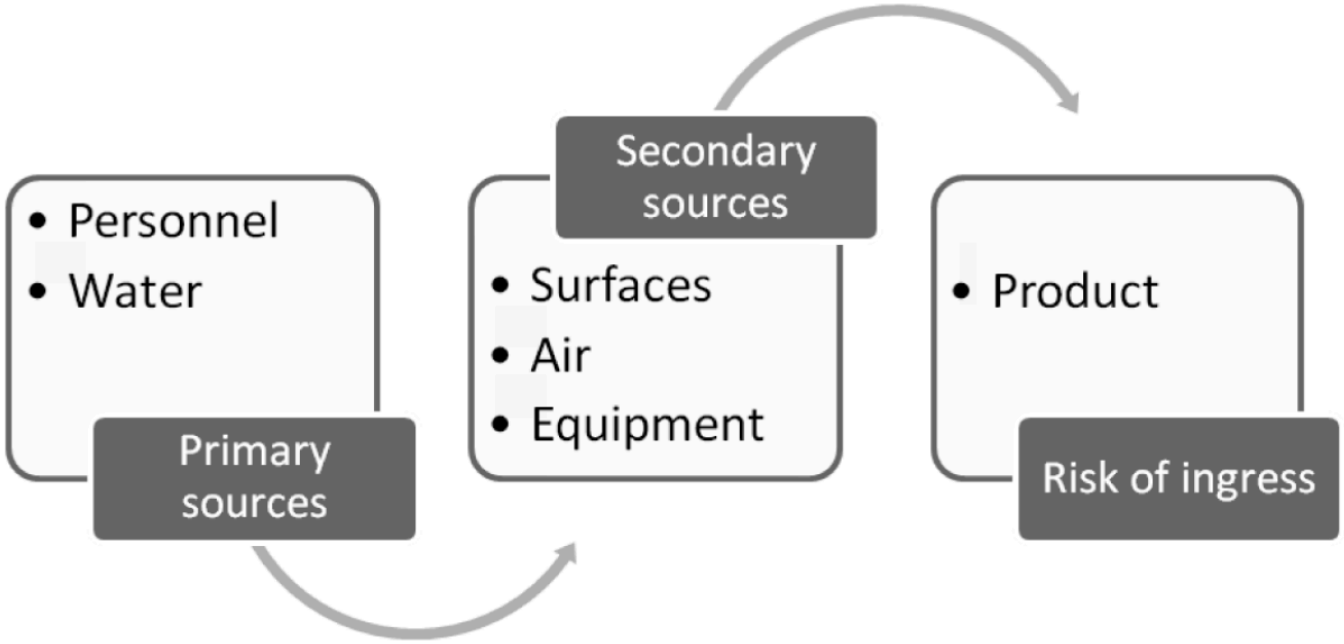


80% of contamination in a clean room comes from people

- While sitting motionless, a person sheds about 100,000 particles
- While walking at 8 Km/H, a person can shed up to 10 million particles **PER MINUTE!**

Contamination Sources

Figure 1 Microbial contamination sources



Movement

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

Video: Walking in cleanroms

Video

Video:

Video

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

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."

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.

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.

PDA TR 62

7.1 Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods

The list below elaborates on design principles for manual aseptic processing.

- Adequate space to perform the work.
- All exposed product and product-contacting components should continuously remain in First Air, i.e., the work location first in the path of HEPA-filtered air.
- Aseptic manipulations should be made in First Air, not having passed over any other components or blocked by the operator's hands.
- The operators should decontaminate or change their gloves on a frequent basis.
- The operators should work as a team. The primary operator(s) should perform all tasks inside the ISO 5 environment. The secondary operator(s) assists in the introduction/removal of items from the ISO 5 environment, and may assist the primary operator(s) with less critical tasks inside that environment. Additional support operator(s) may be necessary to support activities exclusively in the surrounding environment.
- The primary operator should wear sterile gloves and sleeves and never contact a non-sanitized or non-sterilized item.
- The primary operator(s) performs the critical aseptic manipulations within the ISO 5 environment. The secondary operator(s) acts as a support person to minimize the potential of the primary operator touching non-sterile or non-disinfected surfaces. The hands of the primary operator should remain in the ISO 5 environment at all times. (There may be exceptions to this related to positron emission tomography products or radioactive products.) The secondary operator(s) should put on sterile gloves/sleeves prior to any activity inside the ISO 5 environment, or in transfers of items to/from the primary operator. Anytime the primary operator is required to leave the ISO 5 environment, gloves and sleeves (if appropriate) should either be changed or gloves should be re-sanitized prior to reentry to ISO 5.
- Sterilized items should be introduced to the ISO 5 area by aseptic removal of the final wrap around the item as it is being introduced.

... and more

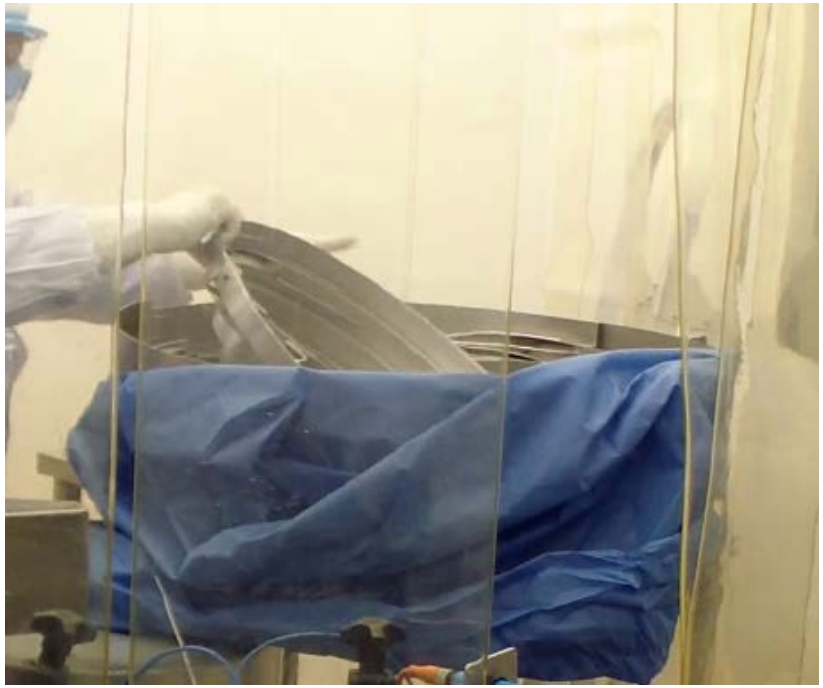
Operator Impact

"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.

- What´s wrong ?



Interventions

- **Interventions: "Less - Critical" and " Critical"** (under vertical unidirectional air flow in a smoke study video picture)

Transfer into grade A

- “Aseptic” and “Support” Operator
- Doctor/ Nurse principle or A/B Operator
- Frequent glove sanitization or change-out
- Double bags

Video

Example of: Correct behaviour

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

Video

Airflow : Working in UDF

Video

Aseptic Techniques

Video

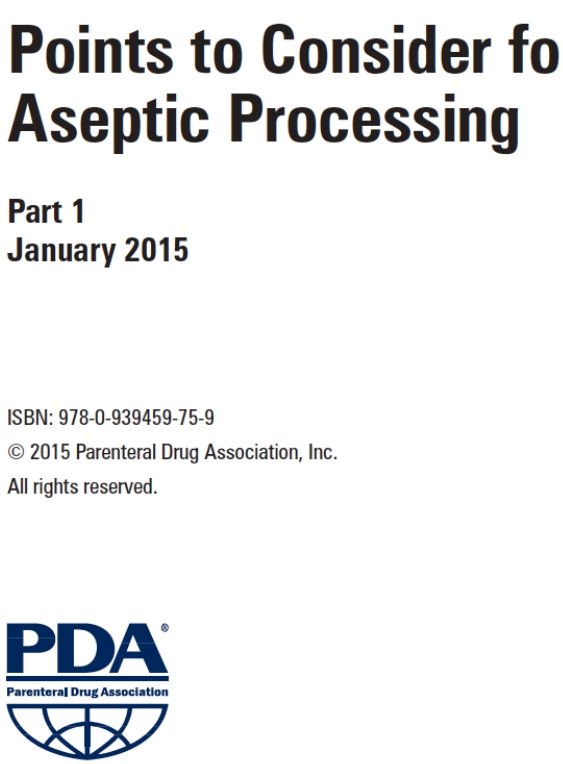
Videos

Video

Good Aseptic Technique – Golden Rules !

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

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



Points to Consider for Aseptic Processing

Part 1
January 2015

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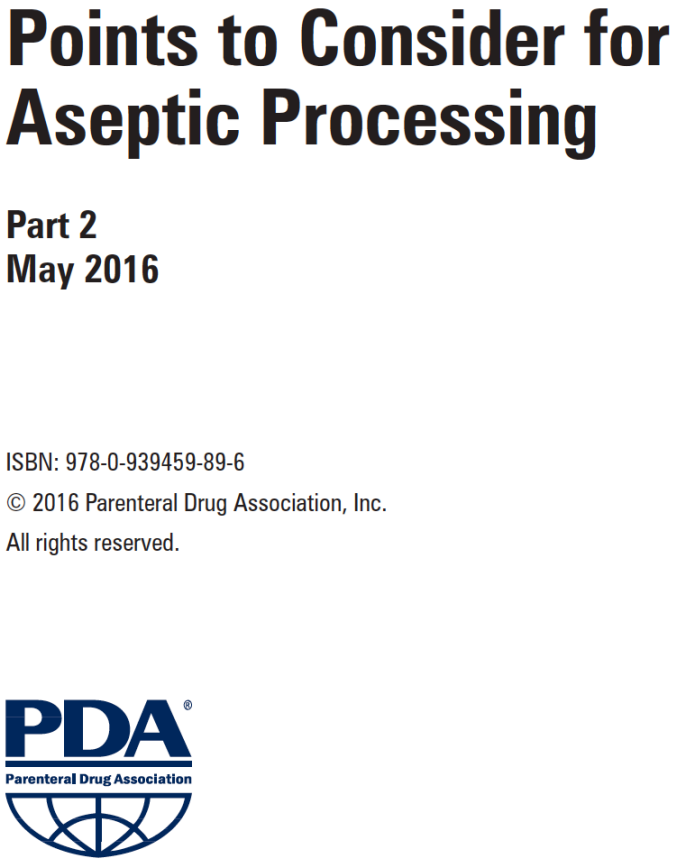
PDA Parenteral Drug Association



Points to Consider for Aseptic Processing

Part 2
May 2016

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PDA Parenteral Drug Association

WARNING LETTER Examples

Aseptic Operations – Behaviors

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

"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

"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

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)

END

Thank You

Questions ?