PDA
Parenteral Drug Association

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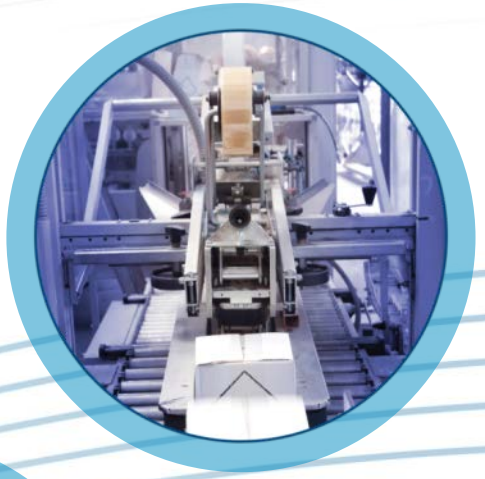
Cleanroom concepts, RABS, Isolators and Good Aseptic Working Practices



By Guenther Gapp

Selected Aspects about

- Conventional Cleanroom concepts/ Aseptic Filling
  - Unidirectional Air Flow
  - First Air Concept
  - Teamwork
- RABS systems and Isolators
  - The difference
  - What´s important to consider
  - Update on TR 34 (Isolators) – Ptc Isolators
- Good Aseptic Working Practices
  - General Rules and practical demonstrations
  - Golden Rules & Pictures and Videos

Definitions

Unidirectional Airflow (Not: Laminar Flow)

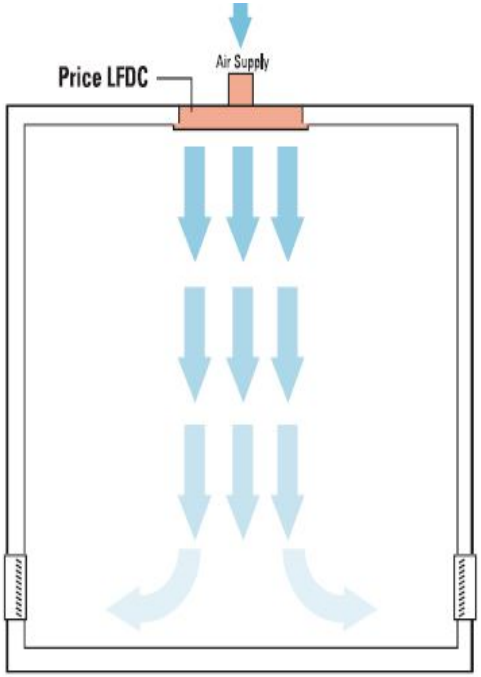


Image source: Price Industries Limited, 2014, http://pricecriticalcontrols.com/content/uploads/assets/literature/catalogs/catalog-pages/section%20e/lfdc.pdf

Definitions (Cont'd)

Non-Unidirectional/Turbulent Airflow

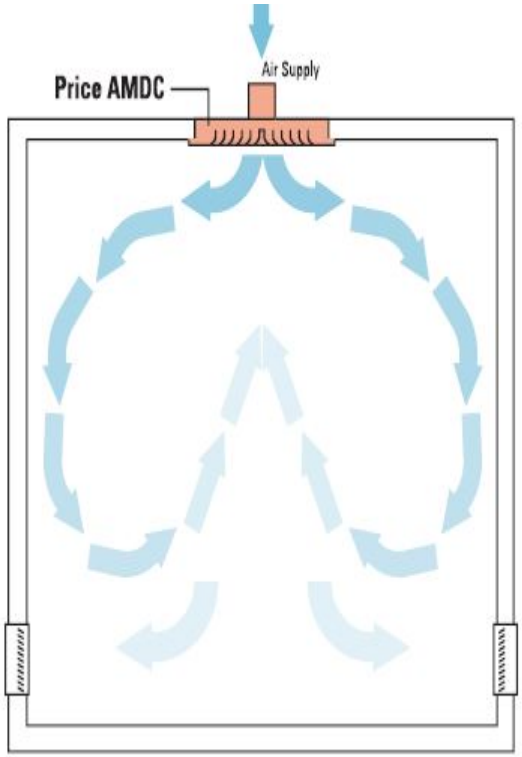


Image source: Price Industries Limited, 2014, http://pricecriticalcontrols.com/content/uploads/assets/literature/catalogs/catalog-pages/section%20e/lfdc.pdf

TEAMWORK – How to build up a Conventional Aseptic filling line?

PDA TR 62

Recommended Practices for Manual Aseptic Processes

Technical Report No. 62

ISBN: 978-0-939459-57-5

First Air (First Work Location)

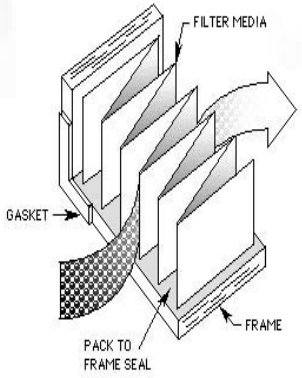
The work location first in the path of HEPA filtered air (8).

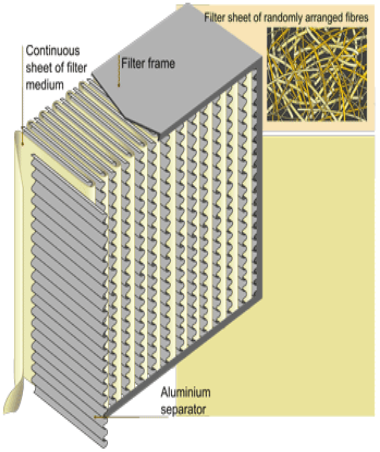
8. NASA-TM-X-66397, NHB-5340.2; *NASA Standards for Clean Rooms and Work Stations for the Microbially Controlled Environment*; National Aeronautics and Space Administration: 1967. ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/19700078206_1970078206.pdf (accessed Jan. 25, 2013).

HEPA Filters (Cont'd)

- Rigid frame with filter pack
- Continuous pleated sheet filter media
- All-glass paper which is composed of an extremely large number of

  randomly oriented micro-fibers
- Retains 99.97% particles greater than 0.3 microns





Smoke Study Video (Source: Youtube)

Definitions – First Air

Airflow Visualization

- Vapor generator (LN2, CO2, H2O)
- Show the actual airflow pattern throughout the unidirectional area.
- Demonstrate the effects on airflow caused by equipment.
- Demonstrates the effects of airflow during interventions.

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

Overview about 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

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

Understanding the Types of Aseptic Processing (Flipchart Demo)

- **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

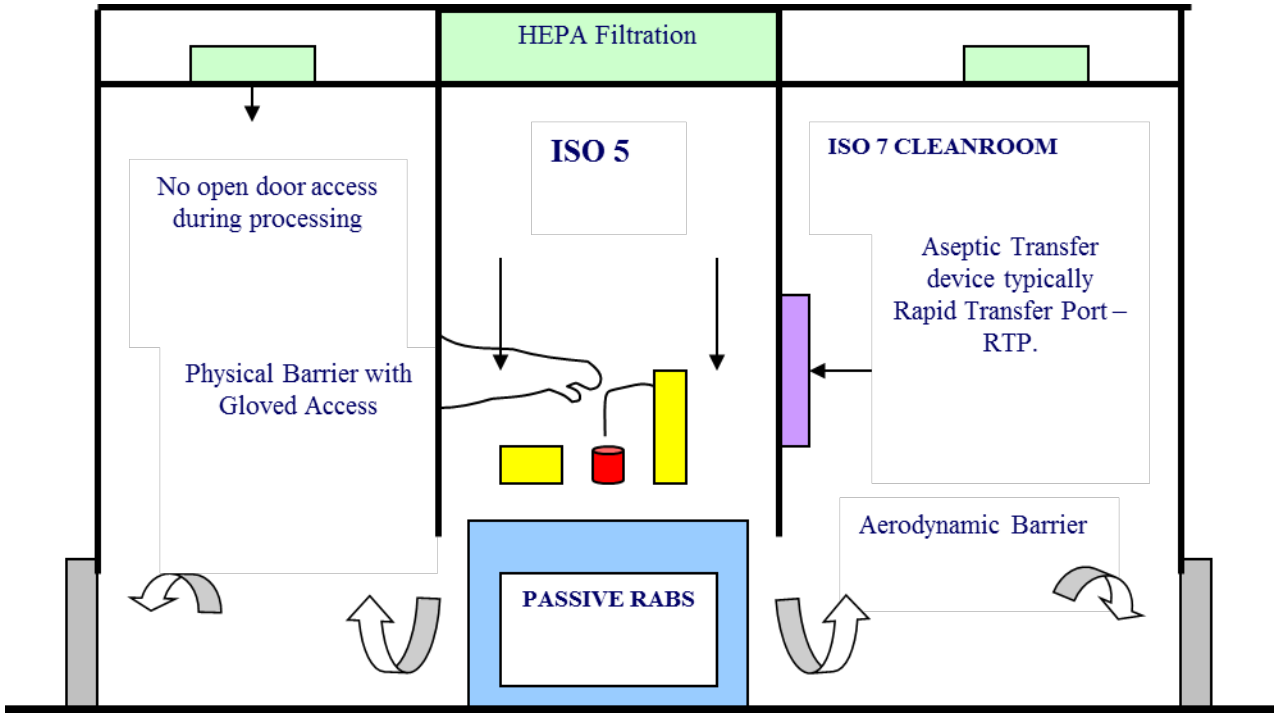


Image Courtesy Bioquell, Inc.

Active Restricted Access Barrier System

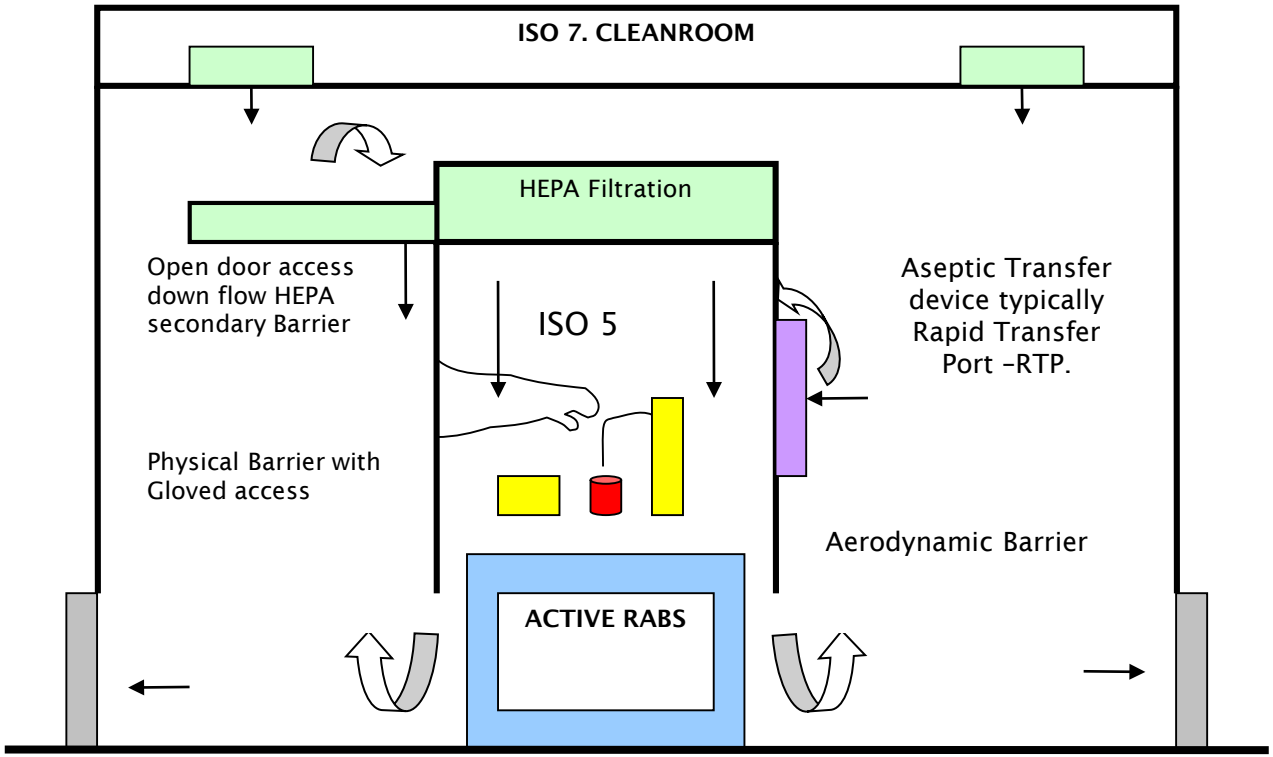


Image Courtesy Bioquell, Inc.

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".)

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:

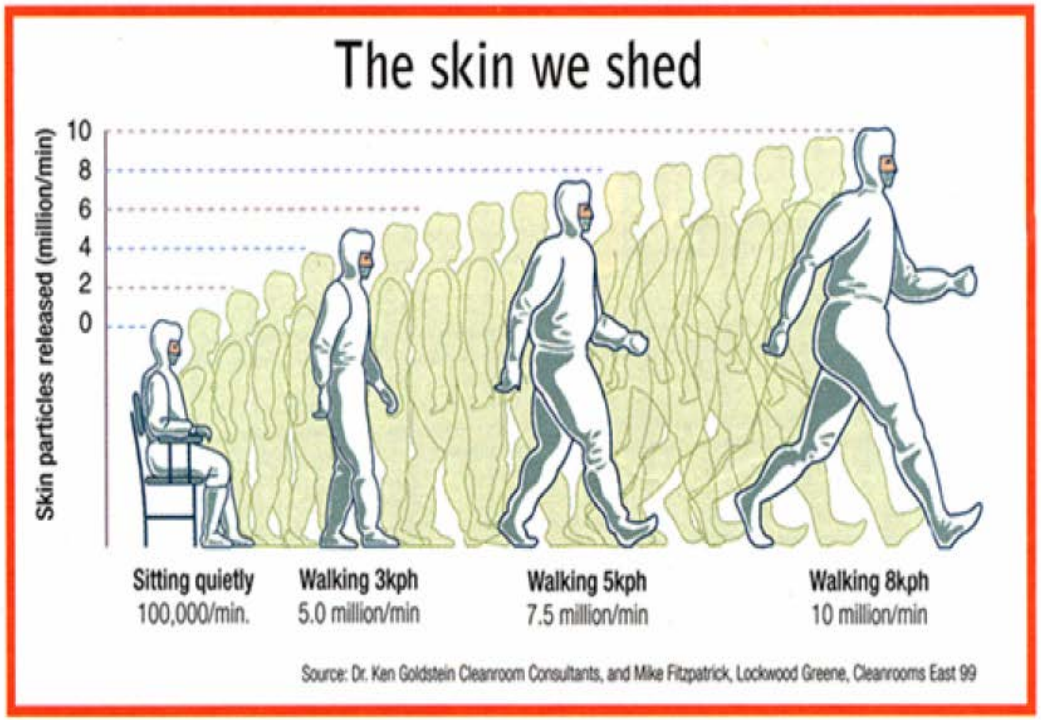
Closed isolator systems exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

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.

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
- ….

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!**

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

Definition

Aseptic

Absence of pathogenic microorganisms or

technique used to prevent contamination by microorganisms.

EU Annex Proposal (2017)

Asepsis - A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product.

Practical Demonstrations about

ASEPTIC OPERATIONS

in our classroom

Video: Walking in cleanroms

Video:

Some potential routes for Transfer of Contamination

- **Airborne**
  - Sourced from personnel and machines
  - Small particles are dispersed (e.g. skin cells) before settling
  - Large (spittle/ dandruff) settle where generated

- **Contact**
  - Contaminated gloves, machinery, clothing, packaging
  - Direct and indirect product contact surfaces by contaminated surfaces

But there are more potential root causes …. in many cases not clearly identified !

Your experience …

My experience ….

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

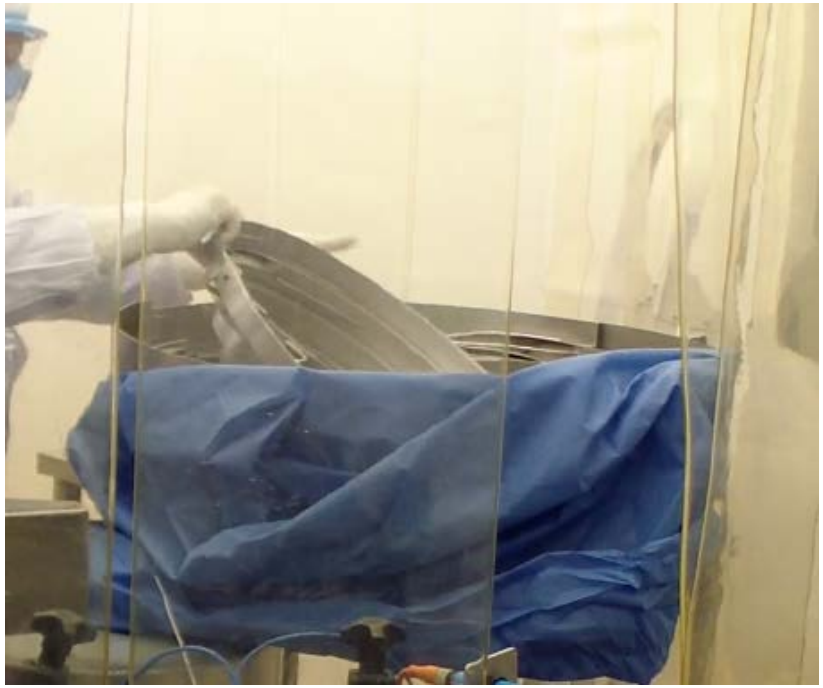
Operator Impact

"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 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

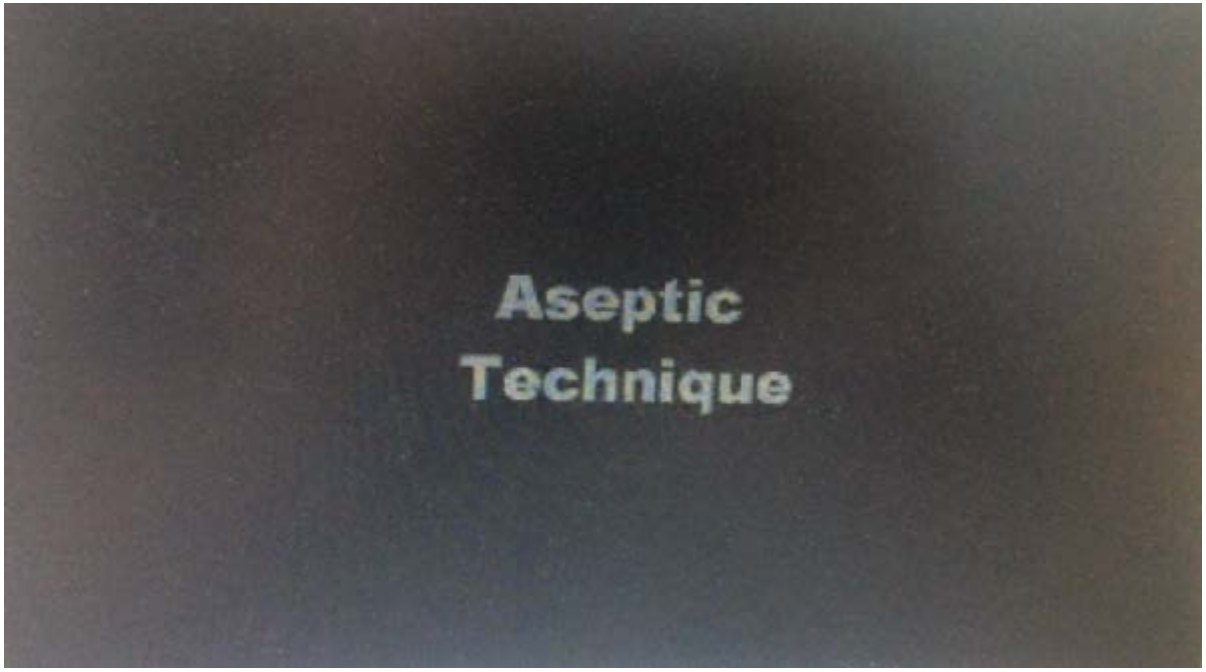
Example of: Correct behaviour

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

Airflow : Working in LF

Aseptic Techniques

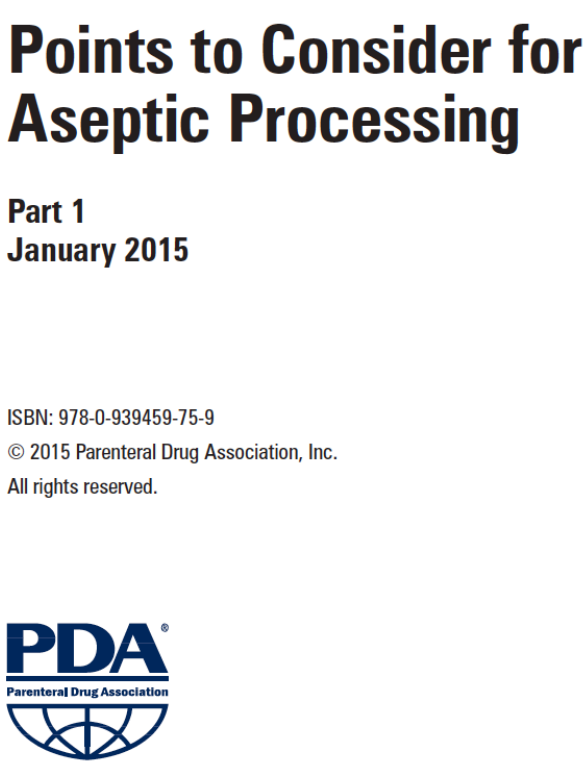


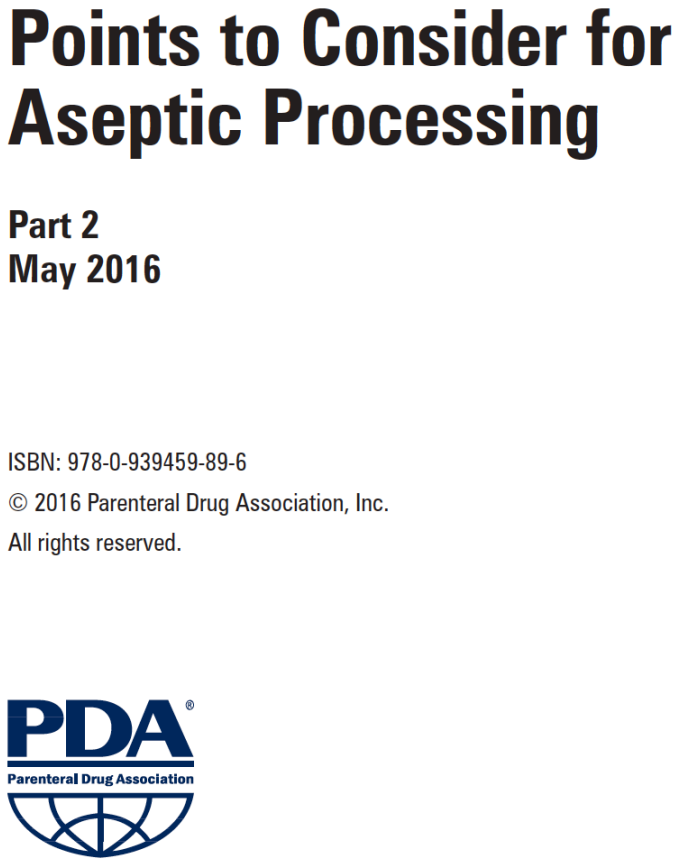
Videos

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, product contact (e.g. syringes, open vials and caps) and indirect product contact surface (e.g. bowl)
- Always move slowly and make slow motions
- 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 !

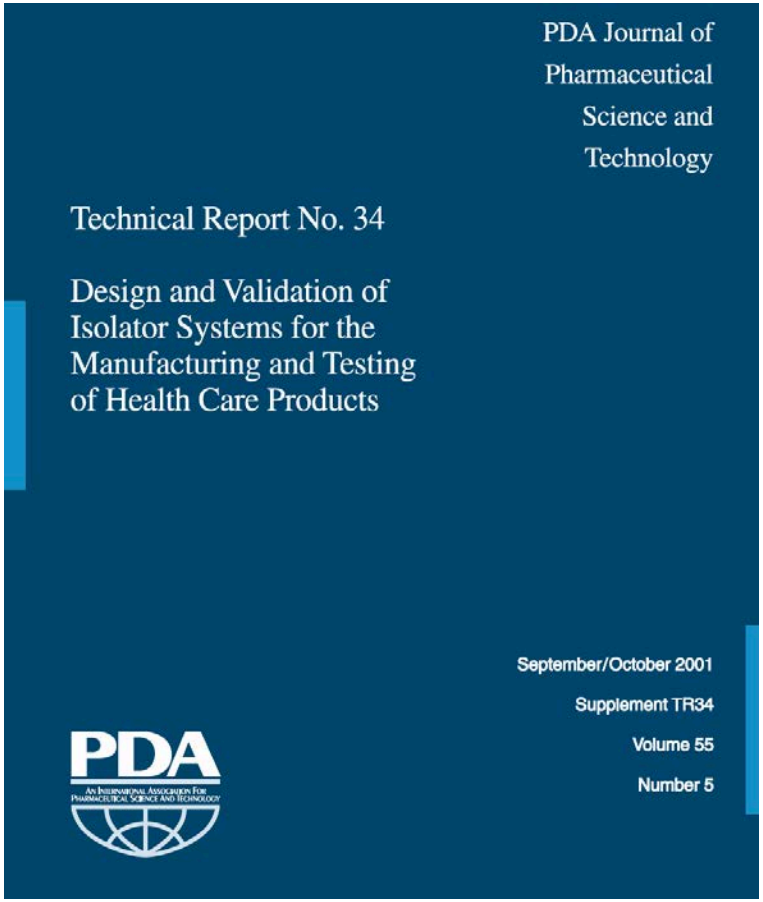




WARNING LETTER EXCERPTS

Aseptic Operations – Behaviors

Update about TR 34 : Isolators



New PDA Taskforce for preparing “Points to Consider for Pharmaceutical Isolators” (started 2018)

- 10 to 15 team- members
- 12 Topics (Problem Statement & Recommendation)
- Current Status
- Timelines
- Based on this document TR 34 will be revised

3 RECAP MESSAGES ...