

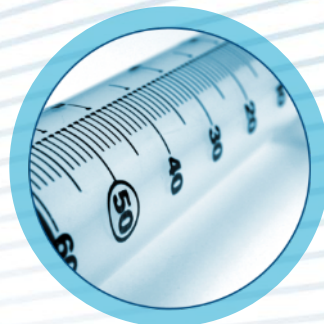
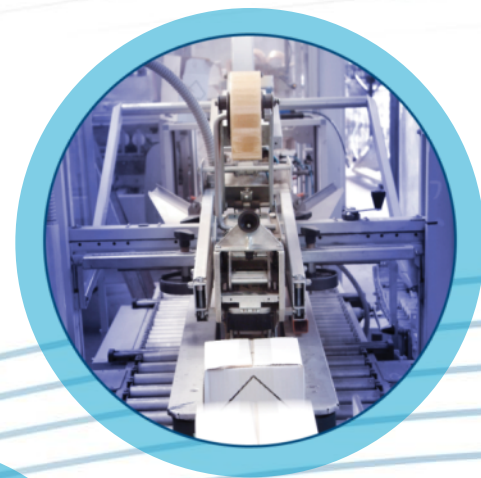


Connecting People, Science and Regulation®

Aspects of Clean Room Concepts and Good Aseptic Working Practices

By Guenther Gapp

Munich, 05 Sept 2019





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 \leftrightarrow . 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 100¹ 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 ft³
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 5: Recommended limits for airborne particle concentration for the monitoring of non-viable contamination

Grade	Recommended maximum limits for particles $\geq 0.5 \mu\text{m}/\text{m}^3$		Recommended maximum limits for particles $\geq 5 \mu\text{m}/\text{m}^3$	
	in operation	at rest	in operation	at rest
A	3 520	3 520	20	20
B	352 000	3 520	2 900	29
C	3 520 000	352 000	29 000	2 900
D	Set a limit based on the risk assessment	3 520 000	Set a limit based on the risk assessment	29 000



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

Table 3.3.1-1: Clean Room Standards - Airborne Particulate Levels (particles/m³)

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

Table 4: Examples of operations and which grades they should be performed in

A	<p>Critical processing zone.</p> <p>Aseptic assembly of filling equipment.</p> <p>Aseptic connections (should be sterilized by steam-in-place whenever feasible).</p> <p>Aseptic compounding and mixing.</p> <p>Replenishment of sterile product, containers and closures.</p> <p>Removal and cooling of items from heat sterilizers.</p> <p>Staging and conveying of sterile primary packaging components.</p> <p>Aseptic filling, sealing, transfer of open or partially stoppered vials, including interventions.</p> <p>Loading and unloading of a lyophilizer</p>
B	<p>Direct support zone for the critical processing (grade A) zone.</p> <p>Transport and preparation of packaged equipment, components and ancillary items for introduction into the grade A zone.</p> <p>Removal of sealed product from the grade A zone.</p>
C	<p>Preparation of solutions to be filtered.</p>
D	<p>Cleaning of equipment.</p> <p>Handling of components, equipment and accessories after washing.</p> <p>Assembly of cleaned equipment to be sterilized.</p>

Source:
EU Annex,
Rev 2017



Critical Area/ Grade A

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally, such conditions are provided by a localised airflow protection, such as laminar air flow work- stations or isolators. Unidirectional air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value), the point at which the air speed measurement is taken should be clearly justified in the protocol. ...

EU Annex 1, rev 2017



UDF

Unidirectional flow - 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 , Fev 2017



FDA Critical Area = EU Grade A

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



Definitions

Unidirectional Airflow (First Air)

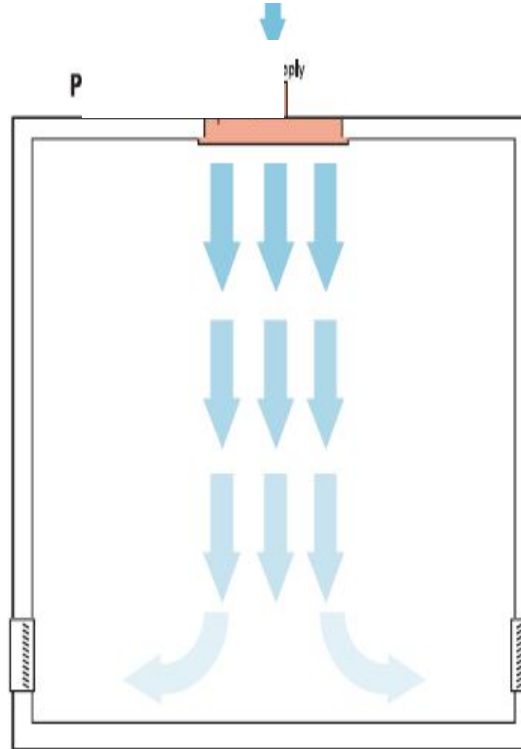
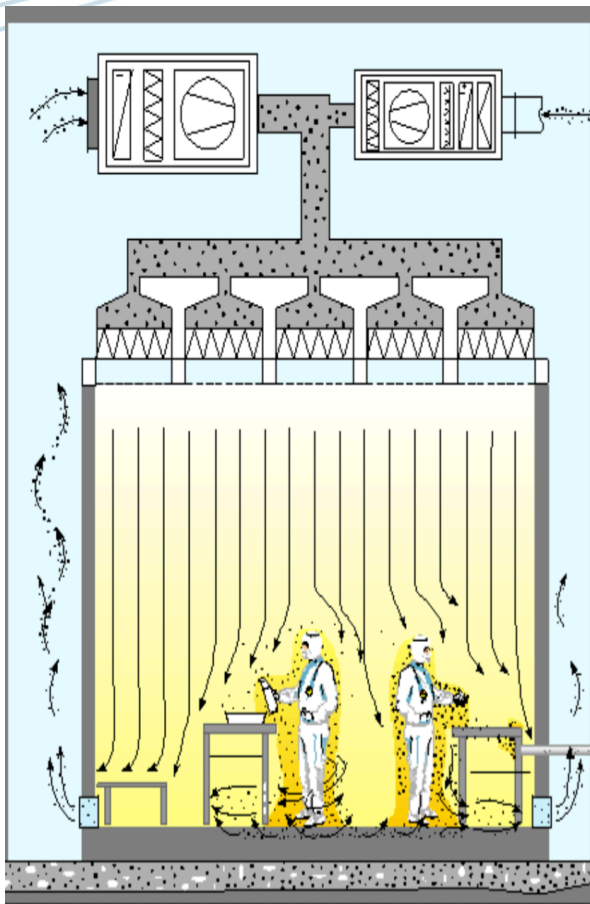


Image source: Price Industries Limited, 2014, <http://pricecriticalcontrols.com/content/uploads/assets/literature/catalogs/catalog-pages/section%20e/lfdc.pdf>



Unidirectional Cleanroom and Cabinet



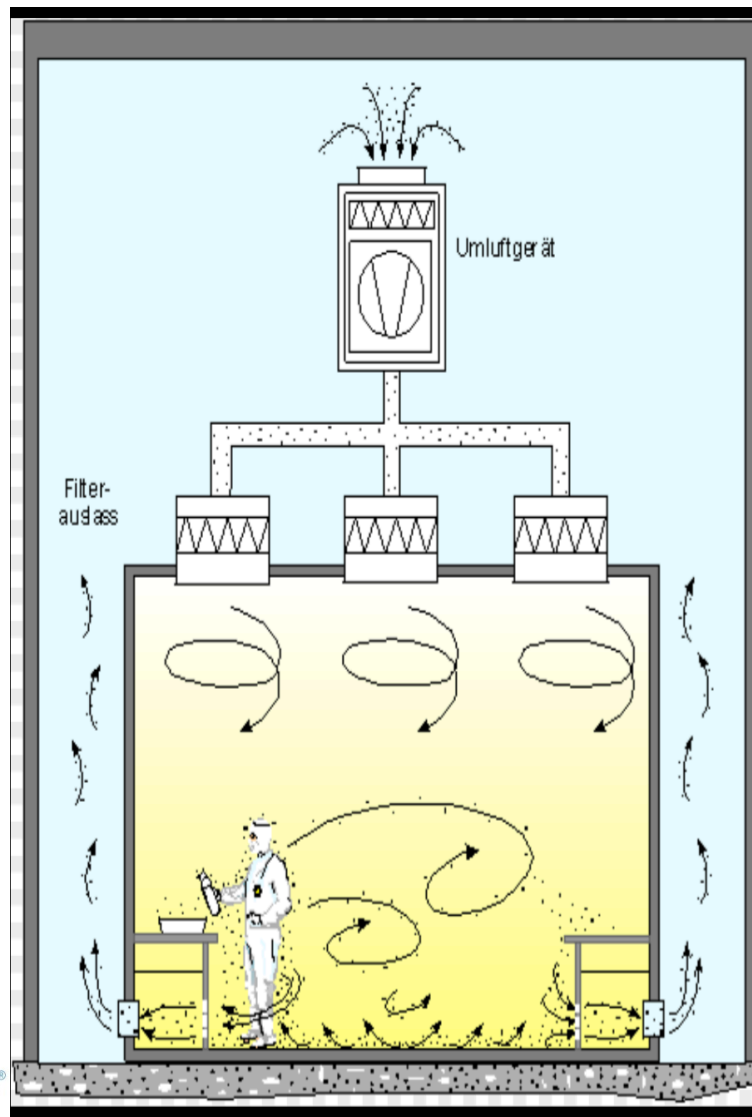
Source: Wikipedia



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)

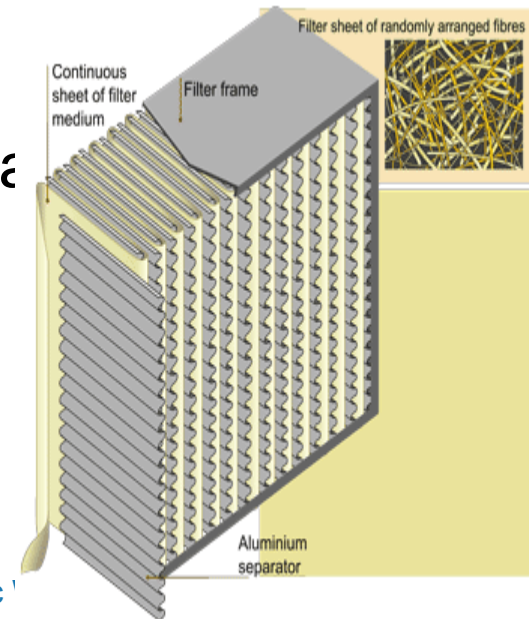
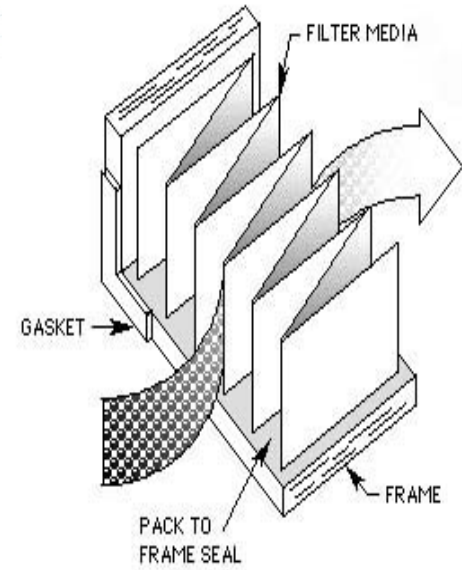
HEPA filter

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 than 0.3 micrometers





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



RECAP : what do we require for an Aseptic filling line and control ?



PDA TR 62

Recommended Practices for Manual Aseptic Processes

Technical Report No. 62

ISBN: 978-0-939459-57-5

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Smoke Study Video (Source: Youtube)





Definition – First Air

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

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





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)

Consider:

- Rigid
 - Separate filling line from personnel
-
- Airflow
 - Glove ports



Image courtesy of Howorth Air Technology



Passive Restricted Access Barrier System

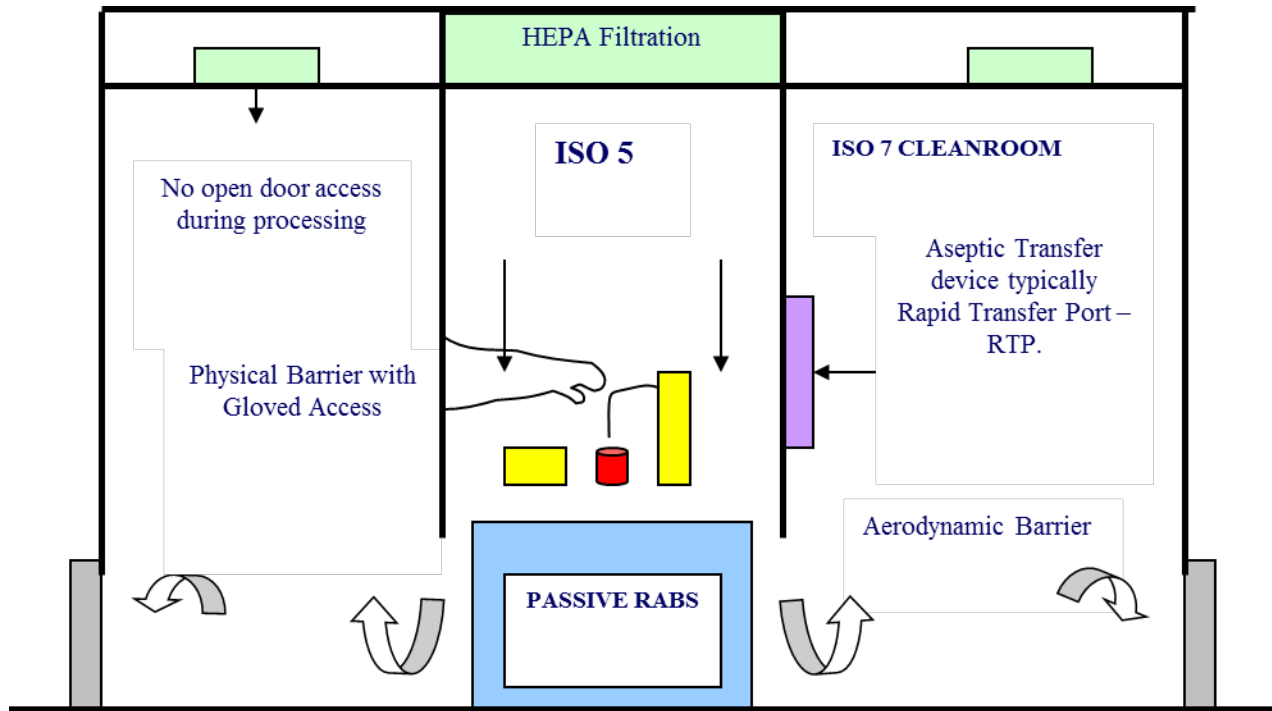


Image Courtesy Bioquell, Inc.



Active Restricted Access Barrier System

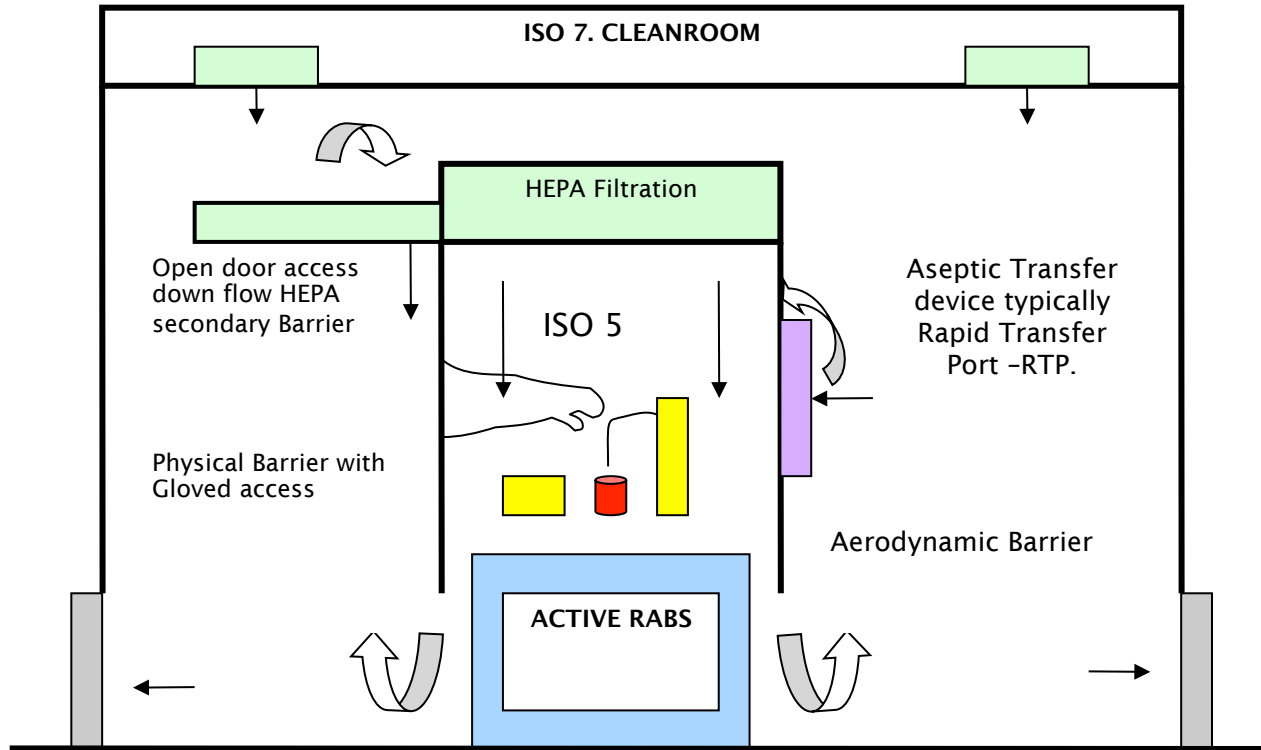


Image Courtesy Bioquell, Inc.



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: Integral HEPA – filtered air supply

Passive RABS: Air supply by ceiling mounted HEPA – filters

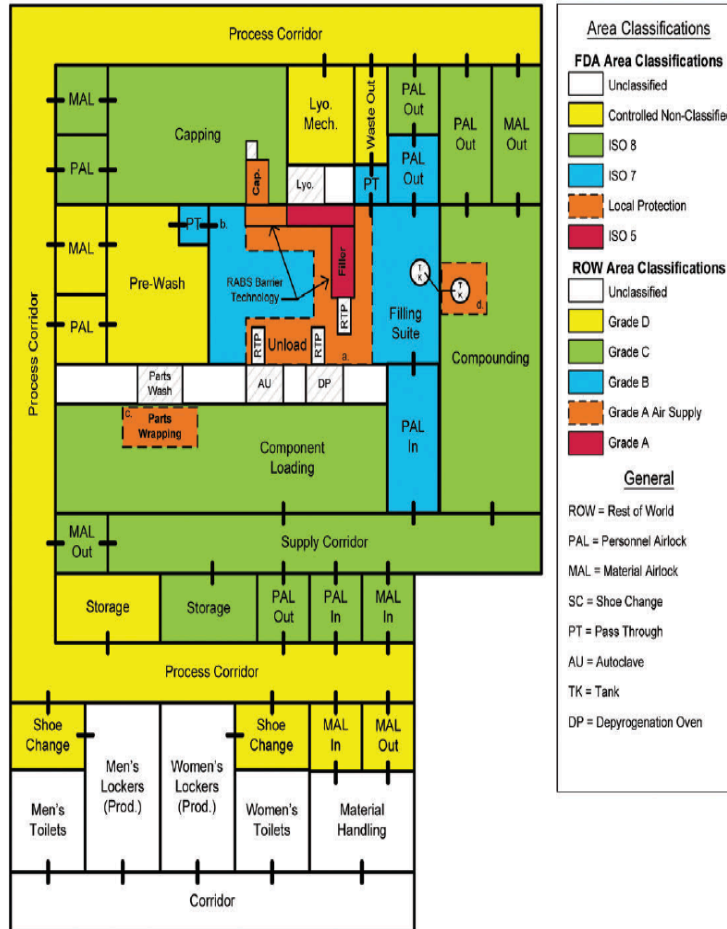
Open RABS: Where there are vents in the barrier that allow air move from grade A to the grade B area

(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.



What can go wrong with isolators ?

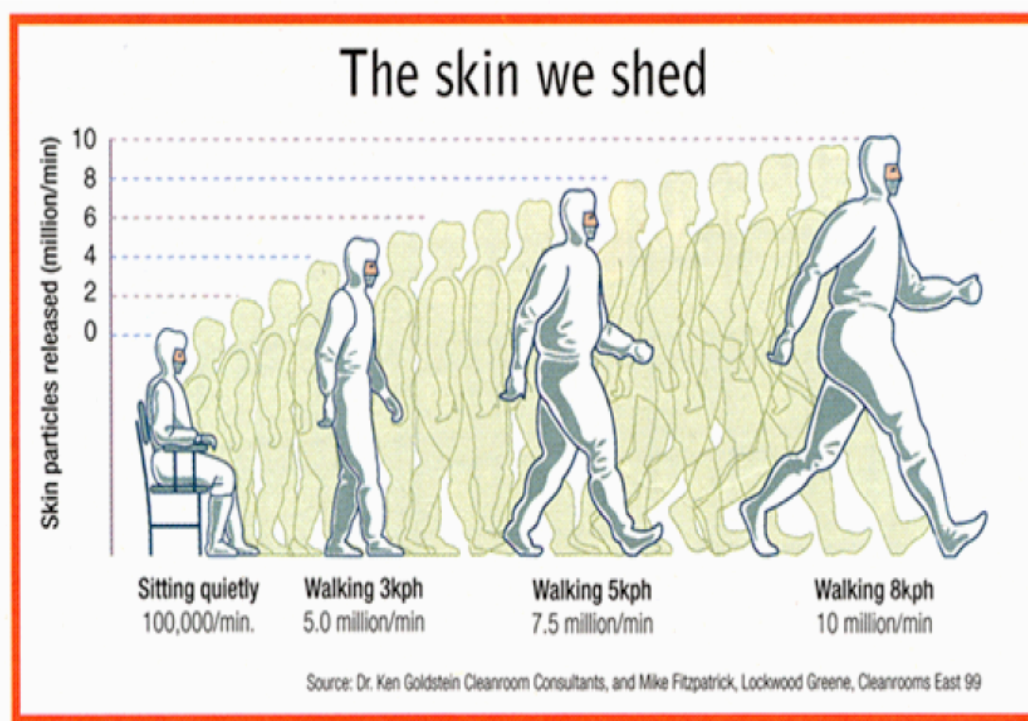
- Cleaning of isolator inside surfaces not done properly
- VHP – decontamination
- Inaccessible surfaces inside
- Loading if Material into isolator (operators/ integrity of bags)
- RTP's and alpha/beta ports
- Integrity of isolators and gloves
- Non- sterile materials introduced
- Pressure drops
- Aseptic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



Best Practices in Aseptic Operations

Are applicable also for RABS and Isolators !

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





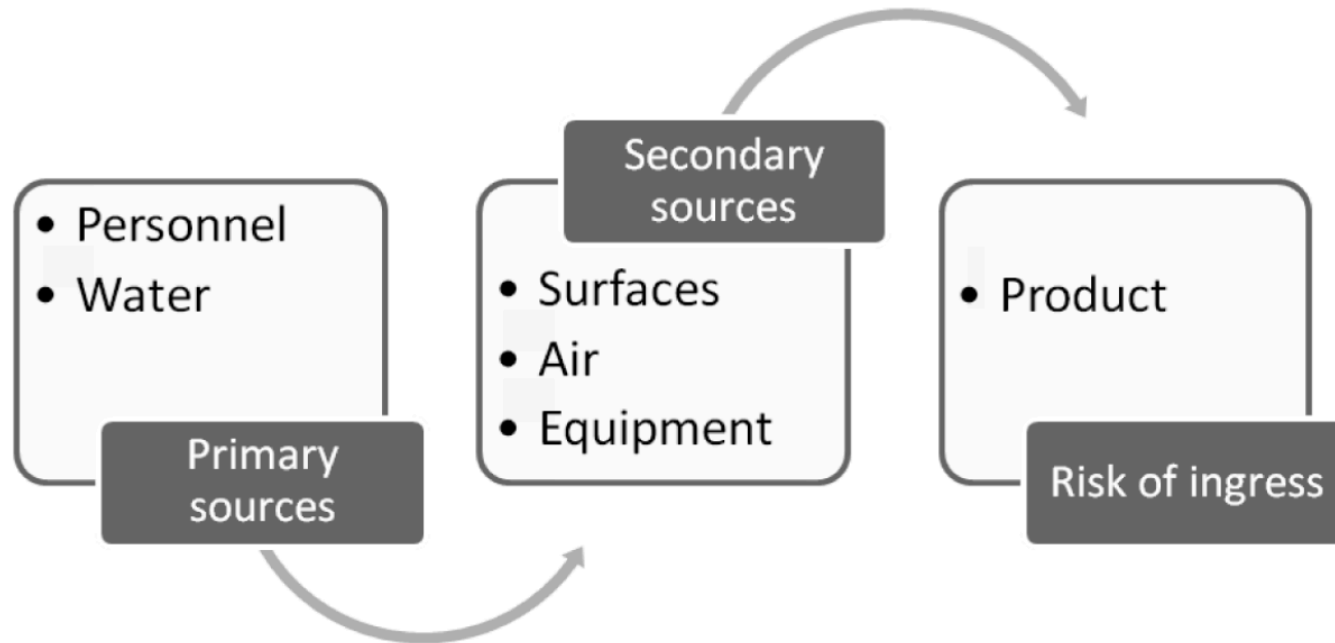
80% of contamination in a clean room comes from people

- 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 cleanrooms





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



Contamination - 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

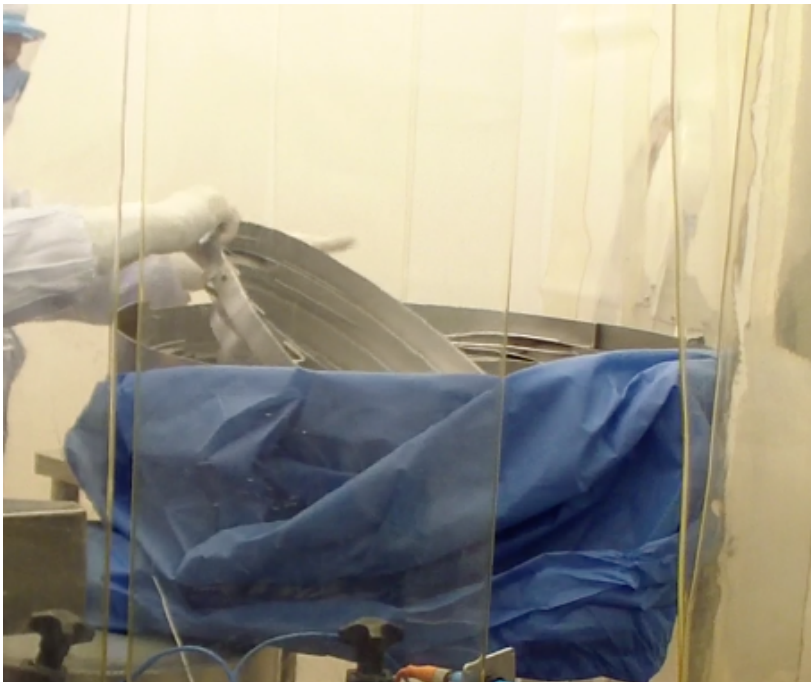
“A well designed, maintained, and operated aseptic process *minimizes personnel intervention*. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases.”

... refer to design limitations on the next slide !

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



➤ What's wrong ?





Correct ?

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



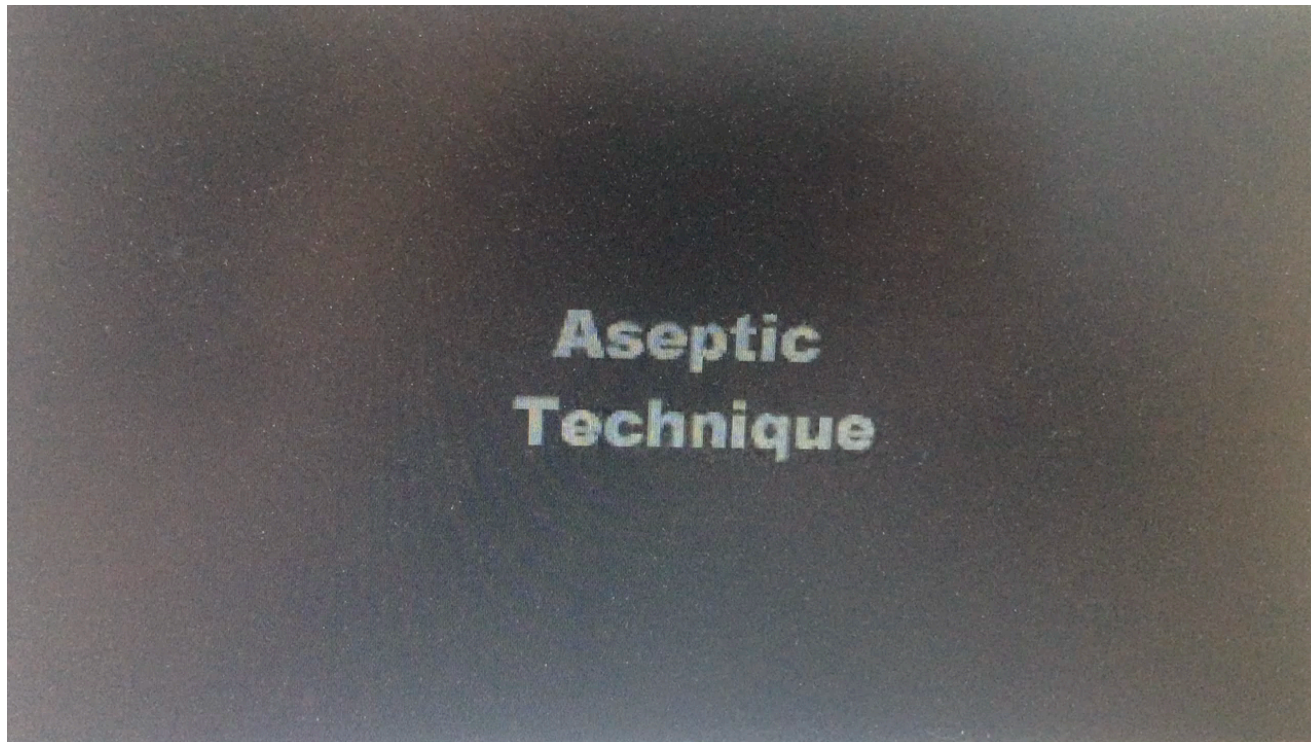


Airflow : Working in UDF



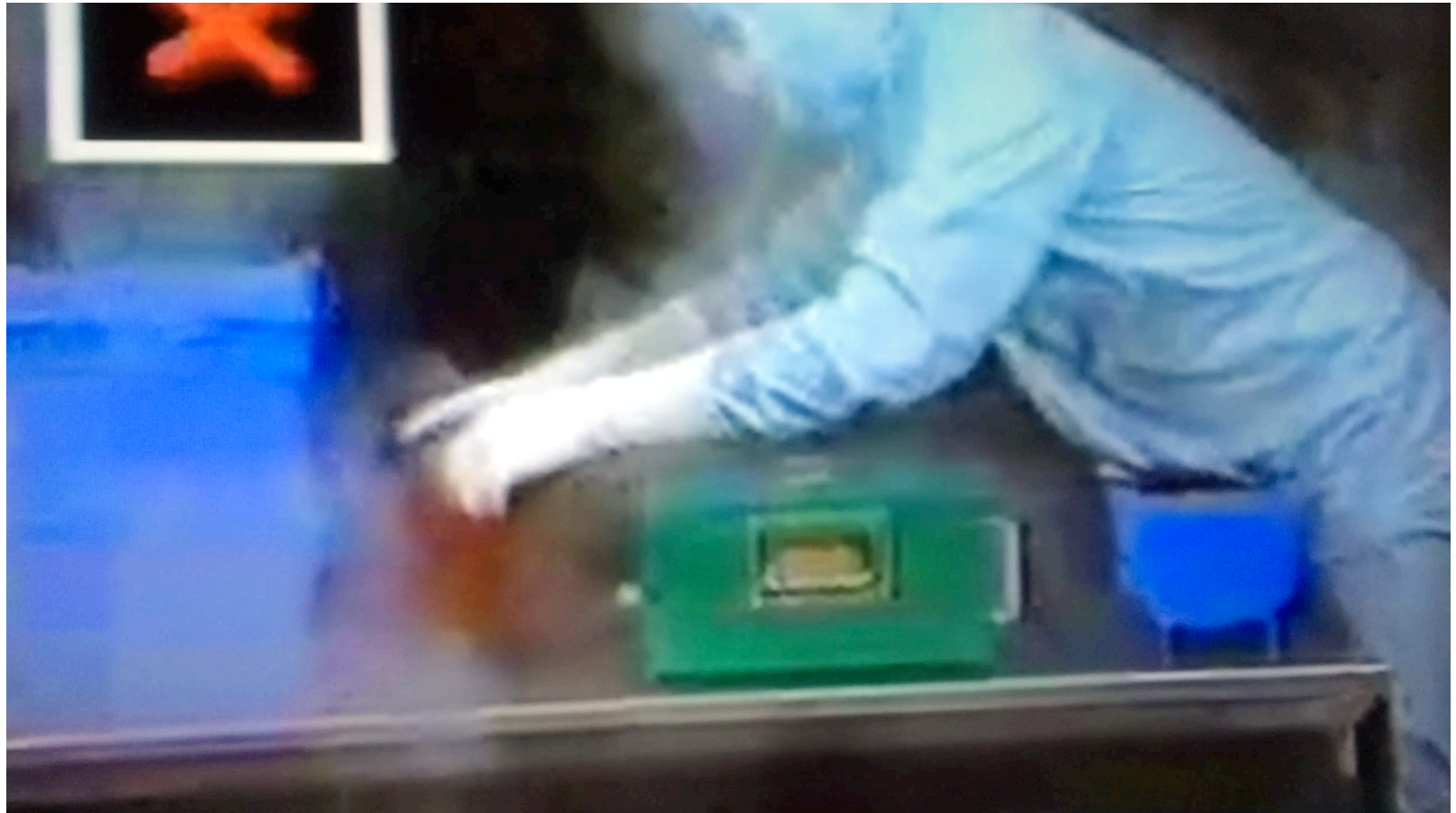


Aseptic Techniques





Videos





CORRECT ?



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

ISBN: 978-0-939459-75-9
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Points to Consider for Aseptic Processing

Part 2
May 2016

ISBN: 978-0-939459-89-6
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WARNING LETTER EXCERPTS

Aseptic Operations – Behaviors

in separate document



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

- 10 to 15 team- members ... 8 active members left
- 10 Topics (Problem Statement & Recommendation)
- Current Status
- Based on this document TR 34 will be revised



3 RECAP MESSAGES ...