STERIS

Life Sciences

Material Transfer Best Practices for Contamination Control

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What We Will Cover…

- Sterilization Modalities
- Material Transfer and Annex 1
- Development of Mitigation Measures
- Equipment Preparation and Wrapping
- Best Practices for Material Transfer
- Case Study: Sterility Maintenance Bags and Cell and Gene Therapy (CGT)

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Sterilization Modalities

Steam

High-temperature sterilization process using steam under pressure

Vaporized Hydrogen Peroxide (VHP)

Low-temperature gaseous process

Dry Heat

High-temperature sterilization and/or depyrogenation process using hot air with little or no moisture

Electron Beam

Exposes products to high-energy electrons

Ethylene Oxide (EO)

Uses a three-part gas process that includes pre-conditioning, sterilization and aeration

Gamma Irradiation

Exposes products to a Cobalt 60 radiation field

X-ray

Uses ionizing energy from high-powered electron beam accelerators

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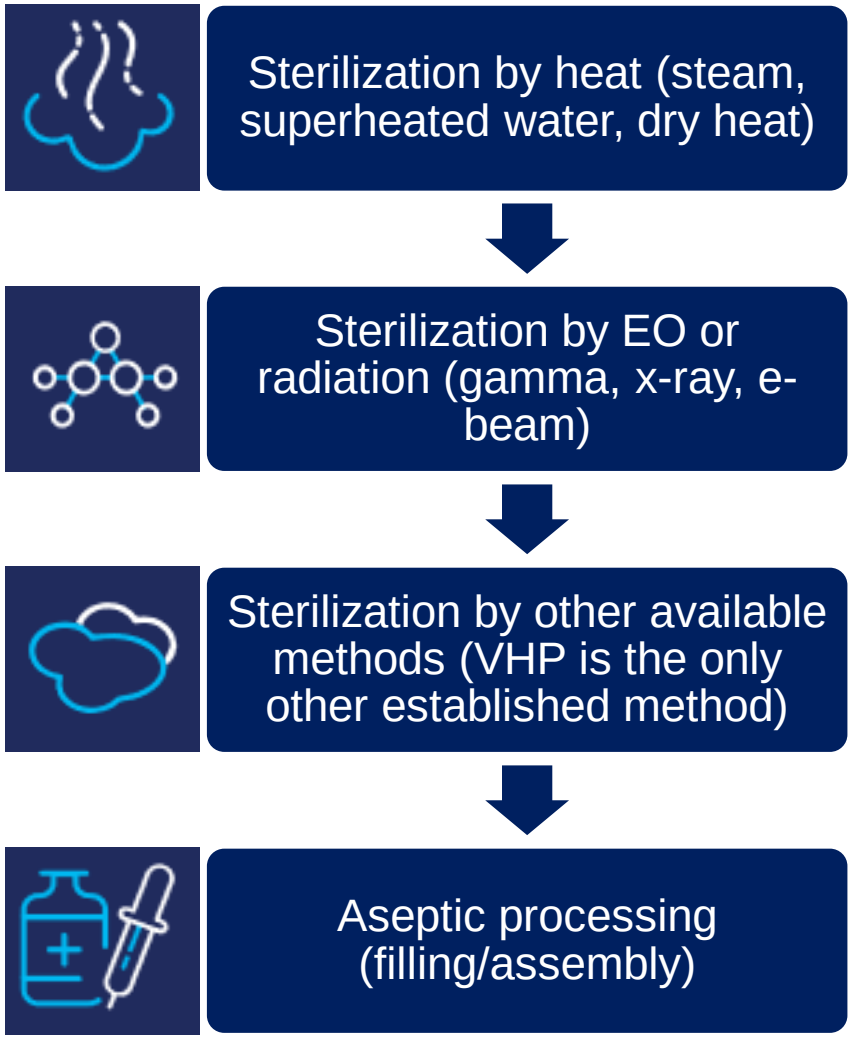
Preferences for Processing Methods

- A Contamination Control Strategy (CCS) is always required for determining process known bioburden **(2.3)**
- Terminal sterilization is always preferred over aseptic processing where possible, and it must be proven that terminal sterilization is not possible **(8.34)**
- Sterilization by heat is always the preferred method for component and terminal sterilization **(8.37)**
- For aseptic area cleaning/washing followed by heat sterilization, unidirectional transfer is always the preferred method for components
  - If this is not possible for components, use a low temperature method by a sporicide or disinfectant transfer **(4.11)**
- Components coming to production can also be pre-sterilized by heat/EO/radiation and transferred to production via material transfer using a disinfectant or sporicide **(8.71, 8.73, 8.47)**
- For aseptic filling, it is required to have enhanced CCS materials, people/gowning, critical spaces (isolators, RABS, cleanrooms) and qualification **(8.10)**



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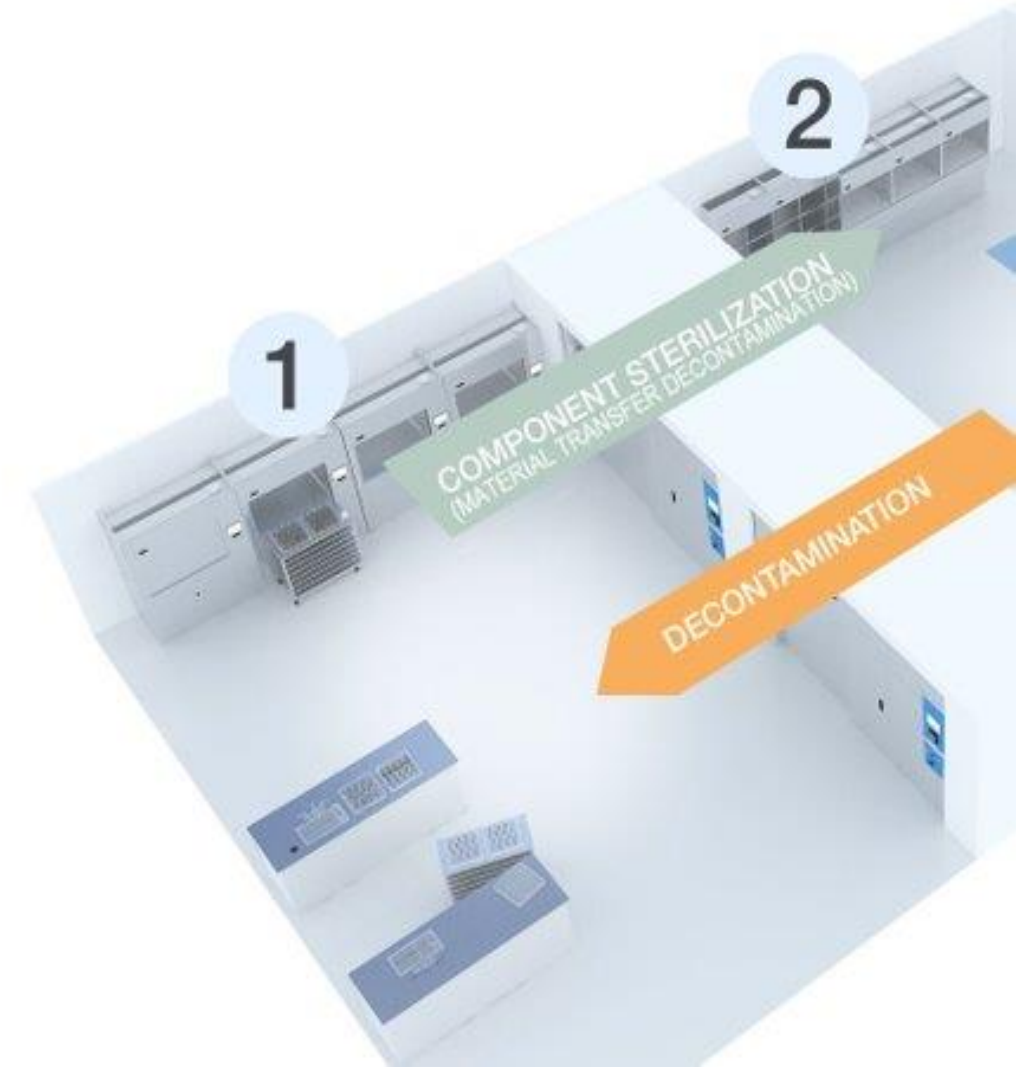
Material Transfer



"4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones **is one of the greatest potential sources of contamination**. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented…."

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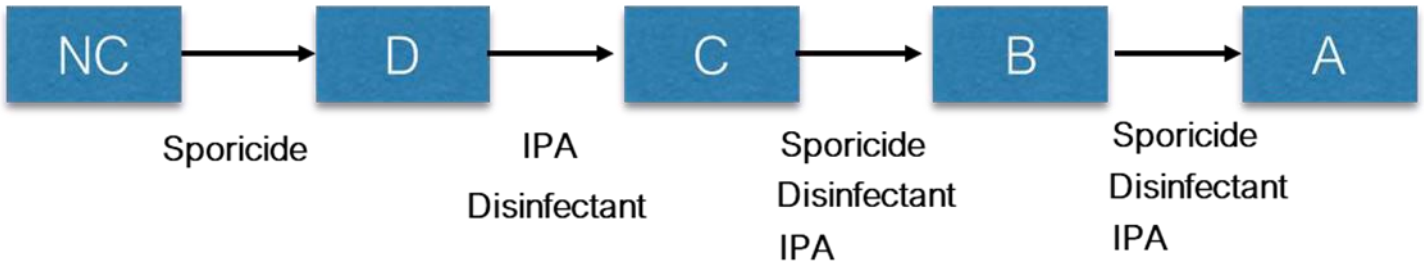
Material Transfer

“4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into these areas through double-ended sterilizers (e.g., through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g., using an effective transfer disinfection process, rapid transfer systems for isolators or for gaseous or liquid materials, a bacteria-retentive filter). …”



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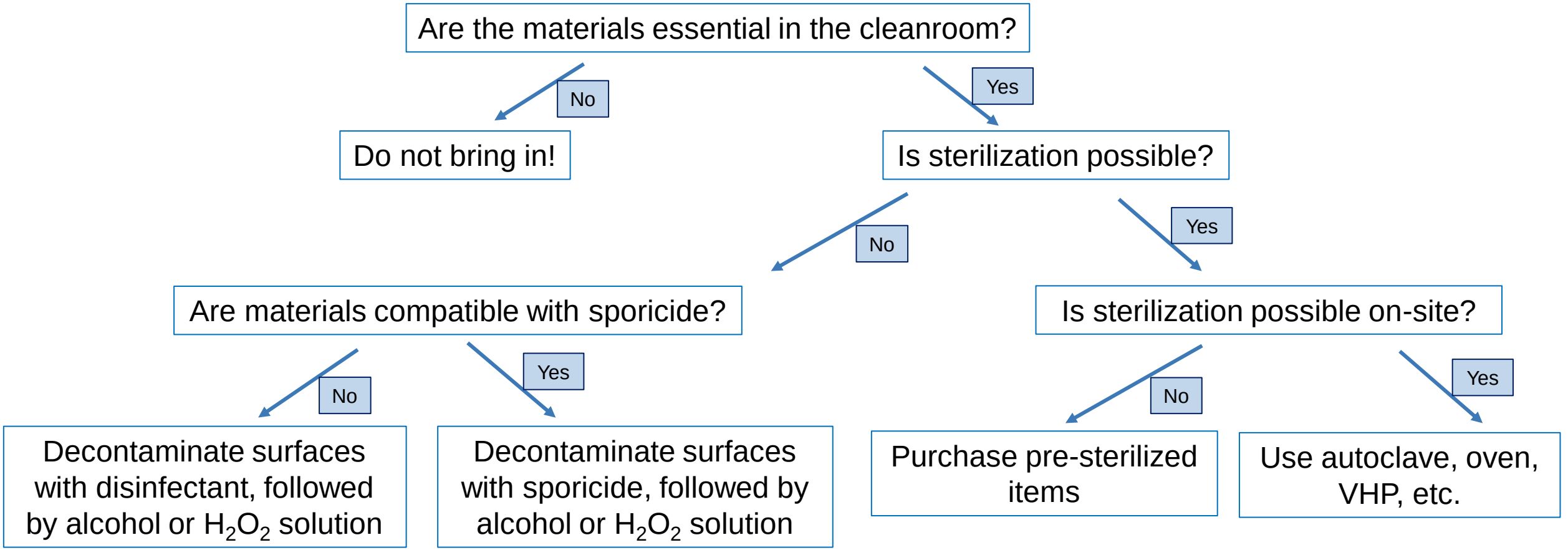
Material Transfer Decision Tree



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Product Contact Equipment Life Cycle

Contamination Control Strategy (CCS)

A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality

The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control

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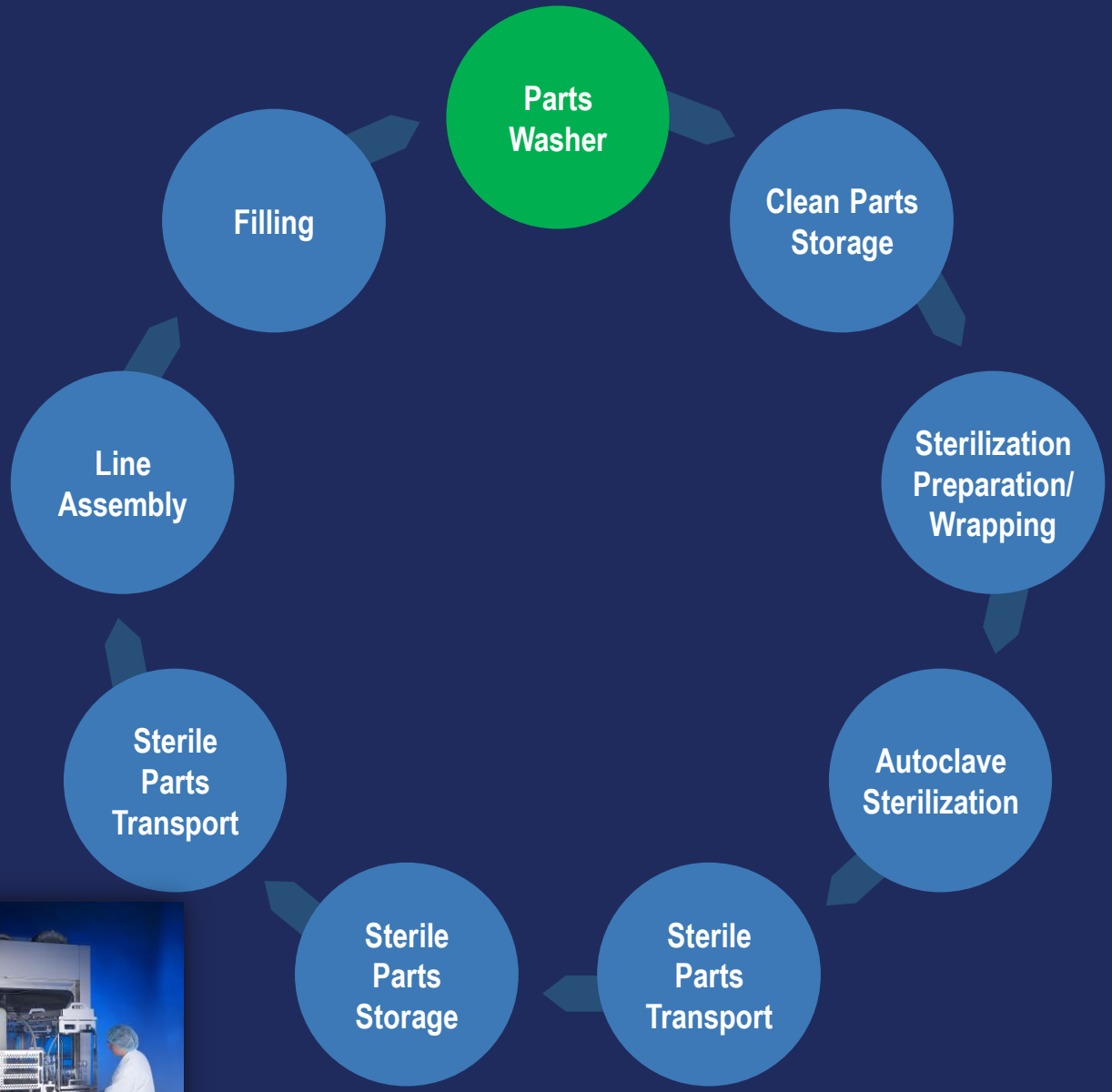
Washing

Cleaning is a critical step to sterilization



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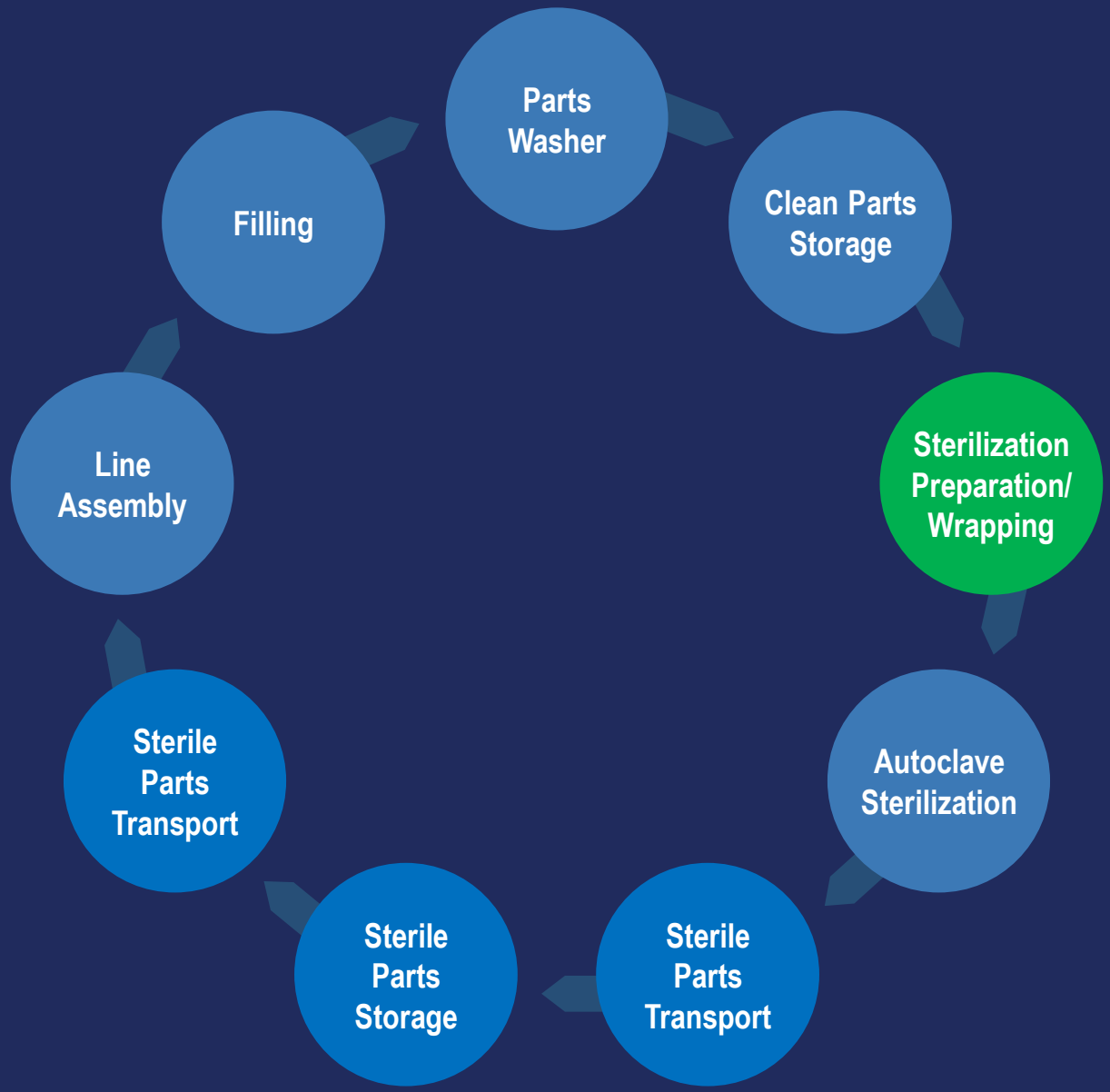
Sterilization Preparation/Wrapping



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What is the Purpose of Sterilization Wrapping?

EU Annex 1, Section 8.48

"Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use."

Manufacturers of ***aseptically filled*** drug product need to ***protect product contact surfaces*** through sterilization, until time of use on the filling line

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STOPPER BOWL COVERS

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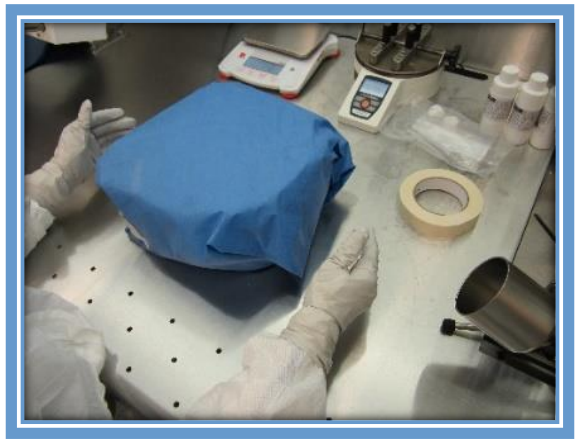
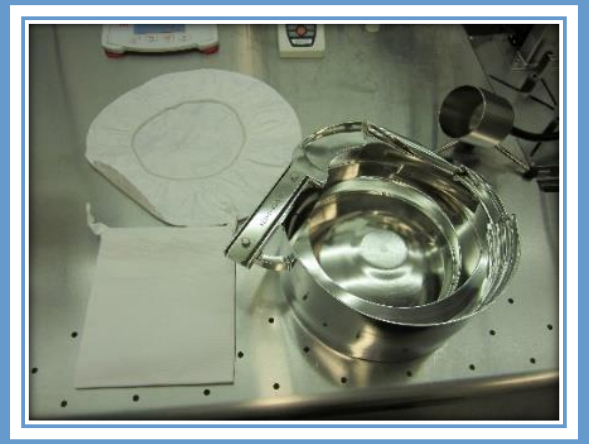
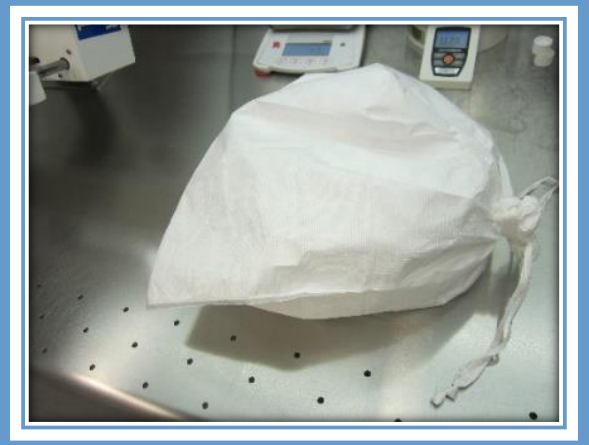
Particle Generation

Wrapping a stopper bowl with a Tyvek® elasticized cover and drawstring sterilization bag is more reproducible and efficient than wrapping with blue cellulose/paper and tape

Less than one-tenth the number of particles (0.5 and 5 microns in size) are generated using Tyvek® compared to cellulose paper







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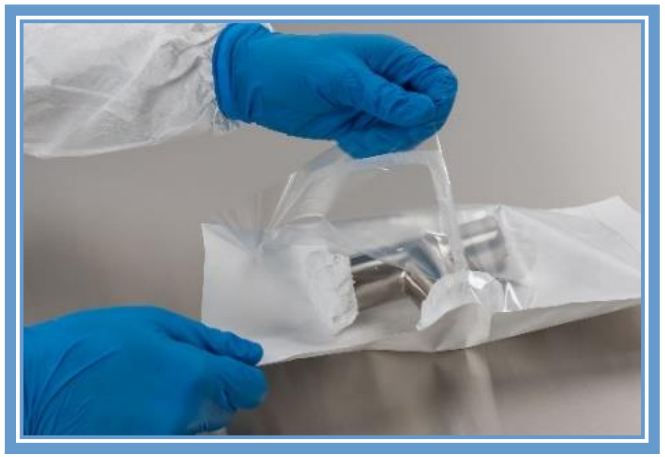
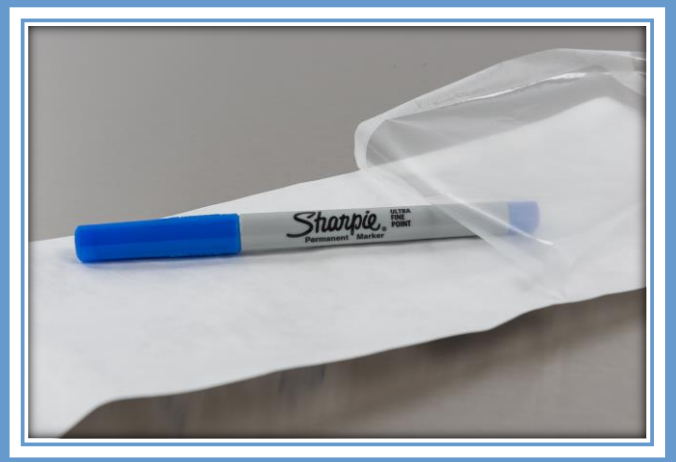
Particle Generation

Peeling open a sealed Tyvek® pouch generates less than one-tenth the number of particles (0.5 and 5 microns in size) compared to a cellulose pouch





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Sterilized Equipment Protection

EU Annex 1, Section 8.46

“Suitable protection after sterilisation should be provided to prevent recontamination. If sterilized items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established.”

Sterilization wrapping

- Microbial barrier
- Validated hold times

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Best Practice Recommendations

Primary and secondary wrapping on product contact surfaces prior to steam sterilization

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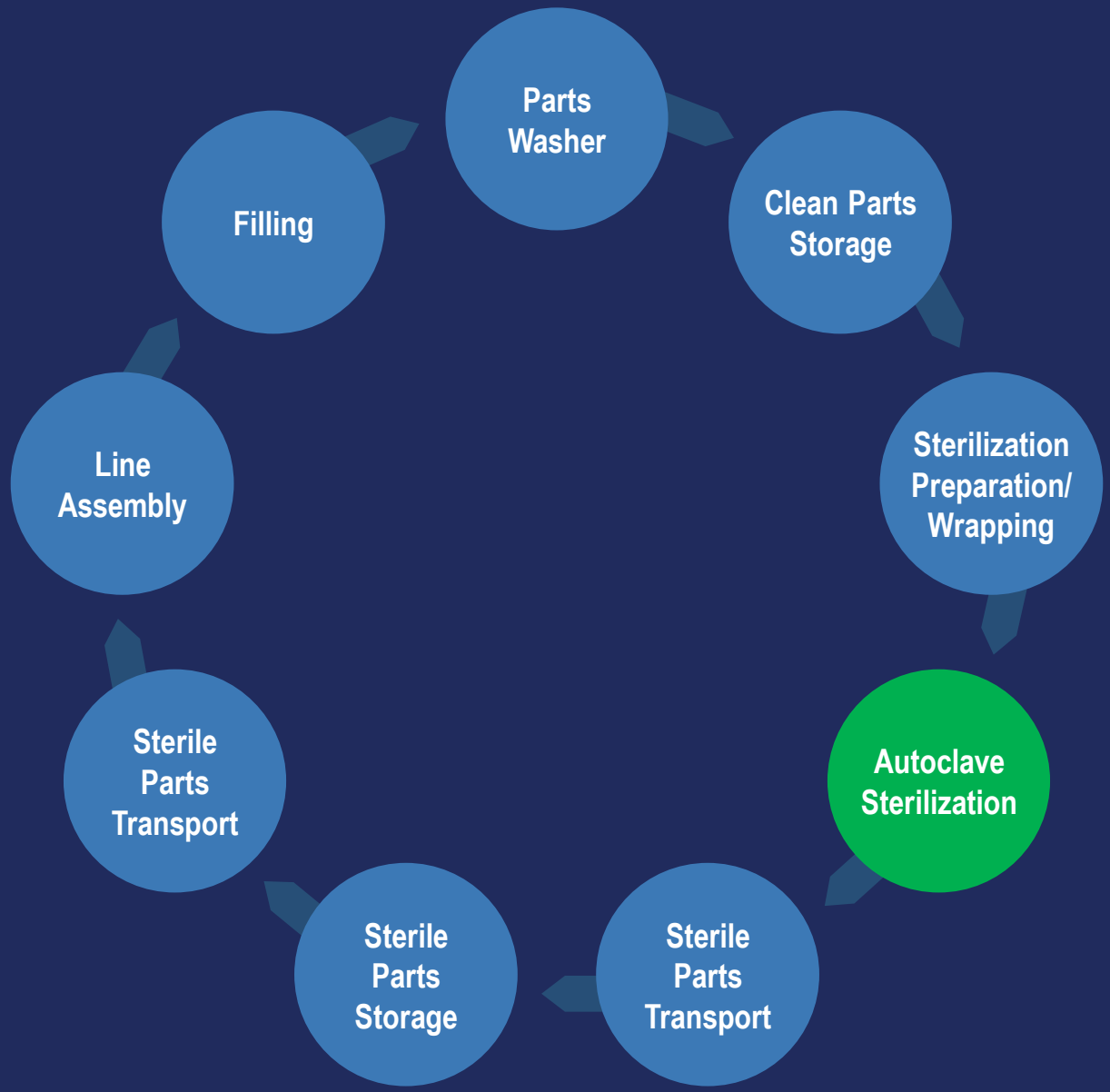
Steam Sterilization (8.37)



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Transportation and Assembly of Sterilized Equipment (8.47)

Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. areas.

Material Transfer - Low Temperature

Grade C
(ISO 8)

Automated Biodecontamination Chamber

Grade B
(ISO 7)

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Automated Material Transfer

Automated transfer of IV bags

Design to meet throughput ISO 9 to ISO 7

6-log biological indicator used

Cycle time ~70 minutes

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Chamber Loading Strategies

Minimize individual component handling

- Prepare product and transfer to the cart
- Optimize carts, hangers

Maximize load per run

- Minimize contact surfaces
- Configure packaging arrangement for load-penetrating airflow
- Simple load arrangement
- Preload smaller items (vials) in totes
- Execute verifications runs with chemical indicators/biological indicators
- Use max load as worst-case scenario

Material Surface Disinfection

Organism	Surface	Treatment (Contact Time)	Baseline Inoculum	Log Reduction	Percent Kill
A. brasiliensis	Self-seal pouch	70% IPA (1 min)	5.58	0.11 ± 0.08	22.72%
		Sporicide (5 min)	5.58	> 4.58	> 99.99%
		Sporicide (5 min) + 70% IPA (1 min)	5.58	> 4.58	> 99.99%
B. subtilis	Self-seal pouch	70% IPA (1 min)	5.24	0.01 ± 0.01	2.48%
		Sporicide (5 min)	5.24	1.47 ± 0.07	96.61%
		Sporicide (5 min) + 70% IPA (1 min)	5.24	1.98 ± 0.03	98.96%

PDA Contamination Control Book 2018 Chapter 7

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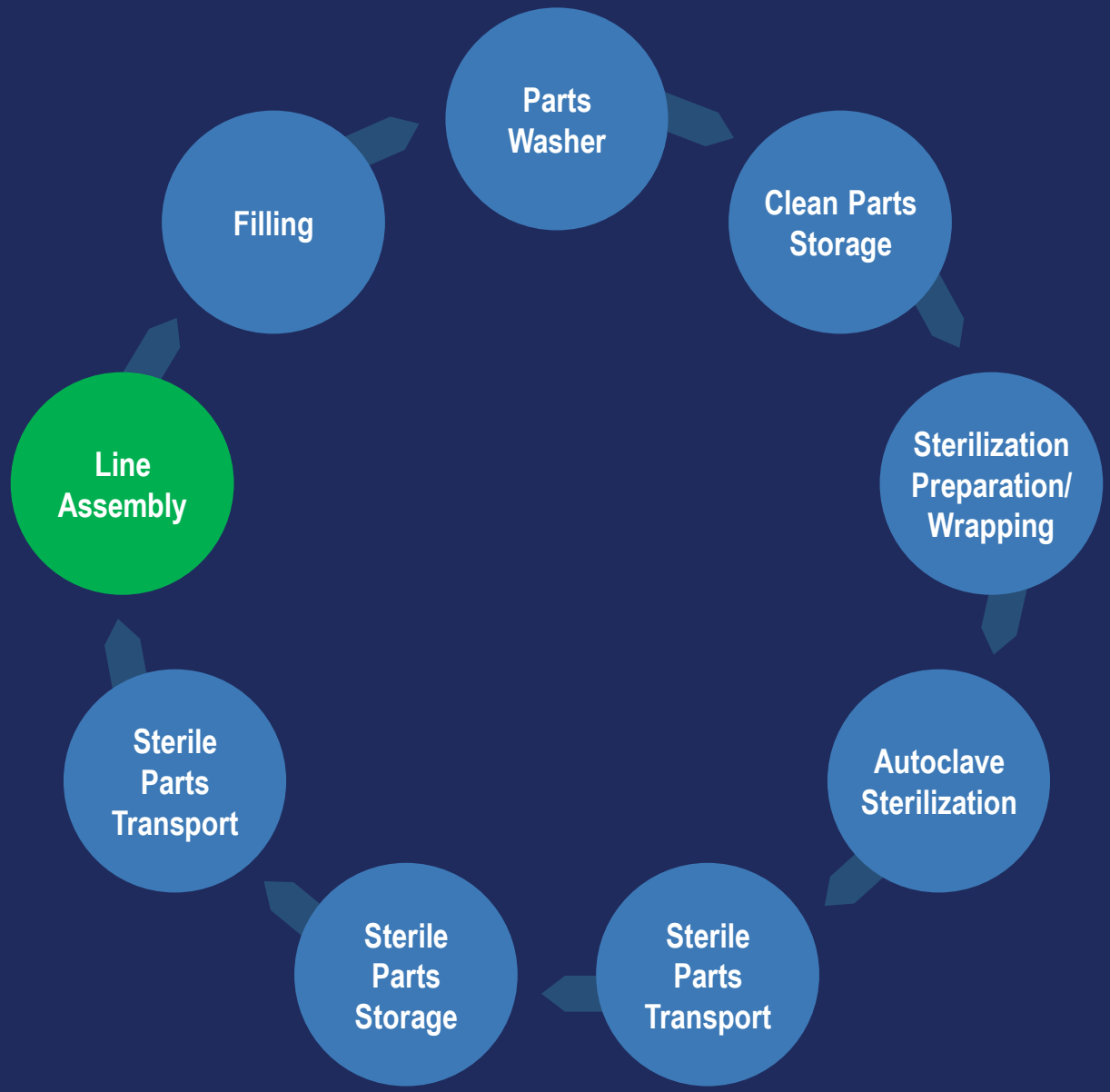
Line Assembly – RABS/Isolators (4.22)

Remove outer layer and stage wrapped/covered parts in RABS/isolator prior to decontamination process (e.g., VHP)

Run VHP cycle and remove primary surface cover through glove ports



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Line Assembly – RABS/Isolator – Stopper Bowls

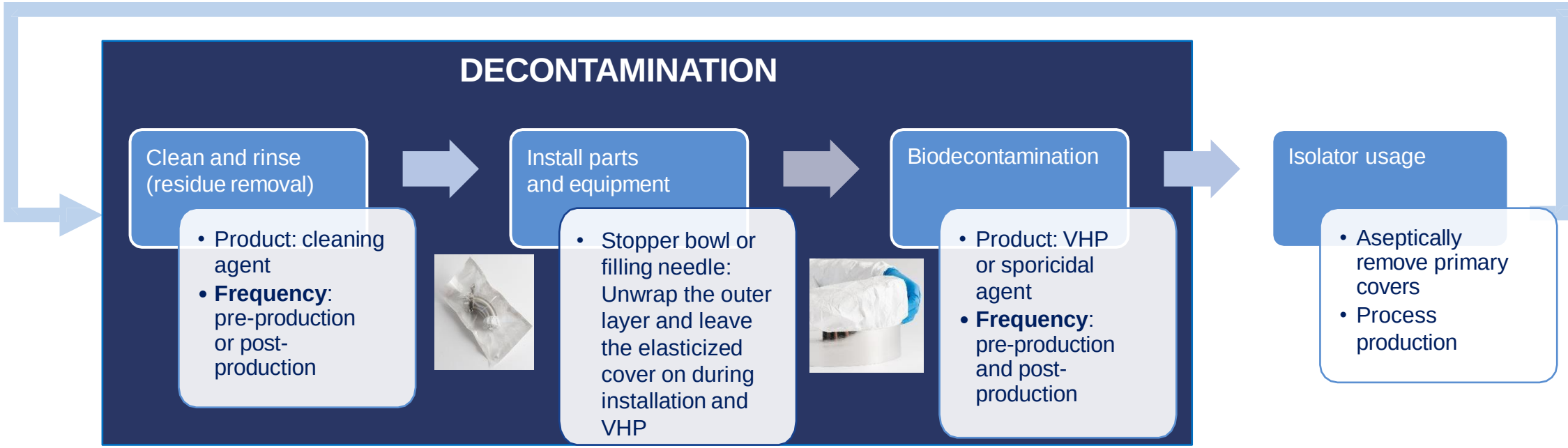
Line Assembly – RABS/Isolator – Filling Needles

Autoclave Sterilization

Sterile Parts Transport

Biodecontamination of Isolators

4.22 ….The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g., gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. **Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.**



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VHP and Wrapping Materials

VHP™ Compatibility

- Advancement of Medical Instrumentation (AAMI) Technical Report (TIR) 17 - “Compatibility of Materials Subject to Sterilization”
- Tyvek® material is high-density polyethylene, which showed “excellent” compatibility with hydrogen peroxide sterilization, observing “no change” after exposure to greater than 100 VHP cycles

VHP Penetration

- During a standard environmental decontamination process in an isolator, a Draeger sensor confirmed removal of VHP from within sterilization wrapping (one layer Tyvek®/PET pouch, elasticized cover and drawstring bag) to less than 0.1 ppm after aeration
- VHP can also penetrate through Tyvek® sterilization wrapping and result in a 6-log biological indicator kill

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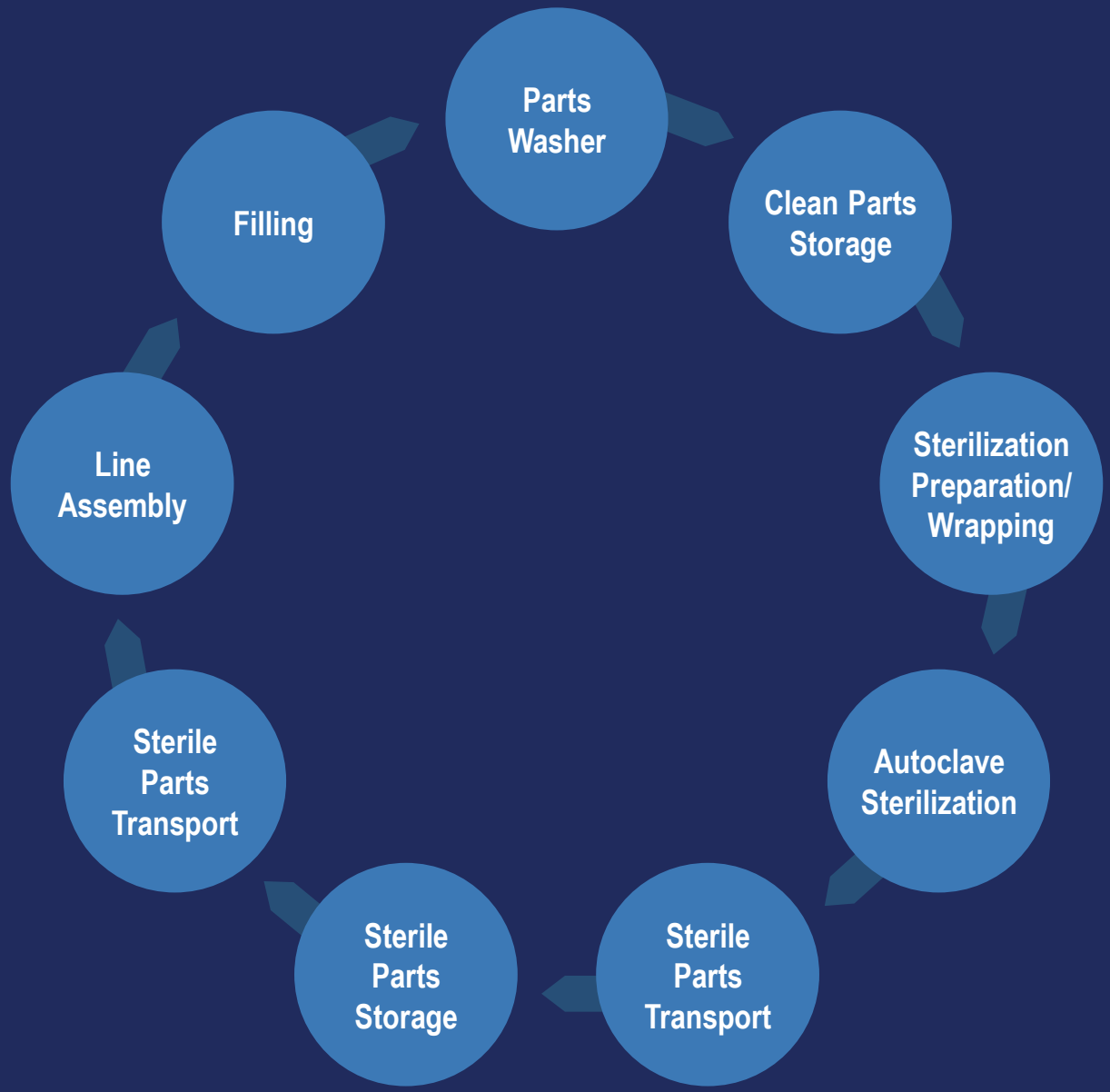

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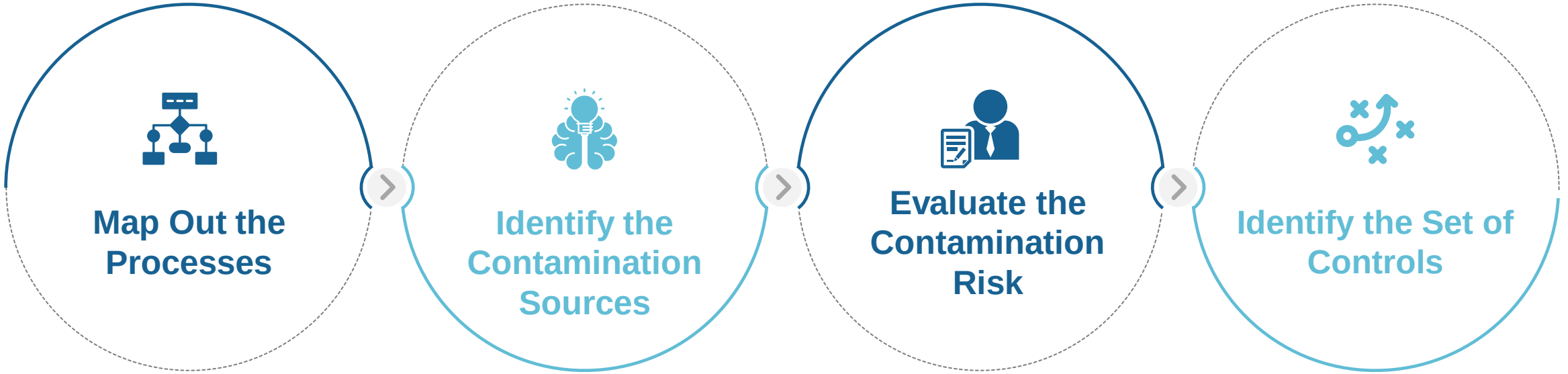
Contamination Control Strategy



EU Annex 1, Section 2.4: Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.

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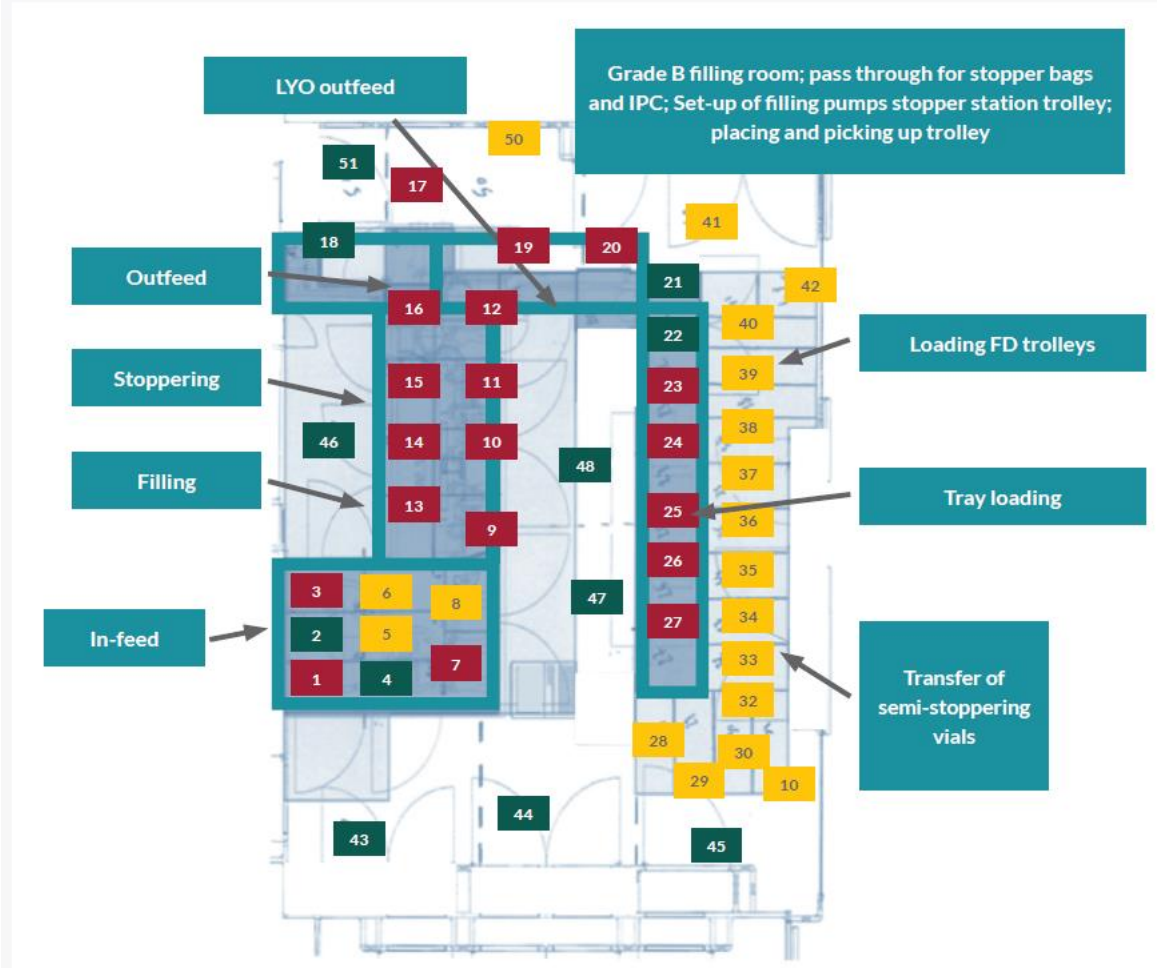
Risk Assessment

Table 9: Rating each grid against six factors and calculating risk score

	Amenability of equipment and surfaces to cleaning and sanitization	Personnel presence and flow	Material flow	Proximity of open product or product-contact materials	Interventions/ operations by personnel and their complexity	The frequency of interventions/ operations	Risk score	Rank of risk score
Rating	1	4	4	8	4	4	2048	12
Grid 1	Depyrogenated glass entering filling line, turntable. 1. Moistening turntable performed with closed doors, when the turntable is empty, at least 1/batch. Silicon wipes are transferred to the grid. Silicon wipe is transferred to grade B through the grid 2. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 3. During set up: placing forceps (open doors) 4. Adjustments of format parts with open doors (not frequent intervention) (one door), empty compartment grids 1–8. Note: silicon wiping only during set up.							
	1	1	1	8	1	1	8	4
Grid 2	No interventions							
	1	4	4	8	4	4	2048	12
Grid 3	Depyrogenated glass enters filling line, turntable. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 2. During set up: placing forceps (open doors) 3. Adjustments of format parts with open doors (not frequent intervention) (one door), empty compartment grids 1–8.							
	1	1	1	8	1	2	16	5
Grid 4	Glass is transported. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 2. Adjustment of format parts with closed doors (not for every batch), empty compartment grids 1–8. A tool is used if necessary.							
	1	1	1	8	1	4	32	6
Grid 5	Glass is transported. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 2. Adjustment of format parts with closed doors (not frequent intervention) (empty compartment grids 1–8). A tool is used if necessary.							
	2	2	2	4	2	2	2048	6
Grid 6	Glass is transported. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers.							
	1	4	4	8	1	4	512	10
Grid 7	Glass is transported. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 2. During set up: bringing tweezers in (open door).							
	1	4	1	8	1	2	64	7
Grid 8	Glass is transported. 1. Manipulation of a container performed with closed doors, forceps (part of set up). If reach over other containers, need to remove the containers 2. Adjusting format part with closed doors (not frequent intervention) 3. During set up: bringing tweezers in (open door) 4. Removing broken vials with closed doors with tweezers (not frequent intervention).							

Figure 3: Example of ratings against the six factors and applying the scoring system to each grid to create a heat map of relative probability of contamination (Note the functional sections in the filling line encased in blue edging)



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Evaluate Contamination Risk

Process Step/Contaminants	Product Residue (Annex 15 – Cleaning Validation)	Particulate	Microorganisms	Endotoxin
Parts Washing	3	2	1	3
Clean Parts Storage	1	3	3	3
Sterilization Preparation/Wrapping	1	4	4	2
Autoclave Sterilization	1	1	3	1
Sterile Parts Transport	1	4	4	1
Sterile Parts Storage	1	3	2	1
Line Assembly	2	5	5	2
Filling Process	3	3	3	2

Risk Score
1 = minimal or no risk
5 = maximum risk

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Identify and Implement Controls

Process Step	Control	Impact
Parts Washing	Validated Cycle Detergents	Process Consistency, Effectiveness Efficiency
Clean Parts Storage	Room Classification Equipment Covers	Minimize Risk of Contamination
Sterilization Preparation/Wrapping	Wrapping Materials Work Instructions	Efficiency, Reproducibility
Autoclave Sterilization	Validated Cycle Wrapping Materials Process Monitoring (Alarms, BIs, CIs)	Process Consistency, Effectiveness Efficiency Sterilization Confirmation
Sterile Parts Transport	Wrapping Materials (Multiple Layers) Sterility Maintenance Bags Surface Disinfection	Microbial Barrier Disinfectant Compatibility
Sterile Parts Storage	Room Classification Sterility Maintenance Bags HEPA/LAF Cabinet Equipment Covers	Minimize Risk of Contamination
Line Assembly	Wrapping Materials Work Instruction Sequence of Activities RABS/Isolator Decontamination (VHP)	Minimize Risk of Contamination Process Consistency, Effectiveness Efficiency Decontamination Compatibility
Filling Process	Aseptic Process Simulation Interventions Pre-Sterilized Tools	Aseptic Confirmation

Case Study: Material Transfer Using Sterility Maintenance Bags

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Annex 1, Section 8.46

- Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. **Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade).** Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.

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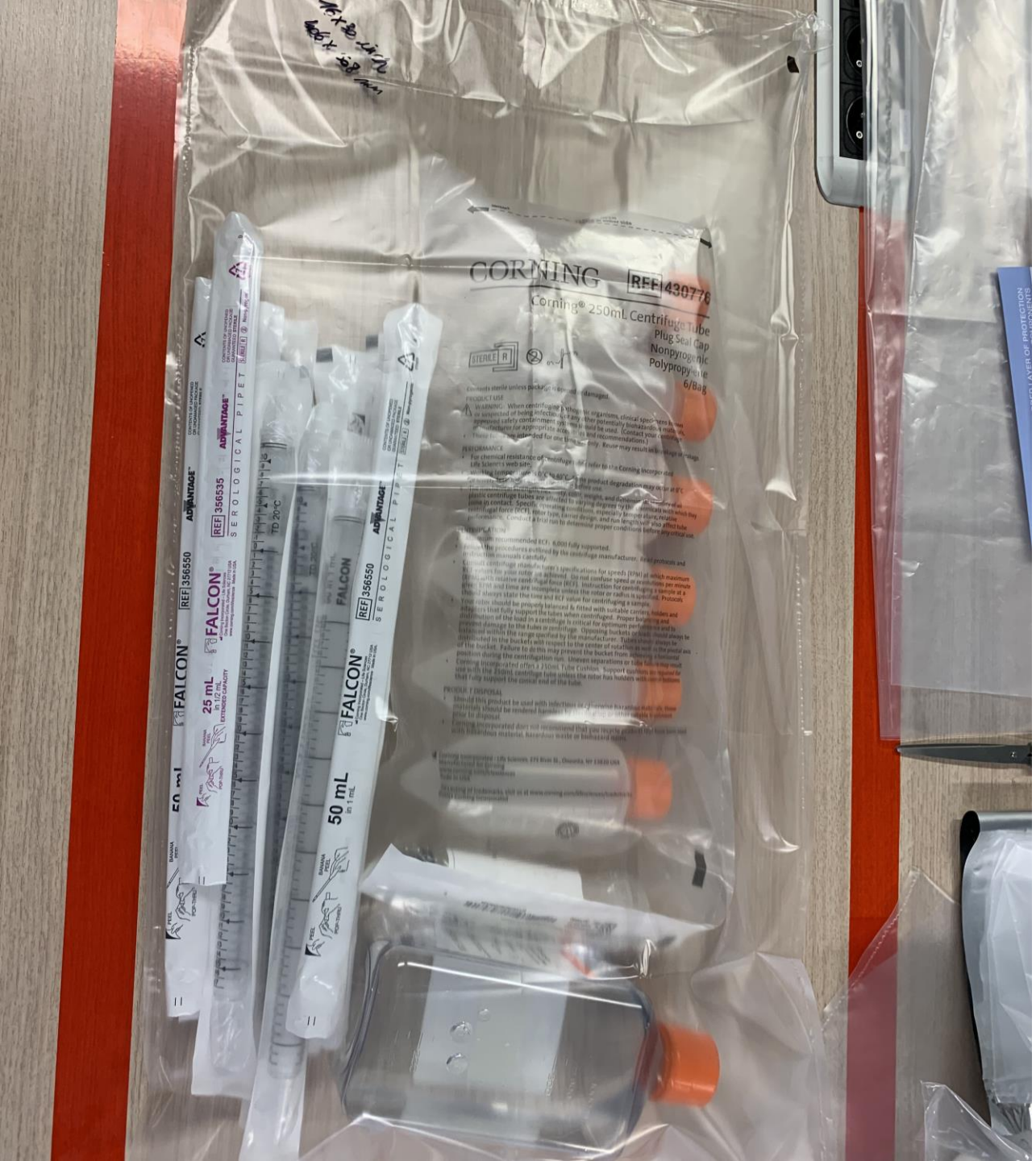

CAR-T Sterile Kits

Multi-layer sterility maintenance bags

- “Kitting” and wrapping materials into the same package in a BSC
- Three layers of sterility maintenance bags
- Transfer materials from one building to another
- While moving from lower classification to higher, removing a layer of bag
- All plastic bags can be wiped with sporicides without penetration into the bag

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Conclusion

Material transfer and sterility maintenance are critical parts of a CCS

Steam sterilization is the preferred method

Alternate surface biodecontamination methods must be used for transfer to critical areas (i.e., isolator, RABS, cleanroom, BSC)

Automated or manual alternatives are available for transfer to critical areas with a preference for automated processes

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