GENESIS ENGINEERS

Design for Aseptic Processing Facilities (APF) Part 1

NIH National Institutes of Health

Introduction

- This training module includes:
  - Two (2) half-day training sessions
  - A 10 question assessment to be given at the end of this course
- This course provides introductory training on Design practices for Aseptic Processing Facilities (APF).
- A module of references is provided to be read between ½ day sessions
- This course is intended for facility management and personnel, laboratory personnel, Quality Assurance (QA), and contractors.

Introduction

- Module content
  - ➢ APF Overview
  - ➢ Definitions
  - ➢ Aseptic Process Regulation
  - ➢ Design Issues
    - Programming
    - Separation
    - Advanced Aseptic Processing

Definitions

- **cGMP** – current Good Manufacturing Practice
  - Regulations enforced by the FDA.
  - Provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.
  - Assure the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.

- The “c" in **cGMP** is added to remind manufacturers that the standard of care is always evolving. Just because a system or practice was acceptable in the past does not mean it will be accepted in the future.

Definitions

- **GEP —** Good Engineering Practice
  - Established engineering methods and standards that are applied throughout the product life cycle to deliver appropriate and cost-effective solutions.
  - Engineering Processes & Systems to meet institutional needs.

- **GEP vs GMP**
  - GEP Serves the institution by assuring good design and decision making to support institutional goals.
  - GMP Serves the patient by assuring good design and decision making to support Safety, Identity, Strength, Purity and Quality (from 21CFR210).

Definitions

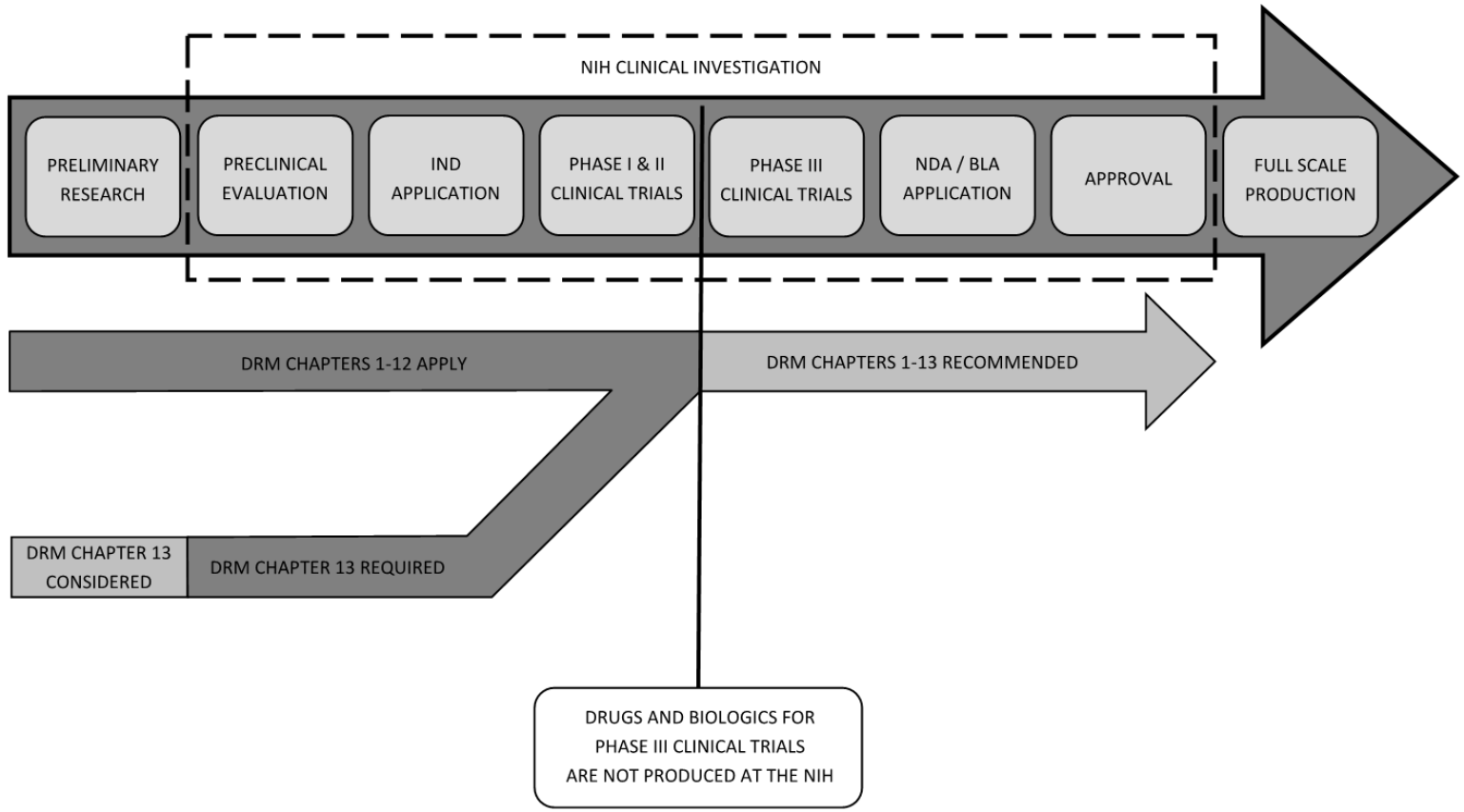
- **GDP –** Good Documentation Practices
  - Established documentation methods and standards that are applied to all cGMP documents that assure clarity and accuracy. These include:
    - Revision History
    - Consistent Dating Practices
    - Formal Approvals
    - Consistent naming, signatures and initials
    - Document Numbering
    - Document Control

Definitions

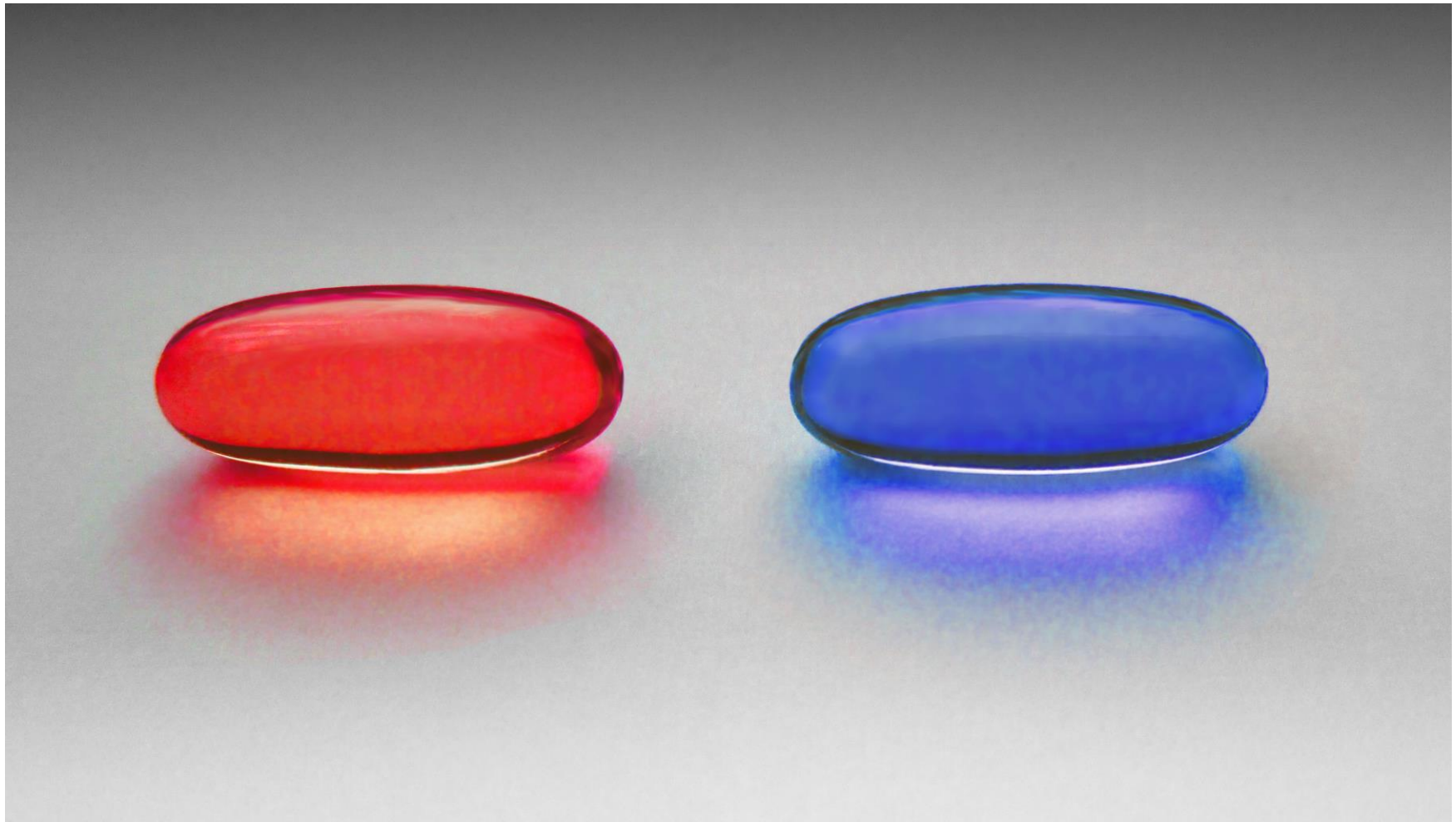
- **Critical Parameter**
  - A room variable (such as temperature, humidity, air changes, room pressure, particulates, viable organisms, etc.) than, by law or by determination from pharmaceutical product development data, affects product strength, identity, safety, purity, or quality (SISPQ).
- **Acceptance Criterion**
  - The predetermined result of a specified test. In HVAC, the upper and lower limits of the room environment (critical parameters). If these limits are exceeded, the exposed pharmaceutical product may be considered adulterated.

Application of Chapter 13

Figure 13.1.0 DRM Chapter 13 Application



BASIC cGMP REGULATION



21CFR 210

PART 210 -- CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

TITLE 21 – FOOD AND DRUGS

CHAPTER 1 – FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER C – DRUGS: GENERAL PART 210 – CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDIING OF DRUGS; GENERAL

210.1 Status of current good manufacturing practice regulations.

(a) …assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation …shall render such drug to be adulterated … the person who is responsible …shall be subject to regulatory action.

21 CFR 211

Sec. 211.42 Design and construction features

- Prevent Contamination and cross-contamination
- Facilitate Cleaning
- Enough Space to prevent mixup of:
  - Receipt / quarantine before release
  - Holding rejected matl.
  - Storage of released matl.
  - Storage of in-process matl.
  - Manufacturing and processing operations;
  - Packaging and labeling operations;
  - Quarantine storage before release of drug products;
  - Storage of drug products after release;
  - Control and laboratory operations;

21 CFR 211

Sec. 211.42-58 Design and construction features

- Aseptic Processing areas need:
  - Environmental Monitoring
  - Maintenance
  - Cleaning and Sanitization “systems” – often SOPs
  - HEPA filters
  - Adequate lighting
  - Adequate Ventilation, temperature, humidity, pressure, dust, microorganisms
  - control of pharmaceutical aerosols
  - Smooth, Hard, Cleanable surfaces
  - Penicillin is separate

21 CFR 211

Sec. 211.48-56 Design and construction features

- Aseptic Processing areas need:
  - Drains need air break (keep drains out of cleanest areas)
  - Water of appropriate quality
  - Adequate washing facilities
  - Pest Control
  - Cleaning and Sanitization SOPs

BIOTECH – REGULATORY VIEW

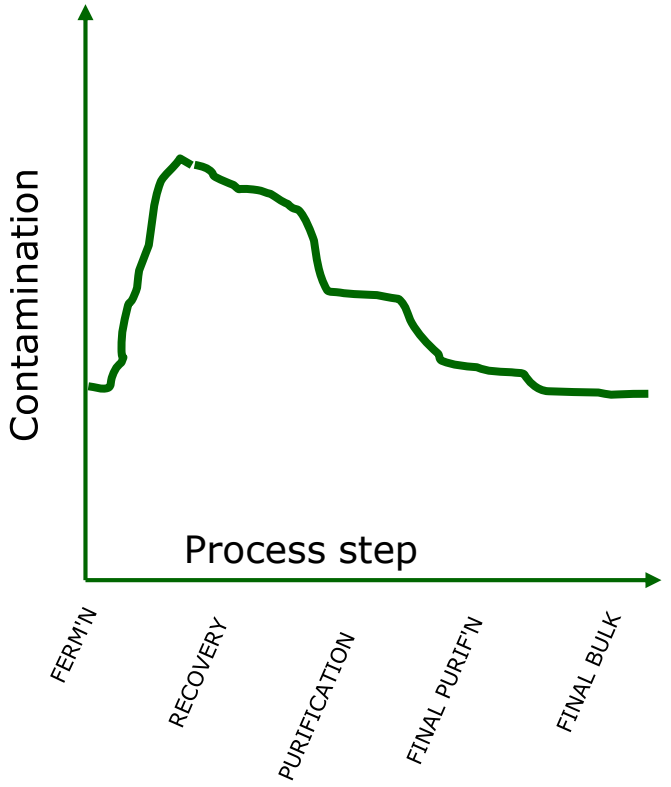
FDA – 21 CFR 600

Sec. 600.11 Physical Establishment

- Similar to Aseptic Processing Areas
- Focus is on exclusion of adventitious organisms, especially spore-formers
- Spore forming organisms and live virus vaccines need special precautions to prevent cross-contamination.
- Where risk is high, a dedicated facility or dedicated area on a dead-end corridor is suggested.
- Tests that use wild virus, bacteria or other pathogen must be separated from production. Equipment exposed to these must be separate or have validated cleaning.
- Follow aseptic guidance for filling and container closure integrity testing

Bulk Bio HVAC Concepts in Biopharmaceutical Guide

Table x-x	Historical Area Classifications				
All Air Classifications Refer to the "In Operation" Condition					
Typical Process	**Protected Process**			**Open Process**	
Step		**Closed**	**Contained**		
	Background Environment	Product/Container Closure Exposure	Product/Container Closure Exposure	Background Environment	Product/Container Closure Exposure
Raw Material Dispensing	CNC	NA	ISO 8	CNC+	Local Protection
Pre-sterilized Matl.Dispensin	CNC+	NA	ISO 5	ISO 8	Local Protection
Inoculum Prep	ISO 8	NA	ISO 5	ISO 7	ISO 5
Seed Train / Cell Expansion	CNC+	NA	ISO 7	ISO 8	Local Protection
Fermentation /Cell Culture	CNC+	NA	ISO 7	ISO 8	Local Protection
Media Prep (Pre-Filtration)	CNC+	NA	ISO 7	ISO 8	Local Protection
Media Prep (Post-Filtration)	CNC	NA	NA	ISO 7	Local Protection
Media Hold	CNC	NA	NA	ISO 7	Local Protection
Harvest / Recovery	CNC+	NA	ISO 7	ISO 8	Local Protection
Purification - Initial	CNC+	NA	ISO 7	ISO 8	Local Protection
Purification - Final	CNC+	NA	ISO 7	ISO 8	Local Protection
Buffer Prep (pre-filtration)	CNC+	NA	NA	ISO 8	Local Protection
Buffer Prep (Post Filtration)	CNC	NA	NA	ISO 7	Local Protection
Buffer Hold	CNC	NA	NA	ISO 8	Local Protection
Column Packing	CNC+	NA	ISO 6	ISO 7	Local Protection
Bulk Filtration	ISO 8	NA	ISO 7	ISO 7	Local Protection
Bulk Filling	ISO 8	NA	ISO 5	ISO 7	Local Protection
Washer Prep	CNC	NA	NA	CNC	100% Exhaust
Hand Wash	CNC+	NA	ISO 7	ISO 8	Local Protection
Clean Equipment Staging	CNC	NA	NA	ISO 8	N/A
CIP Skid	CNC	NA	match process	match process	N/A
Sanitization Closet	CNC	NA	100% Exhaust	CNC	100% Exhaust
Dirty Equipment Staging	ISO 8	NA	NA	CNC	N/A
Autoclave Preparation (wrap)	ISO 8	NA	ISO 7	ISO8	Local Protection
Bulk Product Hold	CNC	N/A	NA	CNC	N/A



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Bulk Bio HVAC Concepts in Biopharmaceutical Guide

Exposure Risk						
		Energy of Process				
		High	Med-High	Medium	Med-Low	Low
Stage of Processing	Bioreactor	Medium	Med-Low	Low	Low	Low
	Harvest	Medium	Med-Low	Med-Low	Low	Low
	Initial Purification	Med-High	Medium	Med-Low	Med-Low	Med-Low
	Final Purification	High	Med-High	Medium	Medium	Medium
	API	High	High	High	High	High
	Innoculum	High	High	High	High	High

Space Classification by Risk						
		Layers or Level of Protection				
		0	1	2	3	4
Exposure Risk	High	ISO 5 (A)	ISO 7 (B)	ISO 8 (C)	CNC+	CNC
	Med-High	ISO 6	ISO 8 (C)	CNC+	CNC	CNC
	Medium	ISO 7 (B)	CNC+	CNC	CNC	CNC
	Med-Low	CNC+	CNC	CNC	CNC	CNC
	Low	CNC	CNC	CNC	CNC	CNC

Notes:

1. A fully hermetic system may be considered equivalent to 3 layer of protection
2. An open micro-environment can provide a >1 log reduction in contaminants, or 1 layer of protection
3. A closed micro-environment can provide a >2 log reduction in contaminants, or 2 layers of protection

ISPE GRADE	Temp ºF (C)	RH %	Final Filter		Design Air Change Rate
			USA	EU	
Grade5	65 +/-5 (18 +/- 3)	30-60	HEPA	H-13* or H-14	N/A
Grade6	65 +/-5 (18 +/-3)	30-60	HEPA	H-13*	50-60
Grade7	68 +/-5 (20 +/-3)	30-60	HEPA	H-13*	15-60
Grade8	70 +/-5 (21 +/-3)	30-60	MERV 15-18 or HEPA	F-9 or H-13*	10-20
CNC+	72 +/-5 (22 +/-3)	25-60	MERV 14/15	F-9	6-15
CNC	72 +/-5 (22 +/-3)	25-60	MERV 11-13	F-6	6-10
UC	N/A	N/A	N/A	N/A	N/A

Vaccines and Live Virus Products?

Filling same as sterile filling

- (But not sterile filtered)

Pathogen production usually in separate facility

- Can be campaigned if well cleaned 21CFR 600.11(e)(4)
- Each unit op protected from other steps
  - Keep away from bio cell/tissue culture
  - Closed processing can have big impact
- Tends to be sterile early in the bulk process
- Pre/post inactivation are separated

STERILE PRODUCTS - REGULATORY VIEW

FDA Guidance for Industry, Sterile Drug Products…

- Critical Area, ISO 5
  - Measured “normally not more than 1 foot away from the work site”
  - Recommend nonviable particle monitoring with a remote counting system
  - HEPA-filtered air velocity sufficient to sweep particles away from filling/closing area.
  - Velocity parameters for each processing line should be justified and appropriate
  - In situ air pattern analysis should demonstrate sweeping action over and away from the product under dynamic conditions.
  - Prevent entrainment of lower quality air into the ISO5 clean area.
  - ISO 5 protection between the filling line and the lyophilizer
  - When stoppered vials leave ISO 5, provide as local protection until capped.

FDA Guidance for Industry, Sterile Drug Products…

- ISO 5 Critical Zone, ISO 7 background and ISO 8 Supporting Rooms
  - 10-15 Pascals (Pa) should be maintained between adjacent rooms of differing classification (with doors closed).
  - When doors are open, outward airflow should be sufficient to minimize ingress
  - ISO 8 at least 20 air changes per hour is typically acceptable
  - HEPA filter integrity should be checked twice a year for aseptic processing room.
  - 0.01% penetration calls for repair or replacement of the HEPA filter
  - Depyrogenation tunnel and oven HEPA filters must be tested.
  - Periodic monitoring of uniformity of velocity across the filter (and to adjacent filters).
  - Velocity should be measured 6” off the filter face and at a defined distance from the work and should correlate to the velocity at the time of air pattern analysis studies.

FDA Guidance for Industry, Sterile Drug Products…

- Isolators
  - OpenIsolators should be positively pressurized approximately 17.5 to 50 Pascals.
  - The interior of the isolator should meet ISO5
  - A Class 100,000 (ISO 8) background is adequate for an isolator
  - “An aseptic processing isolator should not be located in an unclassified room.”

FDA		In-Operation (particles/m3)	Active Air Action	EU, WHO, PIC/S	In-Operation (particles/m3)		At-Rest (particles/m3)		Active Air Action
ISO	USP	0.5µ	Limits	Grade	0.5µ	0.5µ	0.5µ	5.0µ	Limits
ISO5	100	3,520	1	A	3,520	20	3,520	20	<1
ISO6	1,000	35,200	7	N/A					
ISO7	10,000	352,000	10	B	352,000	2900	3,520	29	10
ISO8	100,000	3,520,000	100	C	3,520,000	29,000	352,000	2900	100
N/A	N/A	N/A	N/A	D	N/A	N/A	3,520,000	29,000	200

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Area Classification Harmonization

- Grade A Air Supply and Local Protection
- Definition
  - The terms “Local protection” (LP) and “Grade A air supply” (GAAS) are used to indicate a localized HEPA filtered air supply to reduce the risk of contamination within a specified working zone.
  - This engineering control can be applied to reduce risk in any background classification.

Area Classification Harmonization

- Grade A Air Supply and Local Protection
- Definition
  - LP/GAAS are generally configured with terminal HEPA filtration proximate to the work zone (above, or to one side, as appropriate to the risks) in order to ensure ISO 5 particulate levels.
  - Configuration of the extract to assure a flushing flow of clean air through the area of concern is a key attribute of a well-designed LP/GASS.
  - In certain cases additional engineering controls, such as enclosures can be employed to enhance the air quality within the work zone.

Break

CELL AND GENE THERAPIES

US FDA Office of Cell, Tissue and Gene Therapy (OCTGT)-Regulated Products

- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
- Cell therapy products
- Tissue and tissue-based products
- Cell- or tissue-based combination products
  - Cell/device, tissue/device, other
- Devices used for cells/tissues
  - Processing devices, other
- Tumor vaccines and immunotherapy
- Gene therapy products
- Xenotransplantation products
- Donor screening tests (cadaveric blood samples)

Regulation Reflects the Evolving Nature of Cell-, Gene- and Tissue-Based Therapies

- Cell therapy, gene therapy, and tissue-engineered products are complex living biologics, and are being developed in novel, evolving ways. Regulation of these products commonly reflects their novel, diverse nature.
- Regulations set a framework of criteria that must be met.
  - Safety, identity, purity, potency, and clinical efficacy
- Regulatory agencies, in general, follow a science-driven, risk-based approach in evaluating whether and how these criteria have been met.
  - Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.

Risk-Based Approach to Cell Therapy Regulation

- Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
- Risks, and potential risks
  - Complex manufacturing, complex product
  - Unrelated allogeneic clinical strategy
  - Cells/tissues used in a manner unlike natural function
  - Or, cannot assess risk due to extreme novelty
- Higher-risk products regulated under Public Health Service Act, Section 351

Autologous *vs.* Allogeneic Products: Manufacturing

Autologous/Patient-Specific

- 1 lot per patient
- Increase scale by increasing throughput, manufacture multiple individual products in parallel
  - Automated, functionally-closed process technology - individual product isolation
- Public health risk from each batch is reduced.
- Cell materials are likely less well characterized, more like blood bank risks.
- Self to self risk is low

Allogeneic "Universal Donor"

- 1 lot = 100s or 1000s of doses, "off-the-shelf "products
- Large-scale processing increases risk.
- Population at risk is larger
- Cell materials are likely very well characterized.

Application of FDA Regulatory Requirements

"361" Products

IF a cell therapy product meets criteria 1 ***and*** 2 ***and*** 3, ***and*** (4a ***or*** 4b ***or*** 4c).

1 Minimally manipulated (not activated, encapsulated, expanded *ex vivo* ,or genetically modified) ***AND***

2 Intended for homologous use ***AND***

3 Not combined with a drug or device ***AND***

4a. Does not have a systemic effect, ***AND*** Primary function does not depend on metabolic activity of viable cells ***OR***

4b. Has a systemic effect and is intended for autologous, related- allogeneic, or reproductive use ***OR***

4c. Primary function depends on metabolic activity of viable cells) and is intended for autologous, related- allogeneic, or reproductive use

THEN…

- **Clinical trials, IND/IDE, pre-marketing approval *NOT* required**
- **GTPs *ARE* required**

"351" Products

IF a cell therapy product does not meet one or more of the four major criteria defining minimally manipulated products

THEN…

- **Regulated using IND/IDE framework, clinical trials to establish safety/efficacy**
- **Biologics License required prior to marketing**
- **GMPs *AND* GTPs required**

Nearly any interesting cell therapy meets criteria for the "351" category

US FDA Requirements

Good Manufacturing Practices (GMPs)	Ensure consistent manufacture of safe, pure, potent products
Good Tissue Practices (GTPs)	Prevent infectious disease transmission Donor screening and testing
	Prevent cross-contamination, mixups Product recovery, processing, storage, labeling, distribution
Good Clinical Practices (GCPs)	Ethical, scientific quality standards Protect trial subjects rights, safety, confidentiality Assure credibility of clinical trial data

Core GTP Requirements - 1271.150(b)

- *Directly* related to preventing introduction, transmission, or spread of communicable disease. Other GTP requirements support core cGTPs
  - **Facilities - 1271.190(a) and (b)**
  - **Environmental control - 1271.195(a)**
  - Equipment - 1271.200(a)
  - Supplies and reagents - 1271.210(a) and (b)
  - Recovery - 1271.215
  - Processing and process controls - 1271.220
  - Labeling controls - 1271.250(a) and (b)
  - Storage - 1271.260(a-d)
  - Receipt, pre-distribution shipment, distribution - 1271.265(a-d)
  - Donor eligibility determination - 1271.50, 1271.75, 1271.80, 1271.85

GTP Environmental Control

- Environmental Requirements
  - Control of adventitious and pathogenic organisms
  - Adequate Control Temp. and Humidity
  - Adequate Ventilation and Air Filtration
  - Adequate Cleaning and Disinfection
  - Adequate Maintenance
  - Control Contamination and Cross-contamination
  - Inspect periodically
  - Maintain records

Key Takeaways

- Risk Approach – Critical Issues
  - Autologous vs Alogeneic – how many people are at risk?
  - Product Separation for Cross-contamination/Mixup
  - Process Closure or Enclosure
  - Risk Presented by the Product
    - Cells
      - Genetically Engineered
      - Persistence Outside Controlled Environment
    - Vectors
    - In Vitro Vs. In Vivo
      - Pathogenic
      - Oncolytic
      - Replication Competent

PHARMACIES

Pharmacies

- Hospital and Similar Applications
  - USP 795 – Non- Sterile
  - USP 797 – Steriles
  - USP 800 – Hazardous
- Third Parties
  - 503a – By Patient Prescription, similar to above
  - 503b – Bulk, Not by Prescription

Pharmacies

- USP 797 suggests three (3) options for compounding of an aseptic formulation:
  - Category 1 - BUD <12hrs @CRT(longer at cold temp.)
    - Classified background environment – None, segregated only
  - Category 2 - BUD >12hrs @CRT (longer at cold temp.)
    - Classified background environment – ISO 7
  - Any Category - True Barrier Isolator
    - Classified background environment – ISO 8

Pharmacies

- 797 Differences and Similarities to cGMP
  - Similarity: ISO 5 for sterile preparation in an ISO 7 background with an ISO 8 anteroom.
  - Similarity: Air change rates are viewed as critical
  - Difference: BUD (Beyond Use Date) in USP is not in CGMP
  - Difference: USP has less particle counting.
  - Difference: Airflow visualization is not mentioned in 797
  - Difference: USP checks differential pressure, CGMP monitors it.

Pharmacies

- 797 Differences and Similarities to cGMP
  - Similarity: Pressure Differentials are required between rooms.
  - Similarity: Isolators reduce the classification of background.
  - Difference: USP Has it's own terminology…
    - Ante-area
    - Buffer Area
    - CACI – compounding aseptic containment isolator – is a CGMP RABS
    - CAI – Compounding aseptic isolator – is a CGMP RABS
    - DCA – Direct compounding area – no CGMP equivalent
    - Segregated compounding area – no CGMP equivalent
  - Difference: USP recognizes separation of areas w/o walls

Break

APF DESIGN

Key Rules of cGMP and APF

Facilitate the safe manufacturing of Products

- Protect the patient
  - Design to minimize contamination of products
  - Design to minimize cross-contamination between products
  - Design to avoid mix-up
- Design to facilitate safe operations
  - Design for thorough cleaning
  - Select Materials that resist cleaning chemicals
  - Design resilient and fault tolerant systems
  - Design for operator and public safety
- Document the design and design rationale

Number One Rule of GMP

UNDERSTAND THE PRODUCT

- You don't need to know everything, just a few key things…
  - Route of Delivery
    - Oral
    - Sterile
  - Process and its risks
    - Open processing
    - Not sterile filtered before use
    - No sterility test before use
  - Critical process variables

What makes ATMP Different?

- The Risk Varies Broadly by Process and Product
  - Minimally Manipulated → Genetically Engineered
  - Autologous → Allogeneic
  - Human Cells → Viruses
  - Small Batch → Large Batch
  - Replication Incompetent → Replication Competent

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What makes ATMP Different?

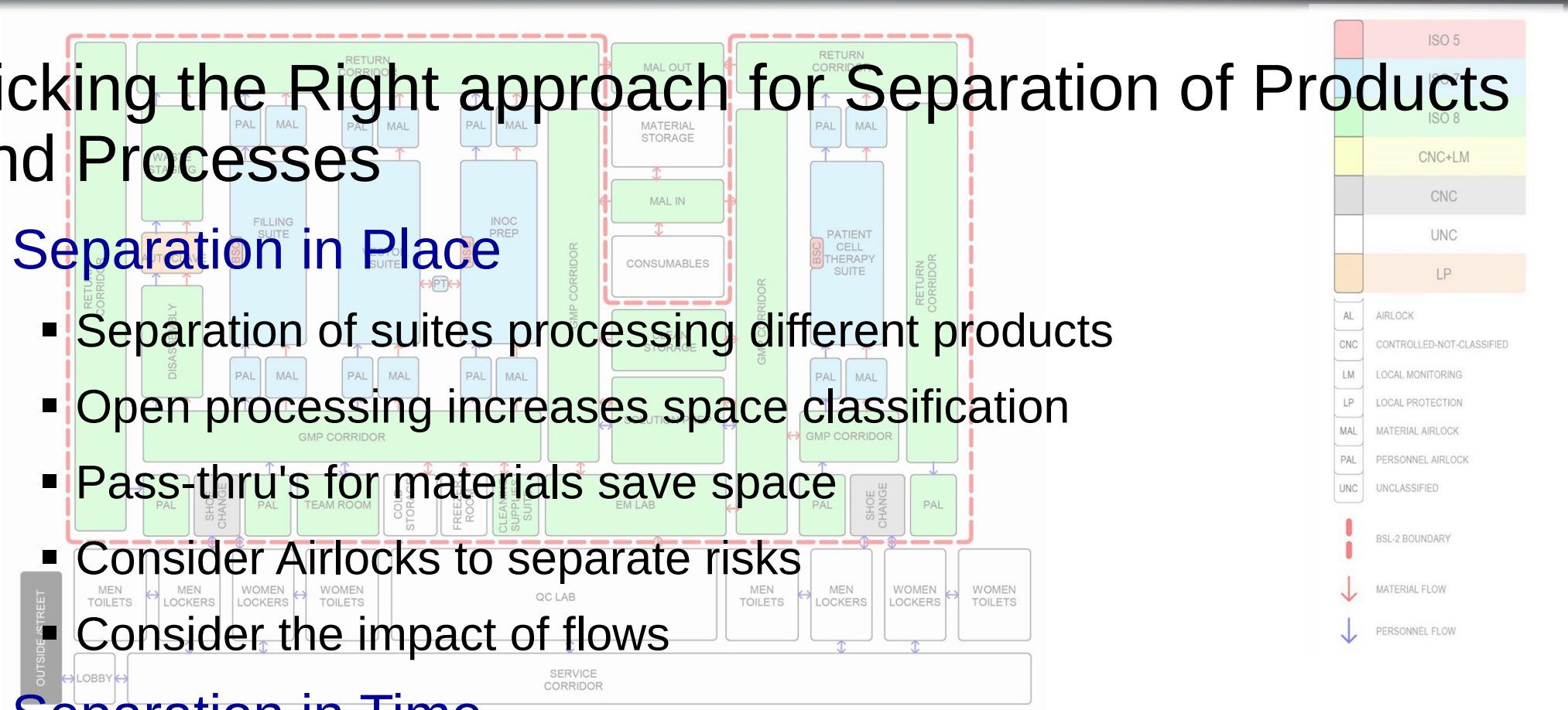
- The Risk Response Varies Broadly Too
  - Blood Bank level GTP GMP → Live Virus Vaccine level

Key Risks to Watch

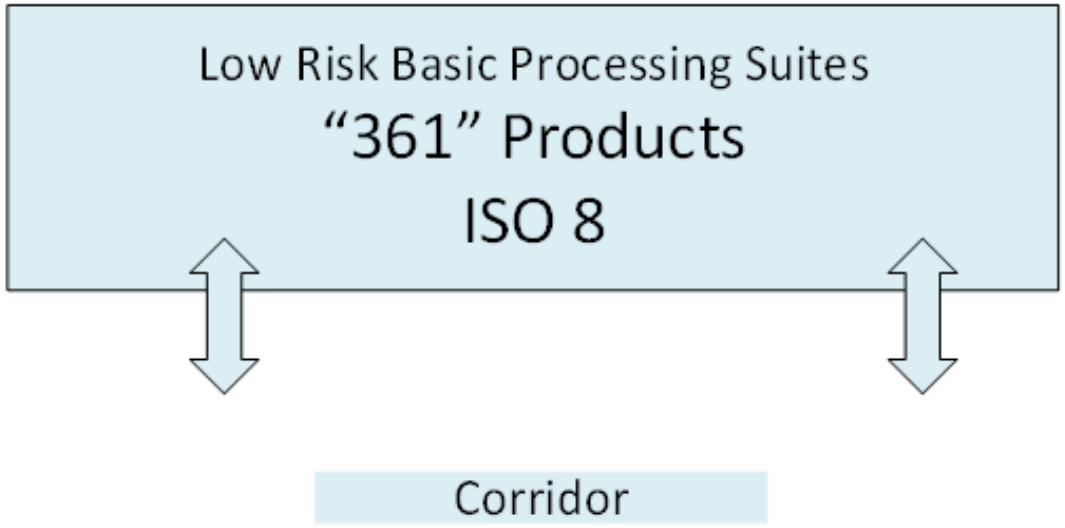
- Can the product be Sterile Filtered?
  - Cell Therapies – The product is the cell itself, not a protein expressed by the cell.
  - Aseptic processing throughout
- Is the process cGMP compatible?
  - Often Developed in Hospitals and Academic Institutions
  - Level of Closure?
- Is a vector present?
  - Replication Competent?
  - Quantity?
- Donor health status?

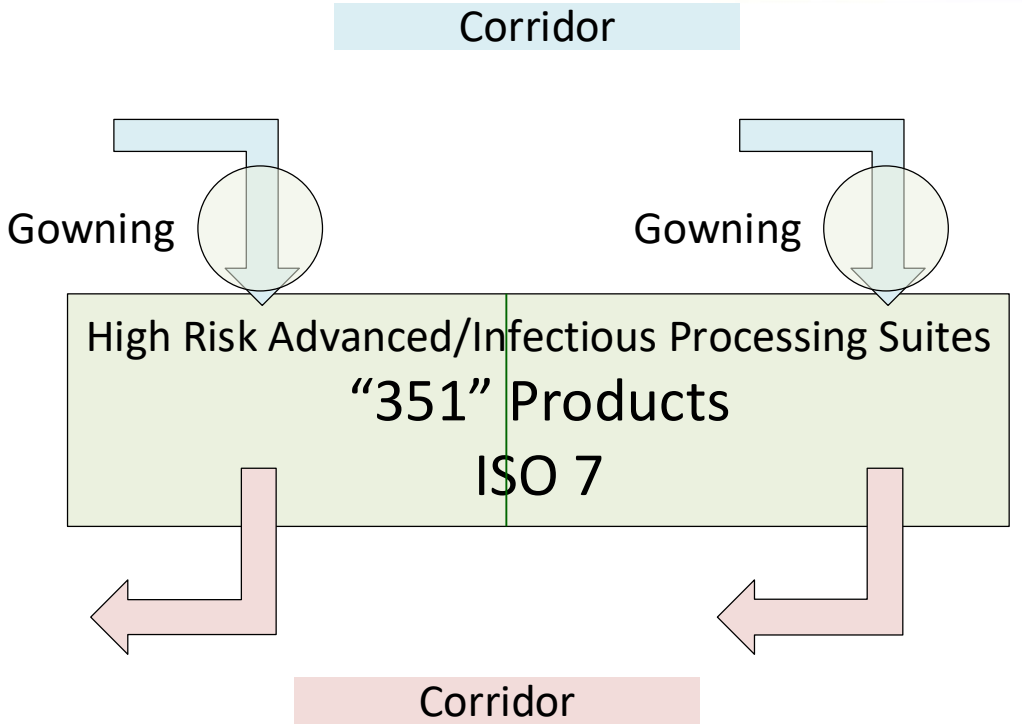
Design Challenges

- Picking the Right approach for Separation of Products and Processes
  - Separation in Place
    - Separation of suites processing different products
    - Open processing increases space classification
    - Pass-thru's for materials save space
    - Consider Airlocks to separate risks
    - Consider the impact of flows
  - Separation in Time



Arrangement of Spaces by Risk

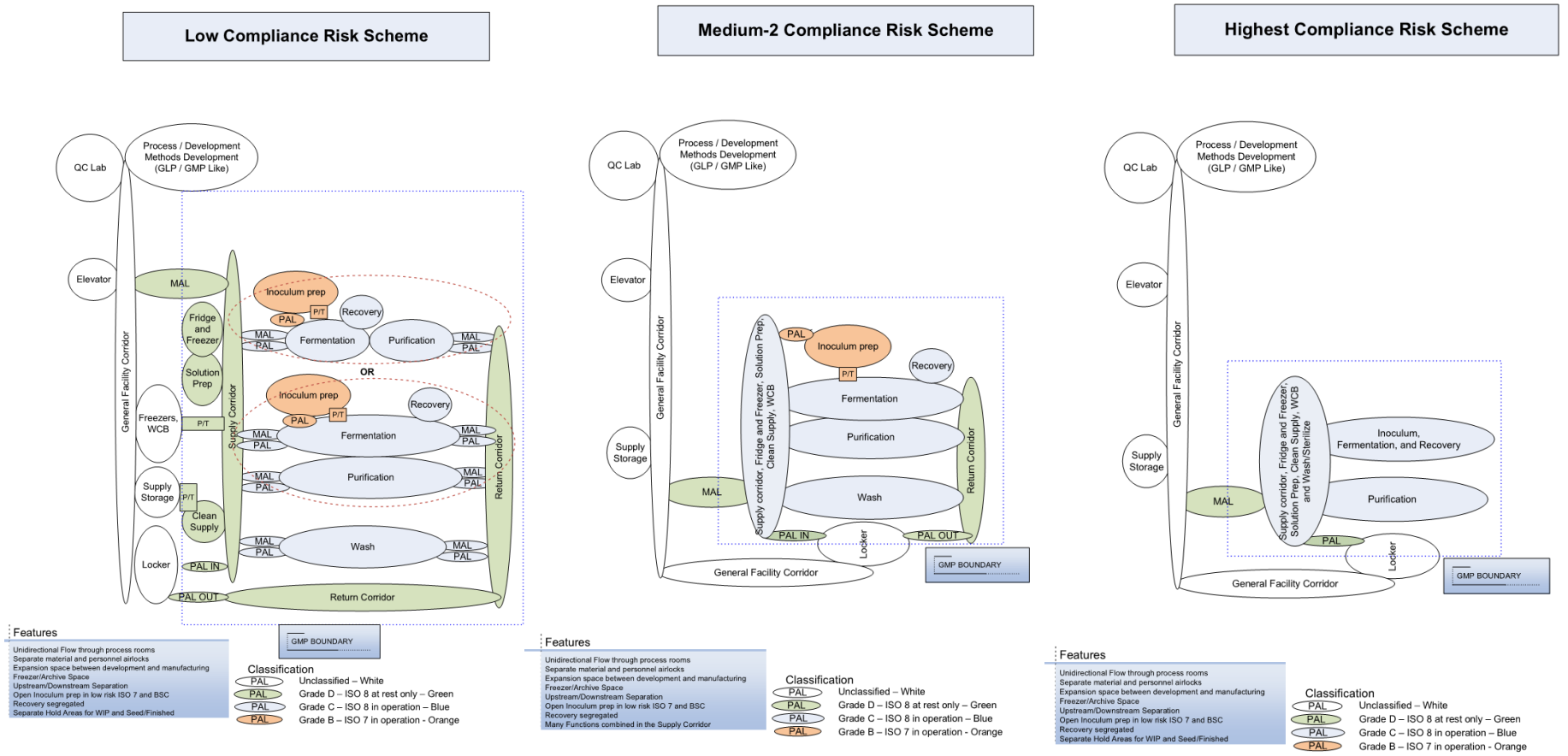




- Bidirectional

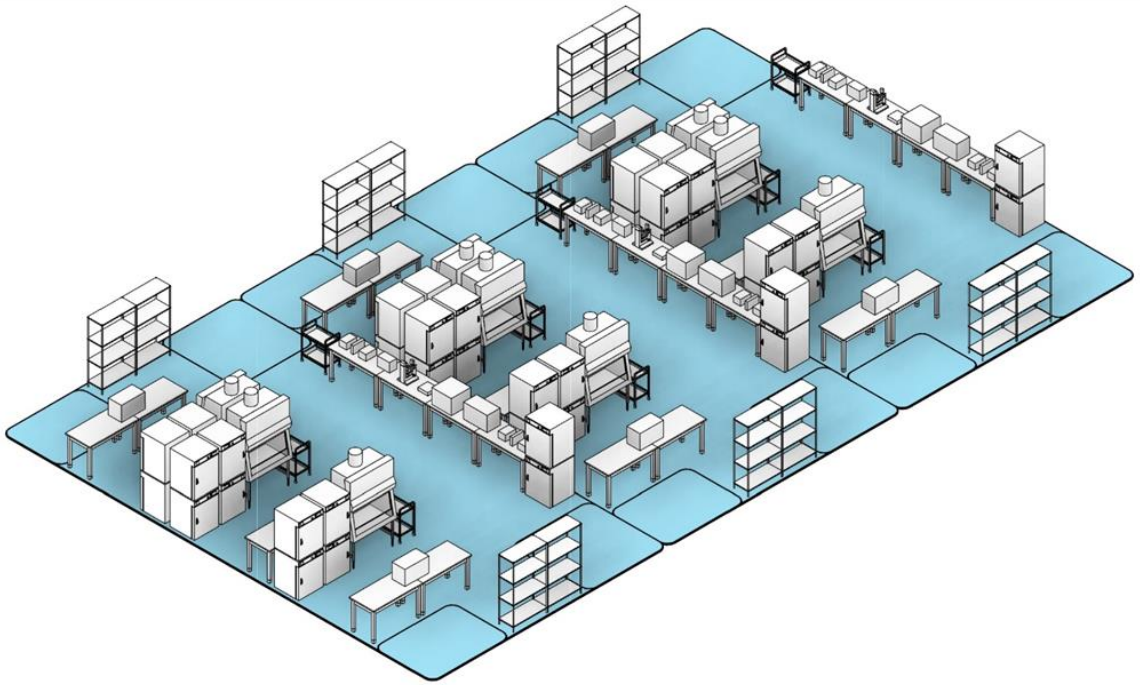
Unidirectional

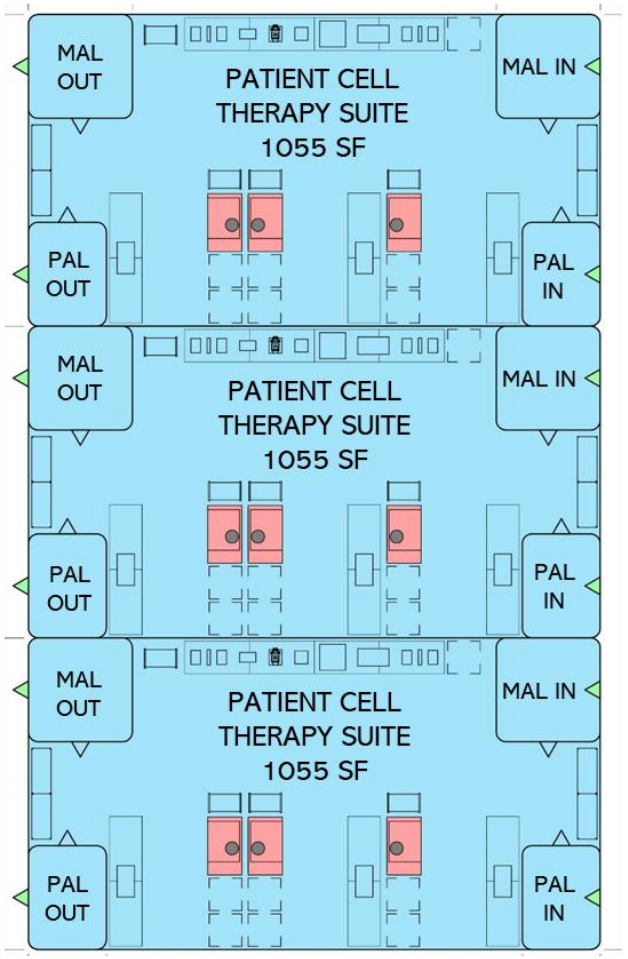
Picking a Separation Approach

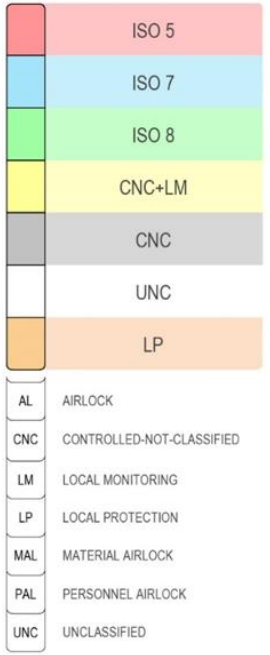


Compliance isn’t about the place you work, it’s about the way you work.

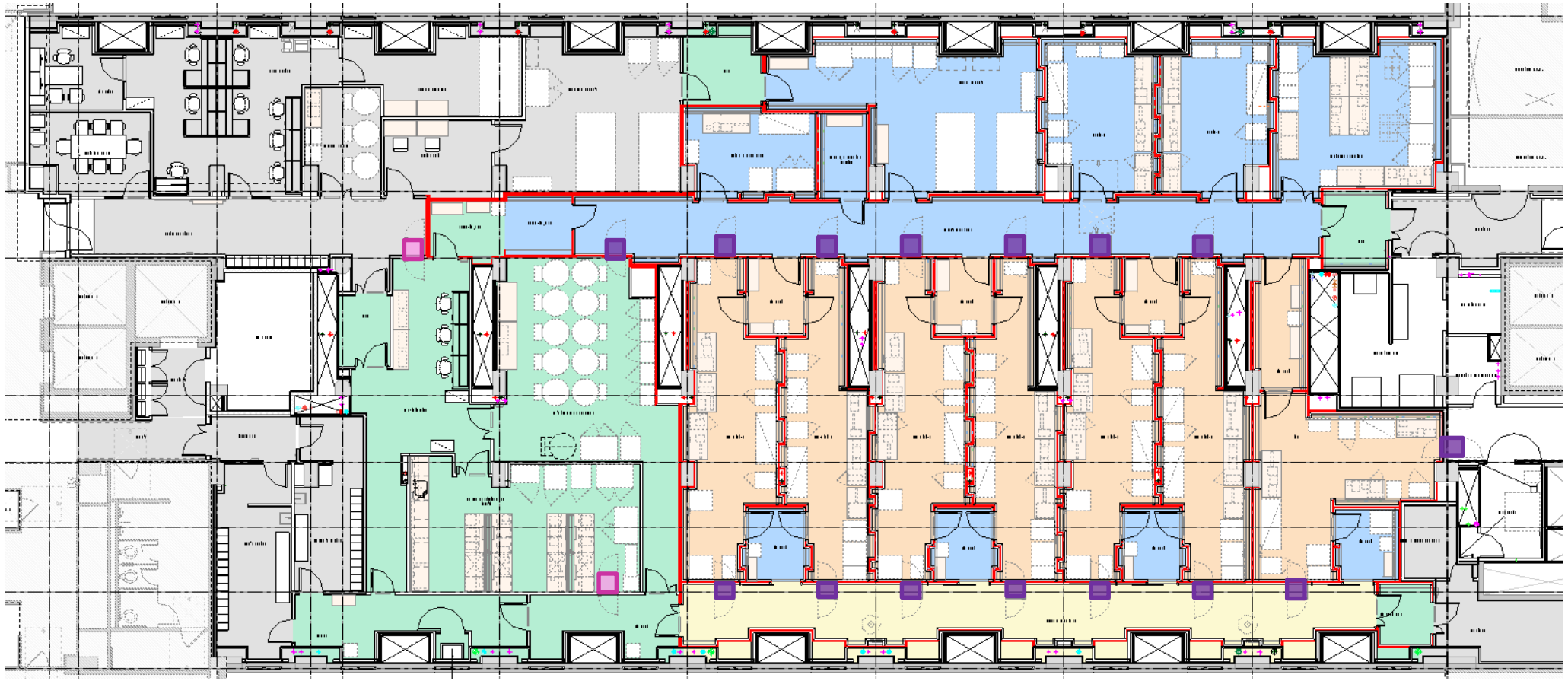
Picking a Separation Approach





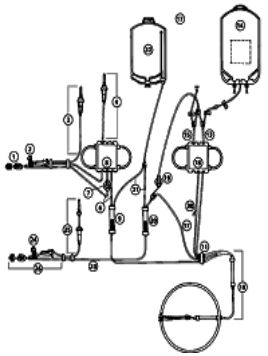


Picking a Separation Approach



Picking a Separation Approach
Closed Systems Reduce Risk

Individualized, patient-specific product manufacturing *at high throughput*



Preloaded, disposable, individualized raw material sets

Separate process environment for each product

Automated processing devices

Practices & Facility Grow Together

- Evaluate Separation
  - Between Patients
  - Between Processes
  - Between Spaces
- Bridge The Gaps (again)
  - Multi Level Cleaning Practices
    - Minor
    - Major

Practices & Facility Grow Together

Gowning Uncontrolled to Plant Uniform and to ISO 8

Areas where personnel do not come into direct contact with product, product processing, processing equipment, processing materials, and/or other processing components

THIS CHANGE OCCURS IN THE LOCKER ROOM.

TAN ZONE CHANGE

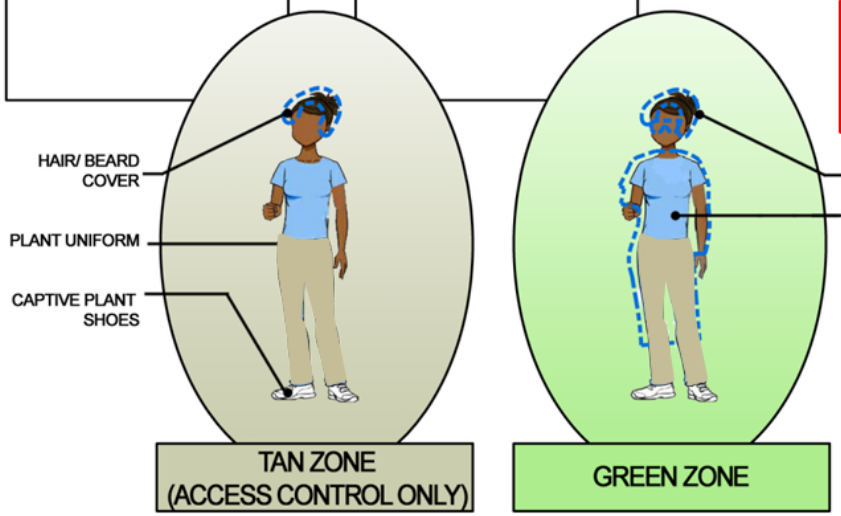
REMOVE
STREET CLOTHING
STREET SHOES
WRISTWATCHES
DON
CAPTIVE PLANT SHOES
PLANT UNIFORM

GREEN ZONE CHANGE

WASH
HANDS IN SINK
DON
GOWN/ LAB COAT OVER PLANT UNIFORM
SAFETY GLASSES
FUNCTION SPECIFIC PPE
HAIR/ BEARD COVER

AREAS WHERE PERSONNEL COME IN DIRECT CONTACT WITH LOW RISK PRODUCT OR INDIRECT CONTACT WITH HIGH RISK PRODUCT. THIS GOWNING IS INTENDED TO PREVENT THE ACCIDENTAL INTRUSION OF HAIRS, FIBERS AND OTHER FOREIGN OBJECTS ONTO WIP AND MAINTAIN THE ISO 8 ENVIRONMENT.

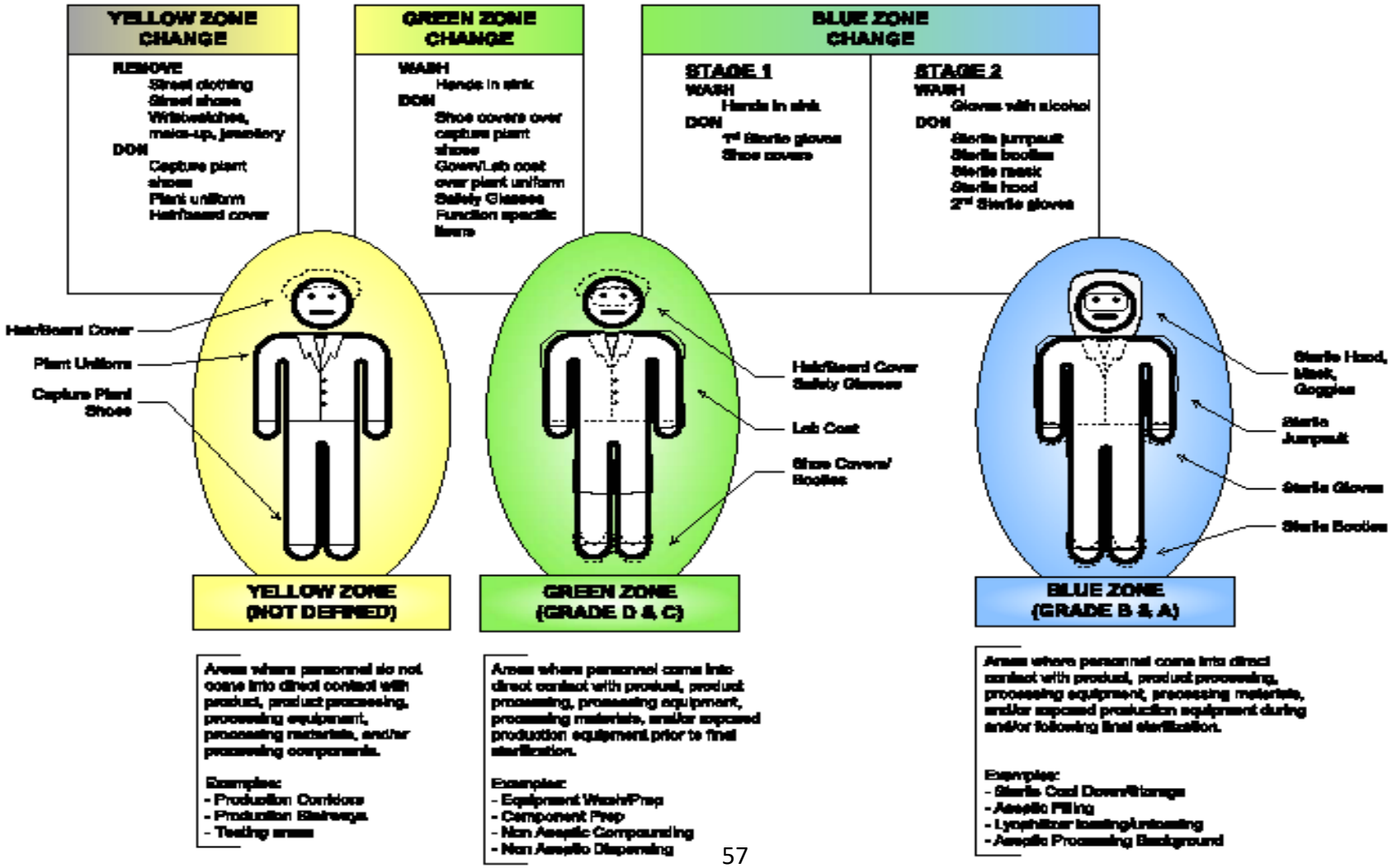
THIS CHANGE OCCURS IN THE GOWN ROOM LEAVING THE LOCKER.



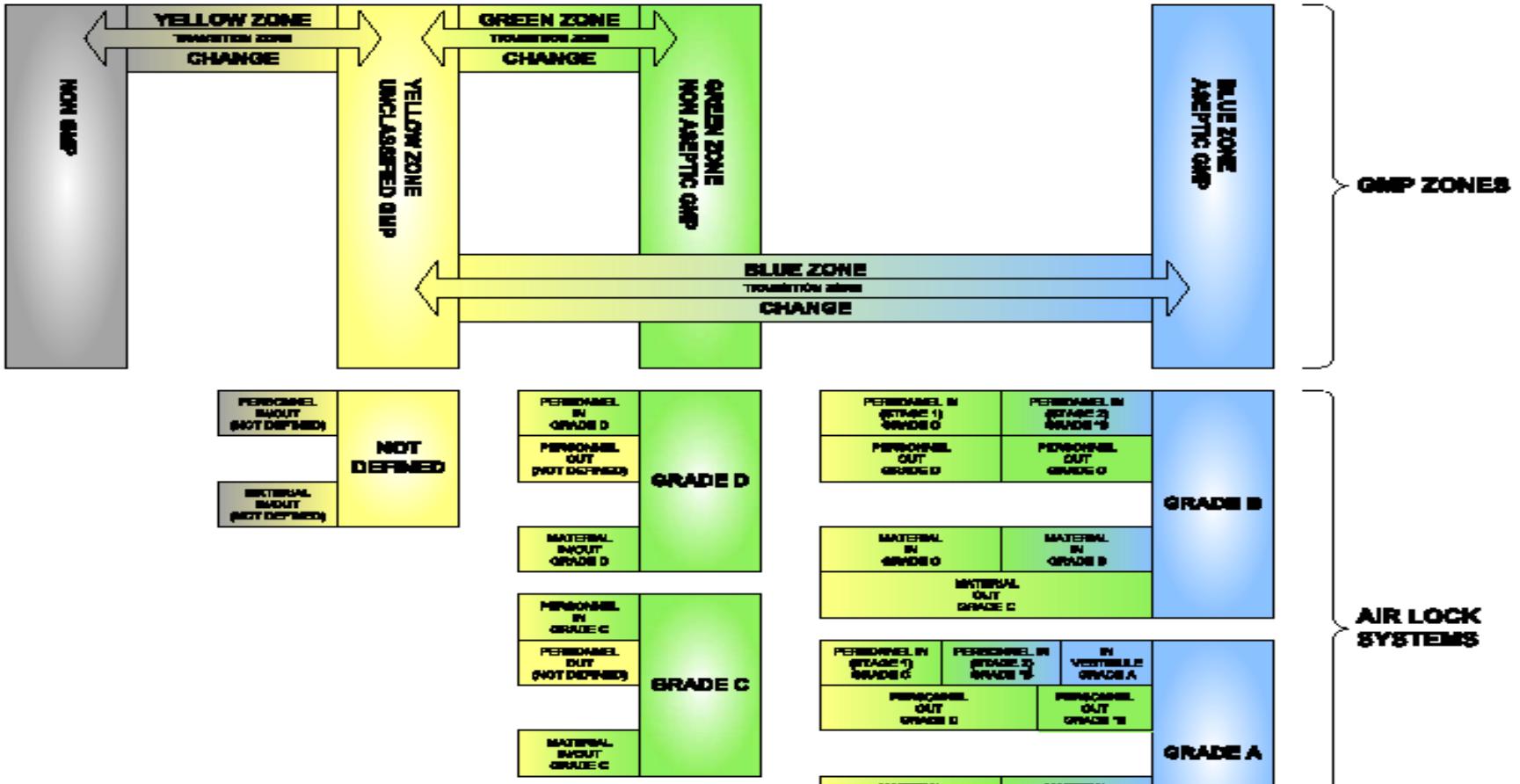
ISO 8 "At Rest" Grade D

ISO 8 Grade C

Practices & Facility Grow Together



Practices & Facility Grow Together



BMS CLASS	QUALIFICATION AT REST 0.5 um	AT REST 5 um	IN OPERATION 0.5 um	IN OPERATION 5 um	DESIGN ACPH	UAF	LWR
CL-1	3,500	0	3,500	0	600*	YES	YES
CL-2	3,500	0	350,000	2,000	60	YES	YES
CL-3	3,500	0	3,500,000	20,000	60	YES	YES
CL-4	350,000	2,000	3,500,000	20,000	40	NO	NO
CL-5	3,500,000	20,000	-	-	20	NO	NO
CL-6	-	-	-	-	20	NO	NO
LP	3,500	-	-	-	600*	YES	-

* Grade B at rest and Grade C in operation

All personnel entering green and blue zones must change out of street clothing.

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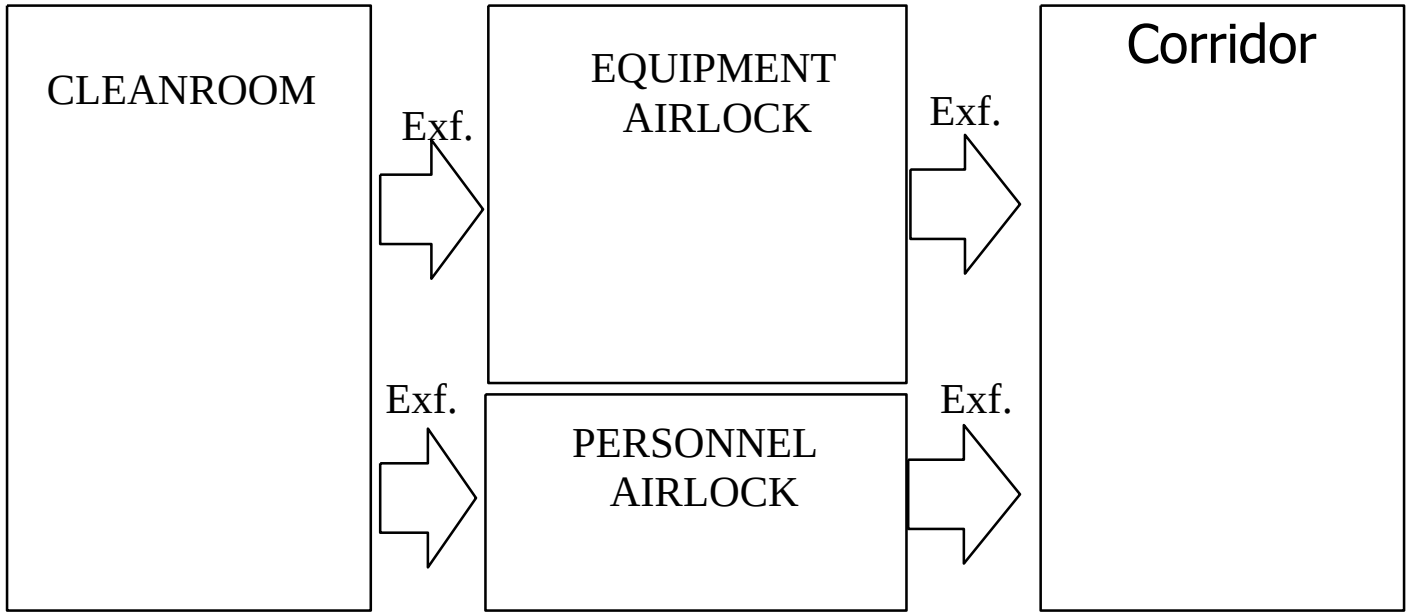
Protecting Cleanrooms from Surrounding Spaces – Airlocks

- Doors open/close Moderately FAST (to minimize time of contamination)
- Materials use larger airlock to permit cleaning/staging and pass-across
- People use smaller airlock (faster recovery time = less time to wait in airlock)

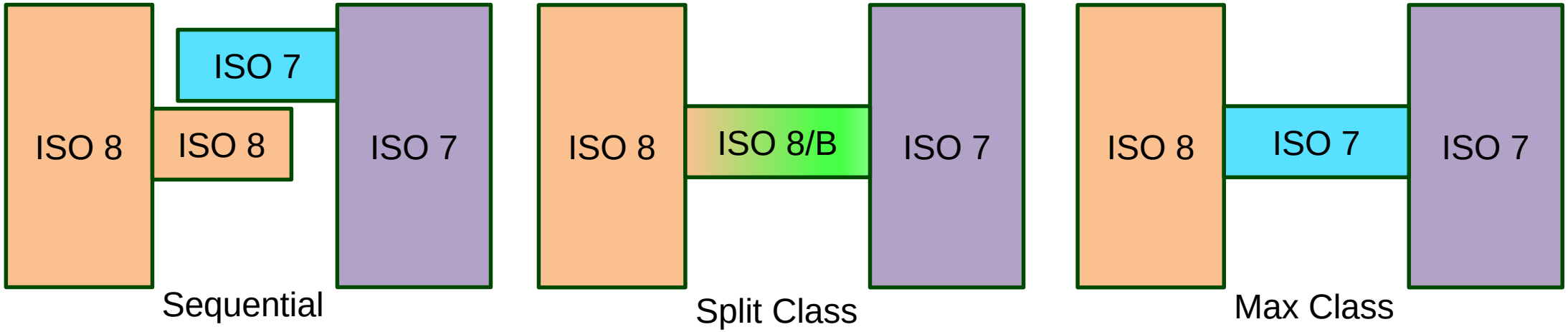


Gowning / Airlocks

Airlocks Design for Separation

…" The final stage of gowning should, in the at-rest state, be the same grade as the area into which it leads."… (Annex 1)

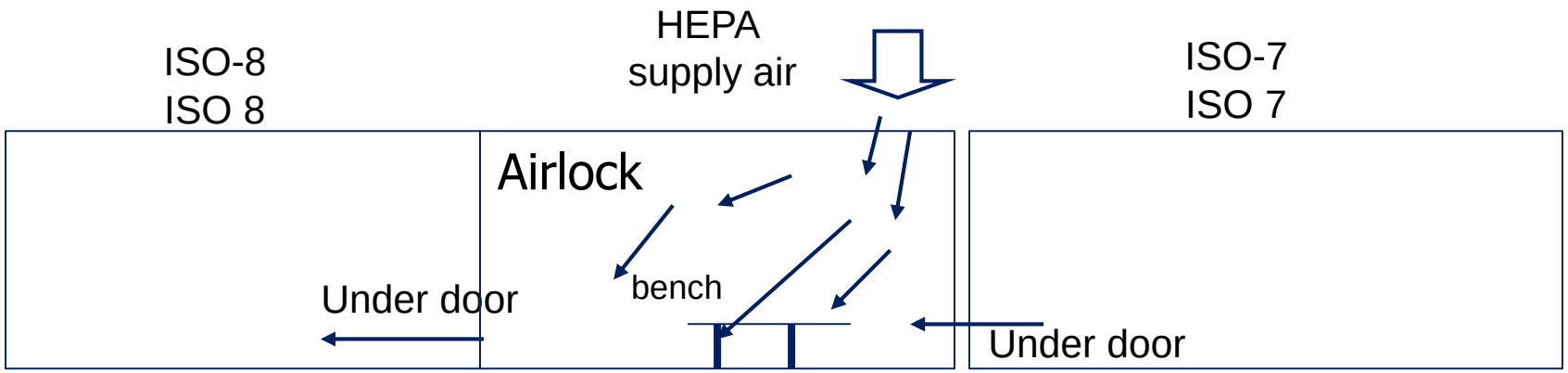
- What is a "final stage"?
- Three common answers:



Gowning / Airlocks

Airlocks Design for Separation – ATMP Guide

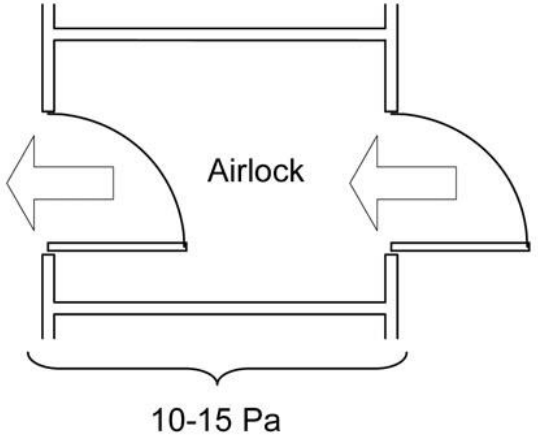
- …"Flushed Effectively"…
  - HEPA supply at clean end, return at less clean
  - Non-aspirating diffuser preferred
  - Long and Low rooms work better



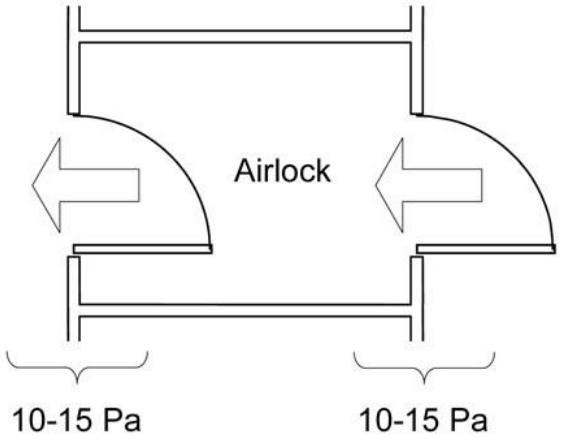
Practices & Facility Grow Together

Airlocks Design for Separation

- Size IS important – large enough for activities
- Performance of small airlocks can be problematic
- Set DP targets for the pressure cascade



Acceptable



Not Required

Break

Requirements by Unit Op

Table 2-3 Baseline Air Quality Classification - Products for US Supply

(See Figures. 3.1, 3.2)

Note - This table is for general engineering guidance only. It is not intended to be used as a GMP. Expert advice from QA departments should be sought for product specific requirements. These Baseline standards may or may not be applicable to any particular application.

ALL AIR CLASSIFICATIONS REFER TO THE "IN OPERATION" CONDITIONS

Typical Process Step	Aseptic Processing (All classification are in operation)		Terminal Sterilization (All classification are in operation)	
	Background Environment	Product/Container/ Closure Exposure	Background Environment	Product/Container/ Closure Exposure
Raw material dispensing	Class 100,000 (Note 1)	Local Protection (Note 2)	Class 100,000	Class 100,000
Compounding & (sterile) filtration feed	Class 100,000 (Note 1)	Class 10,000 (Notes 2 and 3)	Class 100,000	Class 100,000
(Sterile) filtration	Class 10,000	Class 100 (Note 7)	Class 100,000	Class 100 (Note 5)
Initial prep/washing components	"Pharmaceutical" (with local monitoring) (Note 6)	"Pharmaceutical" (with local monitoring) (Note 6)	"Pharmaceutical" (with local monitoring) (Note 6)	"Pharmaceutical" (with local monitoring)
Final rinse of components	Class 100,000	Class 100,000 (Note 2)	"Pharmaceutical" (with local monitoring) (Note 6)	Class 100,000 (Note 2)
Sterilization/ depryogenation of components - loading	Class 100,000	Class 100,000 (Note 2)	"Pharmaceutical" (with local monitoring) (Note 6)	Class 100,000 (Note 2)
Sterilization/ depryogenation of components - unloading	Class 10,000	Class 100(or wrapped/sealed)	Class 100,000	Class 100 (Note 5) (or wrapped/sealed)
Filling and Stoppering	Class 10,000	Class 100 (Note 7)	Class 100,000	Class 100 (Note 5)
Lyophilization - Operation	-	Closed system	-	-
Lyophilization - Transfer	Class 10,000	Class 100	-	-
Capping and Crimping	"Pharmaceutical" (with local monitoring) (Notes 4 and 6)	Local Protection (Notes 2 and 4, and Fig. 2-4)	"Pharmaceutical"	Local Protection (Notes 2 and 4, and Fig. 2-4)
Terminal Sterilization	-	-	"Pharmaceutical"	N/A
Inspection	"Pharmaceutical"	N/A	"Pharmaceutical"	N/A
Labeling and Packing	"Pharmaceutical"	N/A	"Pharmaceutical"	N/A

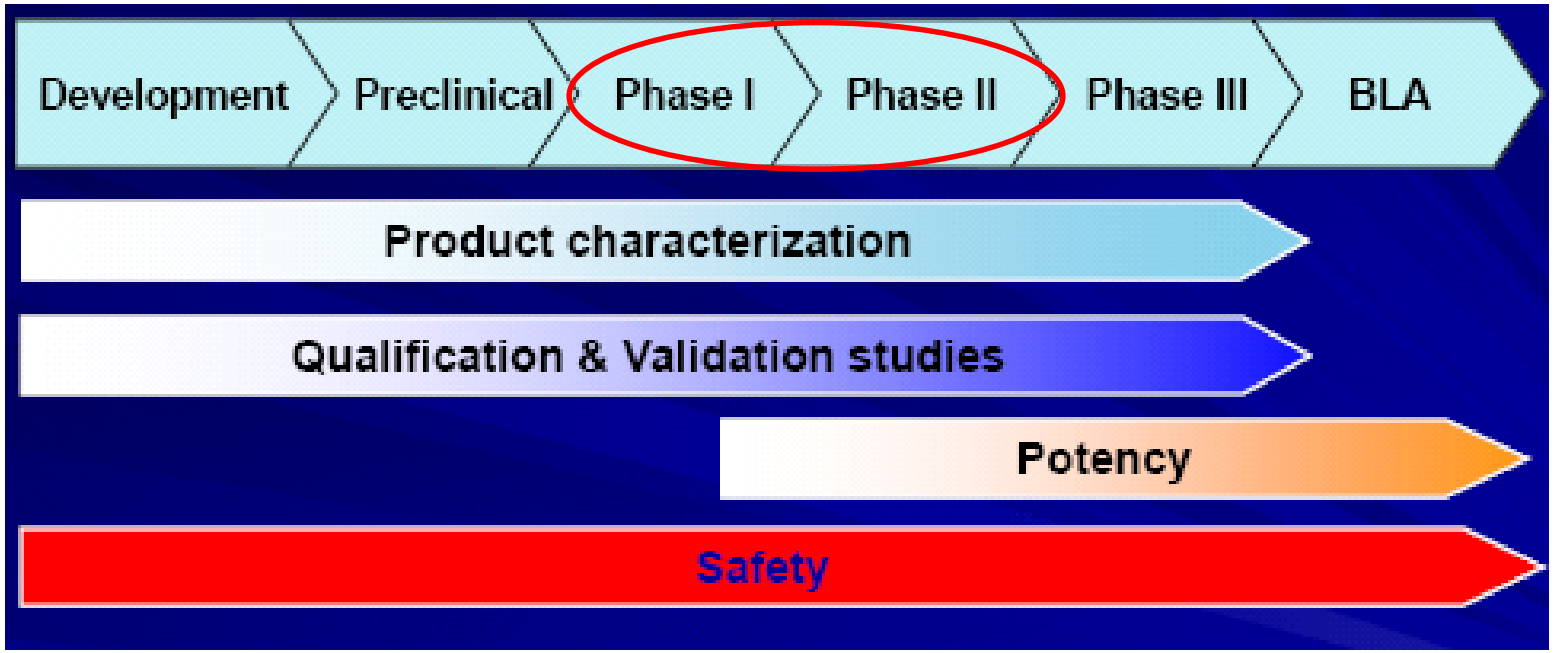
FDA Air Classes are <u>Dynamic</u>

Similar chart for Europe GMPs Exists in ISPE Sterile Baseline Guide

National Institutes of Health

GENESIS ENGINEERS

Regulatory Considerations in Product Development



Product development stage determines key aspects of regulatory review. Safety is a consistent, critical focus throughout product development.

Courtesy Raj K. Puri, MD, PhD
US FDA OCTGT

Phase 1 VS 2 and Beyond

Phase 1

- Adequate work areas and equipment for the intended task.
- Sufficient space
- Clean environment
- Appropriate construction
- Appropriate lighting
- Appropriate HVAC
- Appropriate plumbing, washing, and sanitation
- Appropriate equipment to maintain an air cleanliness classification suitable to the operation performed in the area.
- Appropriate equipment that will not contaminate the phase 1 investigational drug or otherwise react with, add to, or be absorbed by the phase 1 investigational drug; and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures.
- Recommend identifying all equipment used for a particular process and document such use in the manufacturing record.
- Use of procedural controls in a facility promotes orderly manufacturing and aids in preventing contamination, cross contamination and mix-ups (see Section VI.A).

RABS AND ISOLATORS

Barrier & Isolator Technology

- Chapter 9 in the ISPE aseptic guide covers all aspects of RABS and isolator technology.
- Both technologies are well established in the industry and well accepted by regulators. They do provide a significantly increased safety to product and operators.

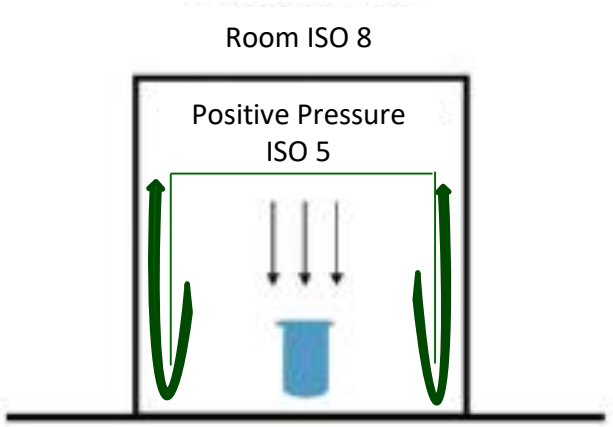
Barrier & Isolator Technology

- Aseptic Isolators

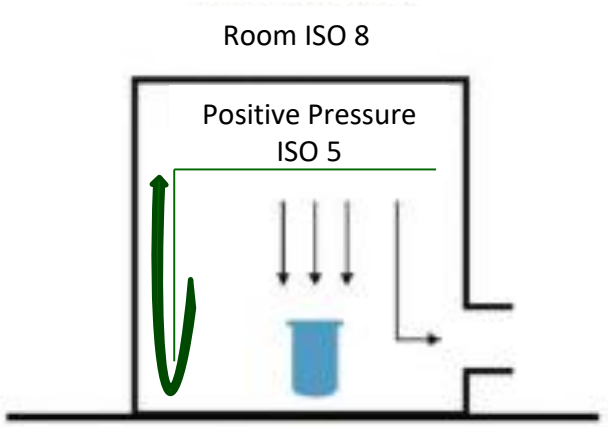
Barrier & Isolator Technology

- Aseptic Isolators

  "*A decontaminated unit meeting ISO5/Grade A conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment.*"



Positive pressure closed Isolator



Positive pressure open Isolator

Barrier & Isolator Technology

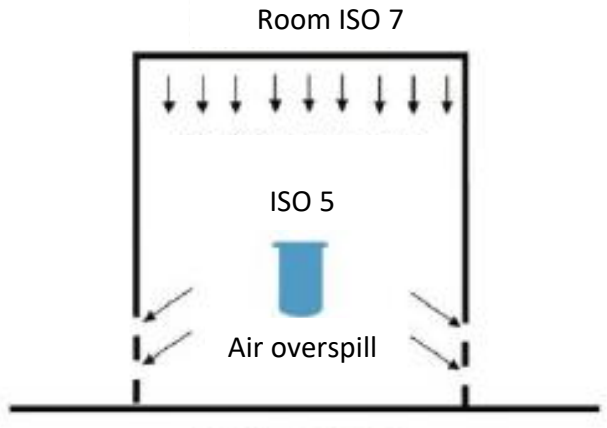
- Restricted Access Barrier Systems (RABS)

Barrier & Isolator Technology

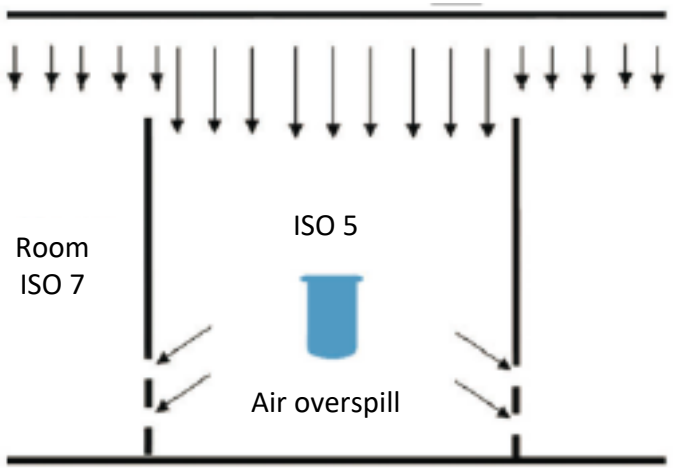
Restricted Access Barrier Systems (RABS)

- *"An aseptic processing system that provides an enclosed, but not closed, environment meeting ISO5/Grade A conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment."*

- *USP Calls this a CAI*



Active open RABS

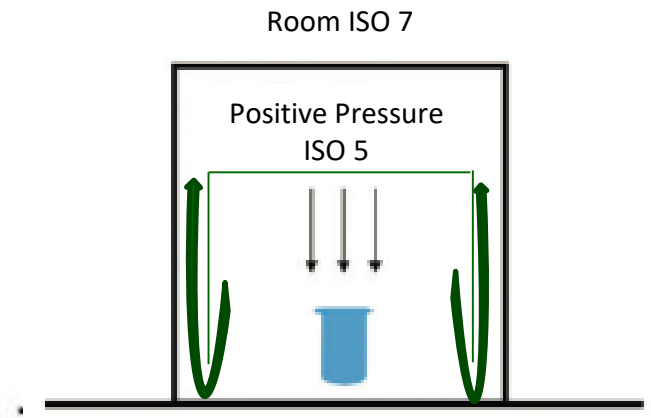


Passive open RABS

Barrier & Isolator Technology

- Closed RABS

  A closed, environment meeting ISO5/Grade A conditions utilizing a rigid-wall enclosure to separate its interior from the surrounding environment without over-spill to the room and without gaseous disinfection.



Active Closed RABS

Barrier & Isolator Technology

- Equipment Design suitable inside RABS and isolators
- Ergonomics are a limitation of RABS and isolator systems, therefore the equipment inside the containment needs to be designed with the following focus:
  - Machine design shall not block the unidirectional airflow and allow the decontamination agent to reach all surfaces.
  - Large components like stopper bowls should be perforated.
  - Avoid occulated surfaces.
  - Format parts should be easily accessible with gloves.
  - Automation is preferred to avoid human involvement
  - During the decontamination mode, all moving parts of the machine shall move in slow motion.

Barrier & Isolator Technology

- System Comparison
- Conventional Clean Room – RABS – Isolator
  - From a regulatory perspective all three option are possible
  - It is well recognized, that Isolators provide a higher protection than RABS and RABS provide higher protection than conventional clean rooms
  - Today new facilities are normally being built, using either isolator or at least RABS concepts for product protection

Barrier & Isolator Technology

- System Comparison
- Isolator Technology
  - Isolators provide the highest product safety and are the technology of choice for aseptic and aseptic/potent products.
  - CAPEX, due to the avoidance of ISO 6 and ISO 7 areas, isolator facilities require smaller foot prints and allow more efficient room/process layouts.
  - OPEX, this results also in reduced operating cost like savings in gowning, energy cost and higher operator availability
  - Isolators achieve an SAL of 10^6.

Barrier & Isolator Technology

- System Comparison
- RABS Technology
  - RABS provide also a high safety, when operated properly.
  - RABS are a good choice to upgrade existing facilities without the need to change the filling system as well.
  - There is no saving neither in CAPEX, nor in OPEX compared to an conventional filling suite.

Barrier & Isolator Technology

- Component and Equipment Transfer
- To maintain the required SAL, efficient transfer methods have to be considered

Option	Batch / Continuous	Safety
No treatment	Continuous	? = very low
Alcohol/Sporicidal (- tunnel)	Batch (continuous)	~ 2-3 log reduction
Pulse light / UV	Batch	~ 3-4 log reduction
Plasma-chamber	Batch	> 4 log reduction
H2O2 airlock	Batch	> 6 log reduction
Dry Heat Tunnel	Continuous	> 6 log reduction
Steam Autoclave	Batch	> 6 log reduction
E-Beam	Continuous	> 6 log reduction

Barrier & Isolator Technology

- Decontamination Cycle Development
- Surface Decontamination H_2O_2
  - H_2O_2 is the most common decontamination agent and is vaporized or nebulized into the critical area. To achieve an efficient surface decontamination, the following needs to be evaluated:
    - Resistance of surface material against corrosion.
    - Decontamination efficiency of all surfaces inside containment.
    - Integrity of the containment to avoid any critical leakage to the surrounding
    - Ability to aerate the agent after the process to avoid any negative impact on the product by residues.

Barrier & Isolator Technology

- Environmental Monitoring
- The environmental monitoring schedules are similar as for classified cleanrooms.
- Gloves have to be included in the monitoring schedules.
- If supported by risk assessments and data, such schedules might be reduced due to the higher level of separation of an isolator compared to a conventional classified area with operator access.

Barrier & Isolator Technology

- Leak Rate
- The integrity of an isolator is relevant to reduce the following risks:
  - Prevent decontamination agent to escape into the surrounding and harm operators.
  - Prevent hazardous product escape during production and cleaning.
  - Prevent ingress of contamination that could harm the product.

There is no general leak rate that is considered good or bad. Considering the three risks, the acceptable leak rate needs to be determined case by case.

Example:
Filling an aseptic product in an open isolator, the only risk is the decontamination agent escaping into the room. In such a case a decontamination agent sensor in the room might give enough safety and a regular leak test can be avoided.

Typical APF Risk Questions

- Is the product Sterile filtered downstream?
- Is the product terminally sterilized?
- How closed is the process?
- Is process susceptible to airborne contaminants?
- Does the process use hazardous chemicals?
- How potent is the product?
- Does the product contain hazardous organisms?
- Does the product support microbial growth?
- Is the product heat labile or moisture sensitive?

Q&A