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Controlling Cross Contamination in a Biologics Facility

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The workshop will present:

- current thinking in relation to new multi product facility design
- strategies for containment and exclusion in relation to HVAC design and controls
- specific PIC/S GMP requirements to minimise cross contamination potential
- methods for assessing the relative hazardous nature of APIs
- contamination contribution of critical pharmaceutical services
- strategies for closed, partially closed and open processing
- application of the ISPE Risk-MaPP assessment of multi product facilities
- PIC/S expectations for cleaning validation and verification

Module Topics

- Current Regulatory Thinking
- Specific PIC/S GMP requirements to minimise potential cross contamination
- Expectations for segregation and separation
- Industry definitions for closed, partially closed and open processing

Some Useful References

- PIC/S cGMP – Chapters 3 and 5
- ISPE Baseline Guide Risk Based Manufacturing of Pharmaceutical Products - Managing Risks Associated with Cross Contamination - 2010
- EMA Draft Guidance (2012) - Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
- Annex 3 - WHO good manufacturing practices for pharmaceutical products containing hazardous substances.
- FDA Guidance Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination 2013.
- Procedures for Determining an Acceptable Daily Exposure (ADE) under Risk-MaPP: Approaches for Developing and Documenting Acceptable Limits for Product Cross-Contamination Purposes. Allan W. Ader, Robert G. Sussman, Tracy A. Kimmel, and Robert H. Ku SafeBridge Consultants, Inc. Mountain View, California and New York, New York

Regulator Consistency / Campaigning (ISPE Risk-MaPP Statement)

- Worldwide, regulators are **not** currently in agreement as to the acceptable level of controls required for the compliant manufacture of highly hazardous compounds (i.e., those compounds that can cause serious adverse effects at low doses) within multi-product facilities.

- Several major regulatory agencies allow for the production of highly hazardous compounds by campaign, provided adequate separation and suitably validated cleaning procedures are present, while other major regulatory bodies do not allow certain highly hazardous compounds in multi-product facilities at all.

Prevention of Cross Contamination in Production – PICs Clause 5.18

Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of **dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing**.

The significance of this risk varies with the type of contaminant and of product being contaminated.

Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials.

Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

Prevention of Cross Contamination in Production – PICs Clause 5.19

Cross contamination should be avoided by appropriate technical or organizational measures, for example:

a) production in segregated areas (required for products such as penicillins, **live vaccines, live bacterial preparations and some other biologicals**), or by campaign (separation in time) followed by appropriate cleaning;
b) providing appropriate air-locks and air extraction;
c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
f) using "closed systems" of production;
g) testing for residues and use of cleaning status labels on equipment.

PIC/S cGMP Separation and Segregation Requirements (Clause 5.19)

Complete segregation expected for:

- Penicillins and Beta Lactam Rings
- Live vaccines **
- Live bacterial preparations and some other biologicals (see later slide).
- Cytotoxics
- Generally means separate building or completely isolated facility within a common building.

** FDA CBER has recently legislated to allow the manufacture of live vaccines in multi-product facilities, provided adequate controls are established to prevent cross-contamination.

PIC/S cGMP Separation and Segregation Requirements (Clause 5.19)

Separation can include:

- Campaign production (separation in time) followed by appropriate cleaning
- providing appropriate air-locks and air extraction;
- controlling recirculation or re-entry of untreated or insufficiently treated air;
- controls over protective clothing exposed to higher risk products;
- using cleaning and decontamination procedures of known effectiveness;
- using "closed systems" of production;
- testing for residues and use of cleaning status labels on equipment.

PIC/S - Production Areas - restrictions on some products

3.6. In order to minimise the risk of a serious medical hazard due to cross-contamination, **dedicated and self-contained facilities** must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms).

- **The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities.**
- For those products, in exceptional cases, the principle of **campaign working** in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.
- The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

What does 'certain' (as per certain additional products, certain antibiotics, certain hormones etc) in clause 3.6 of the Code mean?

- 'Certain' refers to materials known to cause specific (side) effects in low doses. For example, 'certain antibiotics' refers to antibiotics, usually of the beta lactam group, which are known to **cause allergic reactions**.
- 'Certain hormones' refers to hormones that can have **pharmacological effects** if trace amounts cross-contaminate other products. Examples are estrogens and some progesterone-like hormones.
- Manufacturers should evaluate materials that are processed and ensure that adequate control measures are in place.

Current Thinking on Clause 3.6 (Toxicological Approach to setting ADE)

- The clause requirement for certain materials ("certain antibiotics, certain hormones, certain cytotoxic and certain highly active drugs") to be manufactured in dedicated facilities was not very scientific without taking into consideration specific toxicological/pharmacological data.
- The same applies to the definition of the 1/1000 dosage or the 10 ppm criterion in the cleaning validation.
- From this approach excluded are active substances with a genotoxic or a sensitising potential. The toxicological approach is not envisioned to be applicable to:
  - Highly sensitizing materials (e.g. penicillins)
  - Biological preparations (e.g. from live micro-organisms)
  - Non-medicinal products, including pesticides, herbicides

EMA Draft Guidance (2012) - Guideline on setting health based exposure limits for use in risk identification in shared facilities

- **Permitted Daily Exposure (PDE)** as described in Appendix 3 of ICH Q3C (R4) "Impurities: Guideline for Residual Solvents.
- The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.
- EMA cGMPs 10.6. Limits for the carryover of product residues should be based on a toxicological evaluation. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references.

PIC/S – Specific Restrictions

- 5.9. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 5.10. At every stage of processing, products and materials should be protected from microbial and other contamination.

PIC/S and Personnel Protection

- 2.10. Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.
- Apart from this cGMPs is not directly concerned with OH&S compliance within a plant.

Storage of Work In Progress

- 3.8. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination

Equipment Design Standards

3.39. Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

- **Non - Reactive:** Generally 316L SS on all product contact parts
- **Non- Additive**: no leachables from equipment components to the product – gaskets, plastics, intermediate storage, tubing, bags etc.
- **Non- Absorptive**: Equipment must not absorb any product components

Extractables and Leachables Issues

Ph. Eur. Guidance – Section 3.2.2.2(g)

The suitability of the container and closure system used for the storage, shipping, and use of the finished product shall be documented. A possible interaction between the medicinal product and container (closure system) may need to be considered. Suitability of the container must be assessed in relation to the container within.

Extractables **

Compounds that can be extracted from the container closure system when in the presence of a solvent.

Leachables **

Compounds that leach into the **drug product formulation** from the container closure as a result of direct contact with the formulation e.g from rubber stoppers, from syringe components, fungicide in wooden pallets (Tylenol).

** Drugs of particular concern: Ophthalmic, Parenteral, Inhalation via primary and secondary packaging interactions

Highly Potent APIs

Definition of Highly Potent APIs (HPAPI)

The definition of an HPAPI varies depending on the literature however, APIs deemed to be potent may fall into the following categories:

1. A pharmacologically active ingredient or intermediate with biological activity at approximately **150 µg/kg** of body weight or below in humans (**therapeutic daily dose at or below 10 mg**)
2. An active pharmaceutical ingredient or intermediate with an occupational exposure limit (OEL) at or below 10 µg/m^3 of air as an 8hr time-weighted average;**
3. A pharmacologically active ingredient or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses
4. Or, by default, a novel compound of unknown potency and toxicity.

*** The potency of pharmaceutical chemicals is often characterized by OELs in µg/m^3; the lower the value, the more potent the chemical and the greater the level of containment that is required.*

Risks with Steroids Based on Relative potency of the main corticosteroids

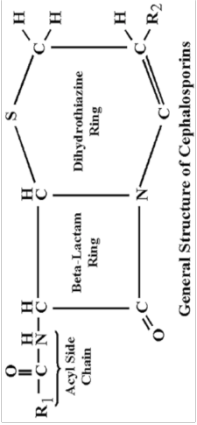
- Corticosteroids have different potencies, for example 1 mg of dexamethasone is as effective as 25 mg of hydrocortisone. Using the inverse of potency we can then rank relative risks from exposure.

- The following table indicates the relative potency of the main products:

Hydrocortisone	1 = lower risk
Prednisone	4
Prednisolone	4
Methylprednisolone	5
Triamcinolone	5
Dexamethasone	25
Betamethasone	25
Cortivazol	50 = higher risk

Penicillian and Beta Lactam Ring Drugs (FDA Guidance)

- Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people.
- Beta-lactam drugs also may be sensitizing agents and cross-contamination with beta-lactam drugs** can induce hypersensitivity reactions as well.
- Accordingly, preventing cross-contamination of other drugs with penicillin (and beta lactam drugs) and is a key element of cGMP manufacturing.
- FDA has clarified that separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is isolated (i.e., completely and comprehensively separated). Must have an independent HVAC system.



- ** This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.

Biologics Manufacture

- **Stage of manufacture** - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I.
- Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow.

cGMP Annex 2 - Biologicals

- The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilization systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.
- Although contamination is likely to become evident during processes such as fermentation and cell culture, prevention of contamination is more appropriate than detection and removal.

Annex 2 – Biologicals Personnel Restrictions

- Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including QC, maintenance and cleaning staff) should be controlled on the basis of QRM principles.

- In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled.
- If such passage is unavoidable, the contamination control measures should be based on QRM principles.

Annex 2 – Dedicated Production Areas

- Dedicated production areas should be used for the handling of live cells, capable of persistence in the manufacturing environment, until inactivation.
- Dedicated production area should be used for the manufacture of pathogenic organisms capable of causing severe human disease.

- **Clause 8** - *Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination using QRM principles:*

PIC/S cGMP Annex 2
Biologicals Separate Facilities

- BCG Vaccines
- Handling of live organisms used in production of tuberculin
- Bacillus anthracis, of Clostridium botulinum and of Clostridium tetani until the inactivation process is accomplished.
- Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.

Serum Used in Cell Culture Medium

- Serum shall be tested to demonstrate free from bacteria, fungi, mycoplasma and viruses.
- Serum shall also be shown to be free from inhibitors of vaccine virus strains.
- Bovine origin serum must come from herds free from bovine spongiform encephalopathy & bovine leucosis virus
- Trypsin shall be bacteriologically sterile and free from mycoplasma and viruses, especially porcine parvovirus

Manufacture of Biologicals
PIC/S cGMP Annex 2

- In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled.
- If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

Annex 2 Biologicals
Premises and Equipment

6. The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risk to the finished product.

7. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems.

The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.

PIC/S Annex 2 Biologicals
Separate Facilities

- 11. Simultaneous production in the same area using closed systems of bio-fermenters may be acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.
- 12. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination.
- For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

WHO – Annex 3 – Some Basics
(HVAC Requirements)

- no direct venting of air to the outside.
- HVAC operation should result in a negative pressure relative to the environment
- air pressure alarm systems for pressure cascade reversal or loss of design pressure status. Design, alert and action limits should be in place.
- HEPA filters in the supply air system should be terminally mounted
- the air pressure cascade should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
- visual indication of the status of room pressures for each room .
- air should be exhausted to the outside through H13 rated HEPA filters and not be re-circulated except to the same area.

Annex 2 – HVAC Controls

- Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area.
- Consideration, based on QRM principles, should be given to the use of single pass air systems.
- The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product safety.

WHO – Annex 3 – Some Basics
(Environmental Protection)

- Neither the hazardous product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.
- If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.
- The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass through hatches, decontamination devices, etc…. with interlocked doors

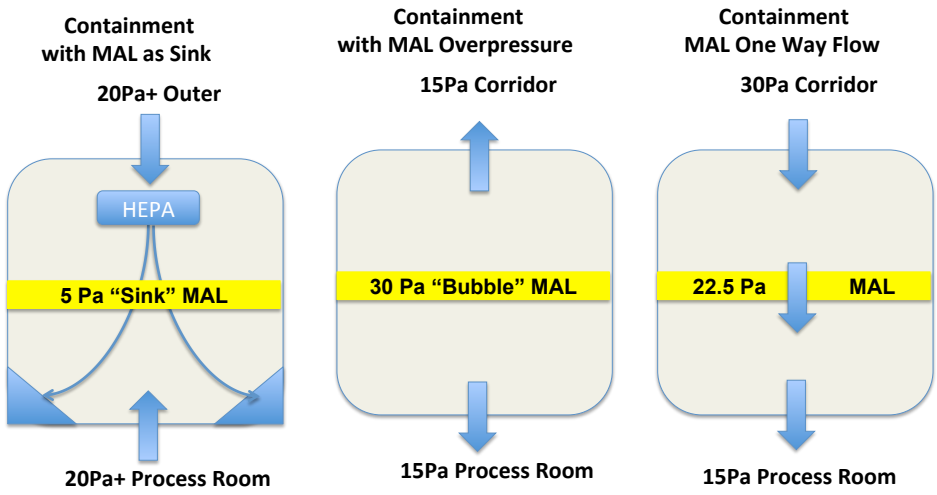
HVAC Systems and Processing Room Environmental Standards

- Cleanroom standards for sterile products are described in Annex 1 – standards are a combination of Grade A/B/C/D and ISO 14644
- **The PIC/S cGMP does not reference a specific standard for air quality for non-sterile manufacturing areas.**
- Manufacturers are required to demonstrate that the manufacturing environment for non-sterile products affords appropriate protection to the products, and prevents contamination.
- Through qualification, validation and monitoring processes manufacturers should justify that the air quality is sufficient for their non-sterile manufacturing areas.
- Consult *WHOs 'Good manufacturing practice: main principles for pharmaceutical products - Heating, ventilation and air conditioning systems for non-sterile pharmaceutical dosage forms'* which provides additional guidance in relation to recommended levels of air filtration.

Documenting Room Specifications - Example

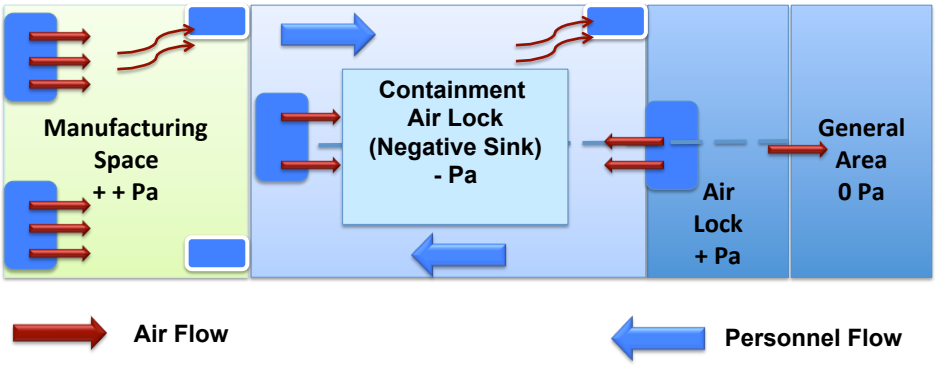
Room Name	Area / m^2	As Built Class	In Op. Class	Target Pressure (Pa)	Air change per Hr	Temp (°C)	(% RH) Max.	Room Air Filtrat'n	100% fresh or Recircul
De-Gown room	3.60	D	**I**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Hand wash room	3.30	D	**II**	30 Pa (25 - 35)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Weigh room	2.40	D	**II**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Mixing room	5.32	D	**III**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Filling room	4.50	D	**III**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Bottle Wash Room	4.95	D	**III**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Wash Room	3.36	D	**II**	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc

Alternative MAL/PAL Designs



Compliance by

Typical Containment Air Lock (with Sterile Facility Protection)



Pass Through Cabinets (PTCs)

- Material pass-through-cabinets (PTC) or pass boxes (PB) can also be used for separating two different zones.
- PTCs fall into two categories, namely a dynamic PTC or a passive PTC.
- Dynamic PTCs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTCs.
- Interlock doors with status and delay
- Validate transfer SOP

"Pre-VI" and "Post VI" Facility and Equipment

- Biological products may undergo viral inactivation steps to reduce the risk of inadvertent contamination ot patients.
- Inactivation steps can occur throughout the processing –are usually dedicated and validated steps
- Facilities are separated into "Pre-VI" and "Post VI" areas as follows:
  - Separate HVAC systems
  - Separate Facilities – interlocked separation
  - Dedicated or controlled employees
  - Dedicated or strictly controlled equipment

Open, Closed and Briefly Open Processing

ISPE - Closed Process
A process step (or system) where the product is not exposed to the immediate room environment (and vice versa).

ISPE - Open System/Process
A system that fails to meet one or more of the requirements that set the criteria for a closed system.

"Briefly Open" processes include:

- Briefly open prior to processing commencing e.g. during equipment set up ….. potential product risk
- Briefly open during processing e.g. taking samples ….. potential product risk
- Briefly open post processing – no product risk but potential environmental risk.

ISPE and Risk-MAPP Approach (Potential Sources of Contamination)

1. Starting Materials Testing
2. Segregation of Potent APIs
3. Equipment Cleaning Programs
4. Facility Cleaning and Sanitation Programs
5. Product Separation & Prevention of Mix Up - Production Controls
6. Mechanical Transfers and Personnel Controls
7. HVAC and Airborne Transfers
8. TSE/BSE Surveillance
9. Product and In process Bioburden Monitoring
10. Environmental Monitoring (EM) Programs

ISPE Risk-MaPP Baseline Guide

Four possible "plausible pathways" for cross – contamination:

1. **Mix up** of APIs during processing and packaging – core GMP
2. **Residue retention** on shared processing equipment – core GMP
3. **Mechanical transfer** from non-product contact surfaces e.g personnel gowns
4. **Airborne transfer** either directly in air or by re-aerosolization of sedimented particulates

Each mode must be assessed.

Routes for Cross - Contamination

Significance: High ↑ / ↓ Low

Product Exposure Routes	Worker Exposure Routes
Processing Mix Up API, process, potency, labeling etc.	**Inhalation**
Retention of Residues Product carryover on equipment contact parts beyond specified limits	**Dermal absorbtion**
Mechanical Transfer Physical transfer to another product on equipment surfaces, ancillary surfaces and gowns	**Ingestion**
Airborne Transfer Settling of aerosols from one product onto another product	**Accidental Injection** – eg. via break in skin

1. Typical examples of "mix-up" pre-conditions:

- overlapping process flows – common processing rooms
- common dispensary areas or transit routes
- common storage areas for change parts – parts uncovered
- inadequate line clearance between products
- the accidental use of dirty equipment
- introduction of rogue materials during sampling
- incorporation of the wrong starting material or excipient
- mislabeling of equipment and/or materials
- unintended transfer of materials or product from one vessel to another containing different product/materials

3. Mechanical Transfer Risks (Moderate Likelihood)

Mechanical transfer includes all routes by which material can be transferred from contaminated non-product contract surfaces into the product.

Risk situations and factors:

- co-location of a process with contaminated equipment
- open or partially open processing or storage
- transfer of the material to the surface
- association of the surface with the product at risk
- release of the material from the contaminated surface to the next product
- Operators transferring to new surfaces via gowning

4. Airborne Transfer – Low(er) Likelihood

The direct airborne transfer route assumes the generation of a stable aerosol which moves to another area where it deposits in significant quantities on another exposed product.

Products are typically separated by physical barriers such as airlocks and cleanrooms, which employ positive or negative pressure gradients to protect rooms and equipment.

Equipment Design Considerations

- Select process equipment that reduces exposure potential, e.g., hammer (and other high energy) mills can result in a far higher exposure potential than cone mills. Charging a bin-blender can provide a lower risk through close coupling than, e.g., charging a V-blender.
- Selection of process equipment that reduces the potential for retention residues should consider:
  - minimizing surface area of product contact parts
  - eliminating ledges and crevices on the product contact parts
  - reducing the frequency of changeover and cleaning
  - using polished product contact surfaces
- **"Leakage assessment"**: – process equipment should ensure nozzles, glands, or entry points to the product processing zone are secure under operating condition.

Risk Assessment Checklist

Consideration	Yes	No
open processes during operation, clean, intervention & maintenance	☑	☑
retained or accumulated product inside the barrier or the room/suite	☑	☑
recirculated HVAC systems for the product room ? Re-filtered ?	☑	☑
leakage of product to ceiling or interstitial space or cavities	☑	☑
retained or accumulated product during HVAC maintenance or repair	☑	☑
transfer of product from the worker's clothing, hands, or feet	☑	☑
manual cleaning of equipment and/or barrier	☑	☑
common equipment cleandown areas	☑	☑
shared HVAC systems serving several rooms or common areas.	☑	☑
reliable pressure differentials between rooms – interlocks ?	☑	☑
transfers of dirty equipment through common processing areas	☑	☑

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