Cross Contamination Control in Parenteral & Solid Orals

By: Amit Sareen

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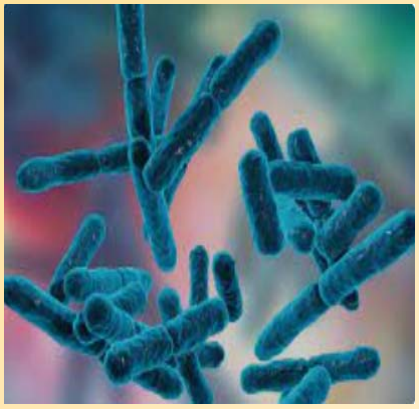
1. DEFINITION

Contamination is the undesired introduction of

- Chemicals (Leftover residue of Previous Process)
- Microbes
- Foreign matter (Dust, Glass & rubber particles, Fibers, Oil, Hairs & Skin fragments) into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage, and transport



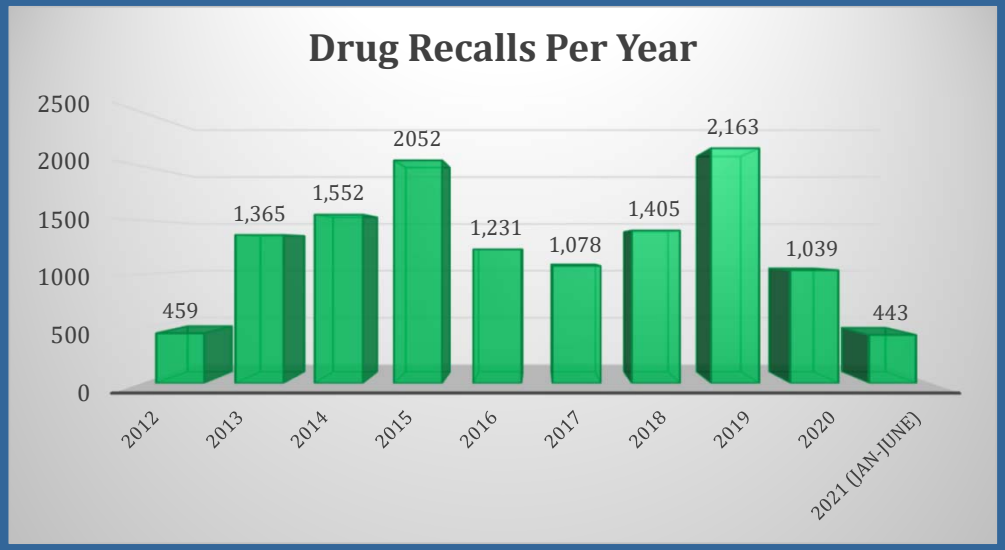
Cross-contamination is the contamination of the starting, intermediate products, or finished products with other starting materials or products during production

Three main types of cross-contamination

- Product – to - Product
- Equipment - to - Product
- Person - to - Product

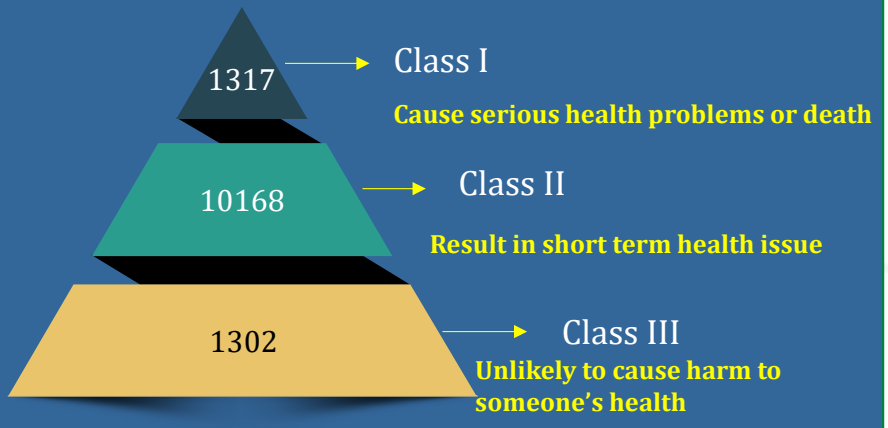
2. BACKGROUND

FDA Drug Recall Statistics Since 2012



- Since 2012: There have been 12,787 total drug recalls issued by the FDA
- On Average, 1,279 drugs are recalled every year

Recall Distribution Since 2012



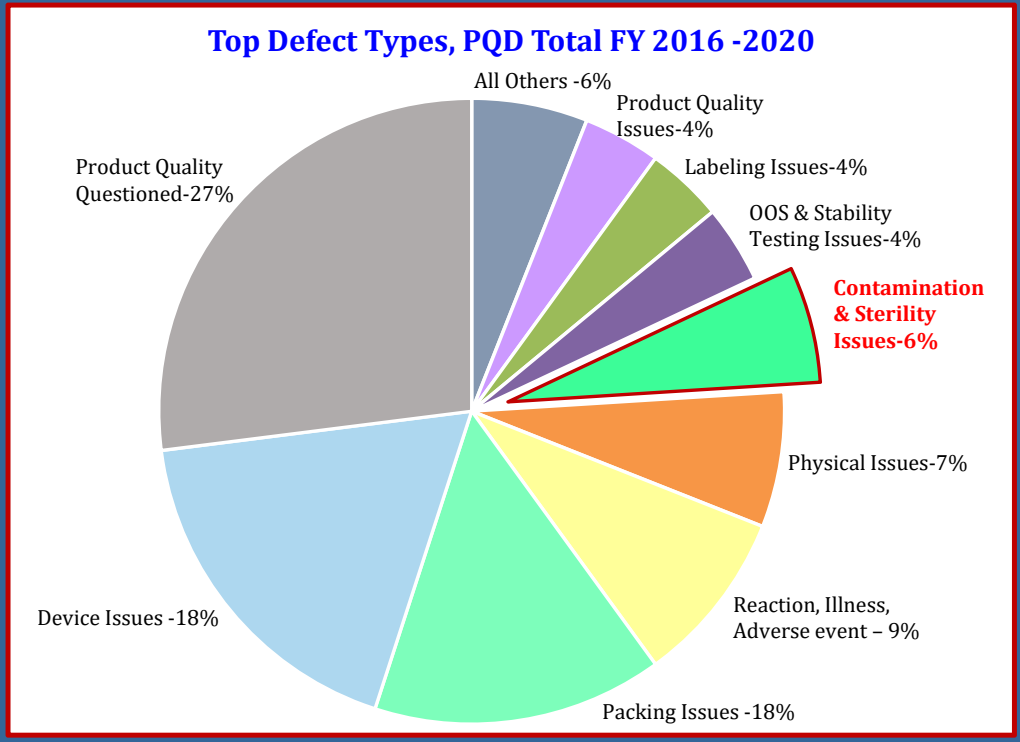
Major Contributes for Recall

- ❑ **Cross Contamination**
- ❑ Mislabeling
- ❑ Adverse Reaction
- ❑ Defective Product
- ❑ Incorrect Potency

References – https://www.maylightfootlaw.com

2. BACKGROUND

PQD – Product Quality Defects



- Contamination is one of the quality defect, leads to product recall
- A **focus area for the industry to improve quality by developing control strategy on cross contamination.**

References – Fiscal year 2020, published by Center for Drug Evaluation and Research office of pharmaceutical quality

2. FEW EXAMPLES OF CROSS CONTAMINATION RECALLS

Sr. No.	Year of Observation	Facility	Brief Description Of Recall Observations
1.	April, 2015	API	*Health Canada closed an API plant* (XXXXX Pharmaceuticals) *in Toronto, due to recall of all* ***nonpenicillin APIs*** *which was* ***cross-contaminated by penicillin.***
2.	Oct , 2018	OSD	Due to cross contamination with other products, XXXXX Pharmaceuticals, **Voluntary recalled 998 bottles** of ***Synjardy (Empagliflozin and Metformin Hydrochloride)*** tablets, 5 mg/1000 mg.
3.	May, 2019	Liquid	*Consumer complaint was raised for contamination of dangerous metal particles including nickel, iron and chromium which was introduced during manufacturing process* ***of Infant's Tylenol*** *at* XXXXX Healthcare's *plant in Fort Washington, Pennsylvania.*
4.	Jan , 2020	OSD	XXXXXX Pharmaceuticals U.S.A., had recalled one lot of **Lamotrigine** Tablets due to cross-contamination with **Enalapril Maleate.**
5.	April, 2020	Sterile	XXXXX USA, voluntarily recalled a single lot of ***Dexmedetomidine HCl in 0.9% Sodium Chloride Injection, 200 mcg/50 mL (4 mcg /mL), 50 mL*** due to presence of ***lidocaine content*** in the lot.

3. BASIC PRINCIPLES (ETHICS TO AVOID CROSS-CONTAMINATION)

- Cross-contamination is a major concern within the pharma manufacturing industry, particularly for products produced at multi-product or shared facilities
- Cross contamination can compromise patient or environmental safety and can have impact on the business

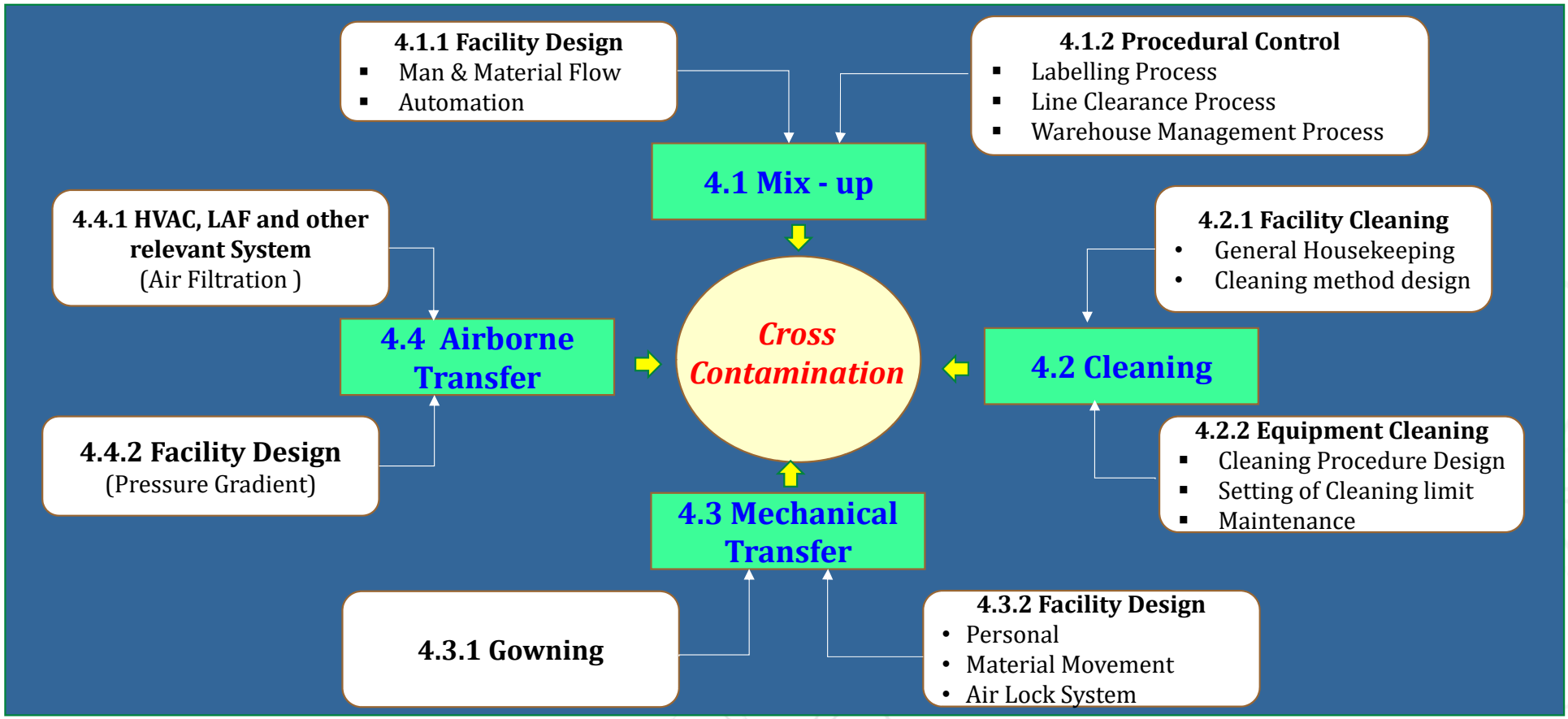
Three Basic Principles to avoid Cross-Contamination

Conversation with Employees regarding cross-contamination

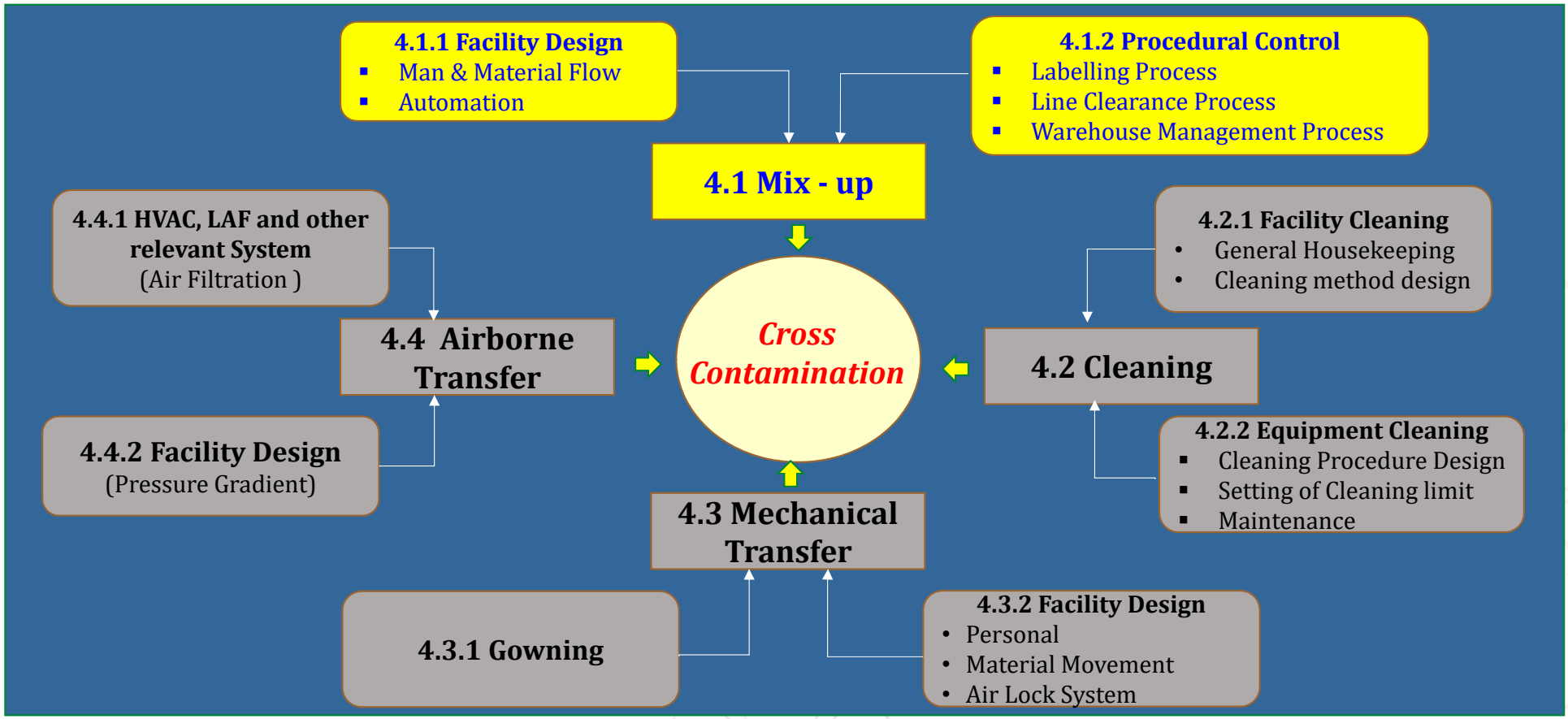
Follow a **robust & disciplined process**

Develop a Quality Culture that empowers everyone to act on any issues they encounter during day-to-day activity

4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS

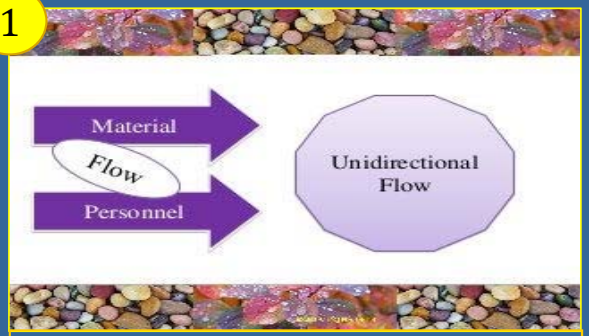


4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS



4.1 MIX-UP CONTROL
4.1.1 APPROACHES RELATED TO FACILITY DESIGN (MAN- MATERIAL FLOW & AUTOMATION)

1



Uni-Directional Material & Personnel Flow

2

Material Identification System

3

Warehouse Management System

4

Product Dedicated Facility (e.g. Penicillin, Oncology & Contraceptive etc.)

5

Designated Storage Area for Cleaned Equipment's

6

Designated Storage Area for Uncleaned Equipment's

4.1 MIX-UP CONTROL

4.1.2 APPROACHES RELATED TO PROCEDURAL CONTROL

1

Restrict & Control the entry of unauthorized persons (those who are involved in other product processing)

Authorized Personnel Movement & Access Control

2

- To avoid errors with respect to correct name, description, stage of material along with its storage
- In process labels with different color

Labelling Practice

3

To control cross contamination of different products due to personnel movement in high potent product facility(common corridor or /during product processing)

Air Shower for De-dusting

4

To avoid carryover of previous product

Product Dedicated Equipment Change Parts

4.1 MIX-UP CONTROL

4.1.2 APPROACHES RELATED TO PROCEDURAL CONTROL

5

To ensure equipment /line is free from previous product traces to avoid mix-up/Cross contamination

Visual Verification Process In Line Clearance

6

- Evaluating hard to clean area
- Emphasizing on checking during line clearance

Hard to Clean Area

7

Assuring/confirmation/cross checking of correct processing/cleaning

Doer & Checker Mechanism

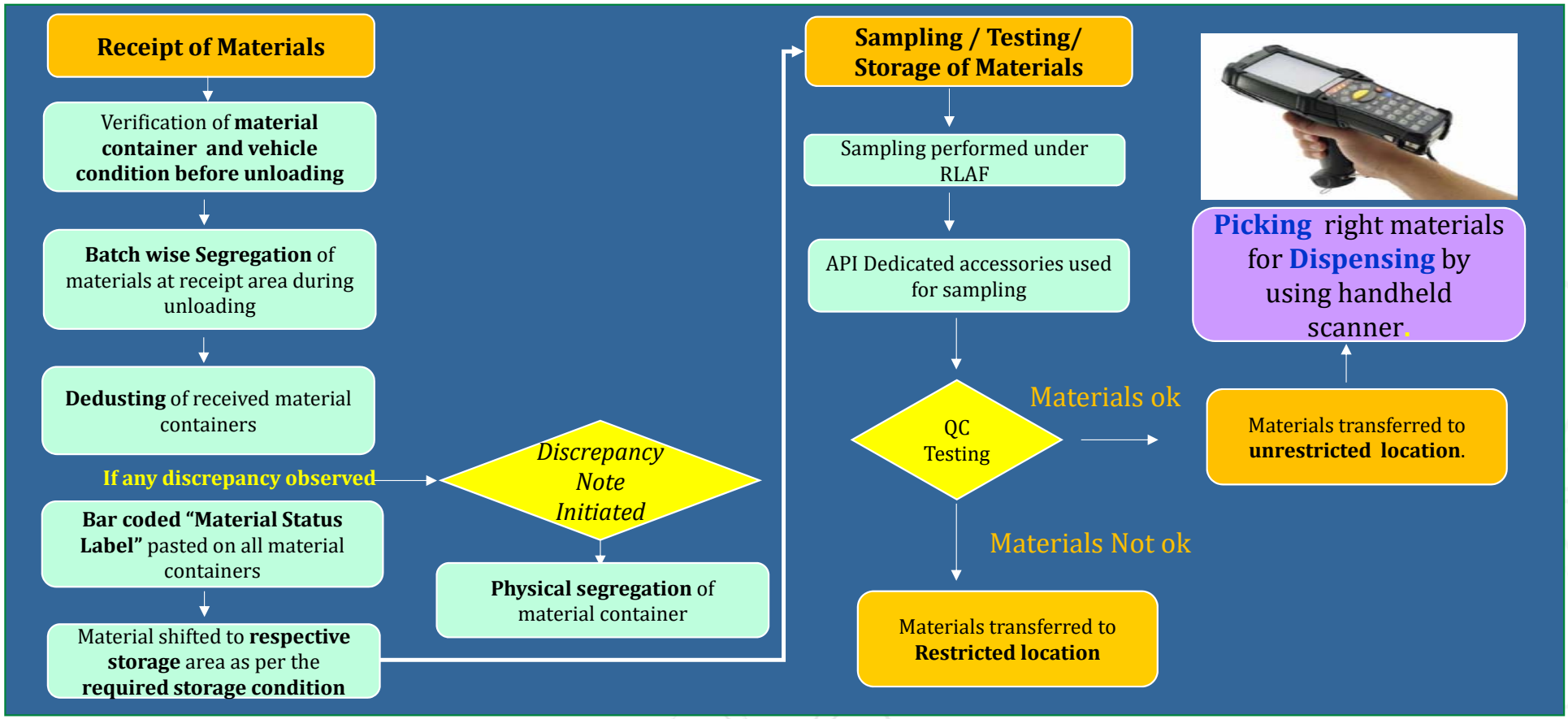
8

Rinse/Swab sampling method to be established for verification of traces of previous product

Periodic Cleaning Verification

4.1 MIX-UP CONTROL

4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING (SAP ENABLED WAREHOUSE)



4.1 MIX-UP CONTROL

4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING

Cross Contamination Controls at Material Dispensing

Hand held Scanner for material Picking

Line Clearance procedure of Dispensing Booth

- Usage of PPEs (Gloves/Goggles/ Over gown/Booties)
- Changing of gloves & gown during change of API & Colored materials

Dedicated dispensing accessories Used

4.1 MIX-UP CONTROL

4.1.2 APPROACH IN WAREHOUSE FROM MATERIALS RECEIPT TO DISPENSING

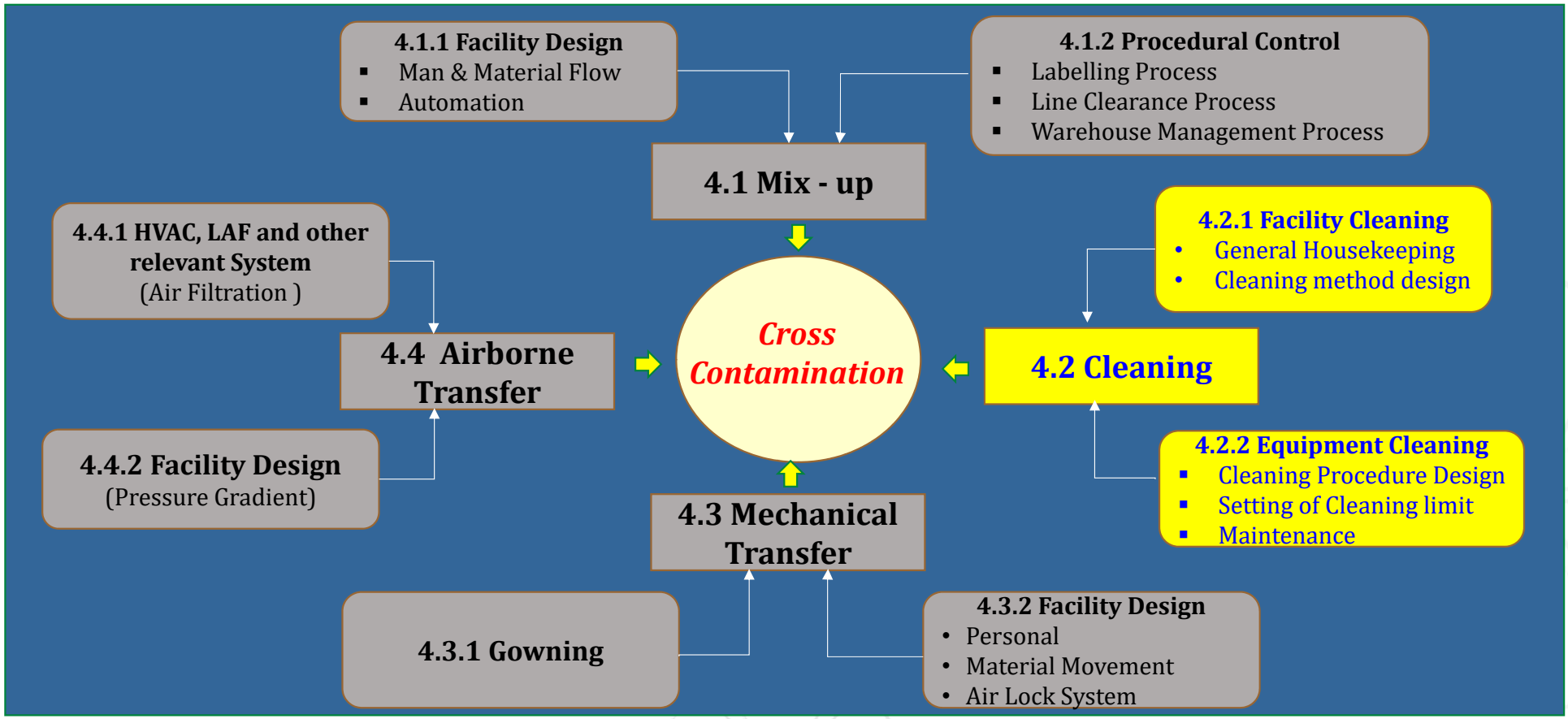
Cross Contamination Controls at Material Dispensing

- Dispensing under RLAF
- Cleaning of return riser filter during product changeover

Dispensing of high potent drugs in Isolator

Incase of high potent product dedicated SS container with lid shall be used

4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS



4.2 CLEANING CONTROL

4.2.1 METHODOLOGY FOR HOUSEKEEPING ACTIVITIES

Trained Person for Housekeeping

Application Methods

Wet Contact Time & Use - Dilution

Disinfectant Efficacy (DE) Study

Recovery Control

Selection and Rotation of Cleaning Agents

4.2 CLEANING CONTROL

4.2.2 METHODOLOGY FOR INTERMITTENT /BATCH TO BATCH CLEANING

Isolator Decontamination

Cleaning of Dust collector tubing & bags

Filter Cleaning

Intermittent Cleaning of Dusty Operations

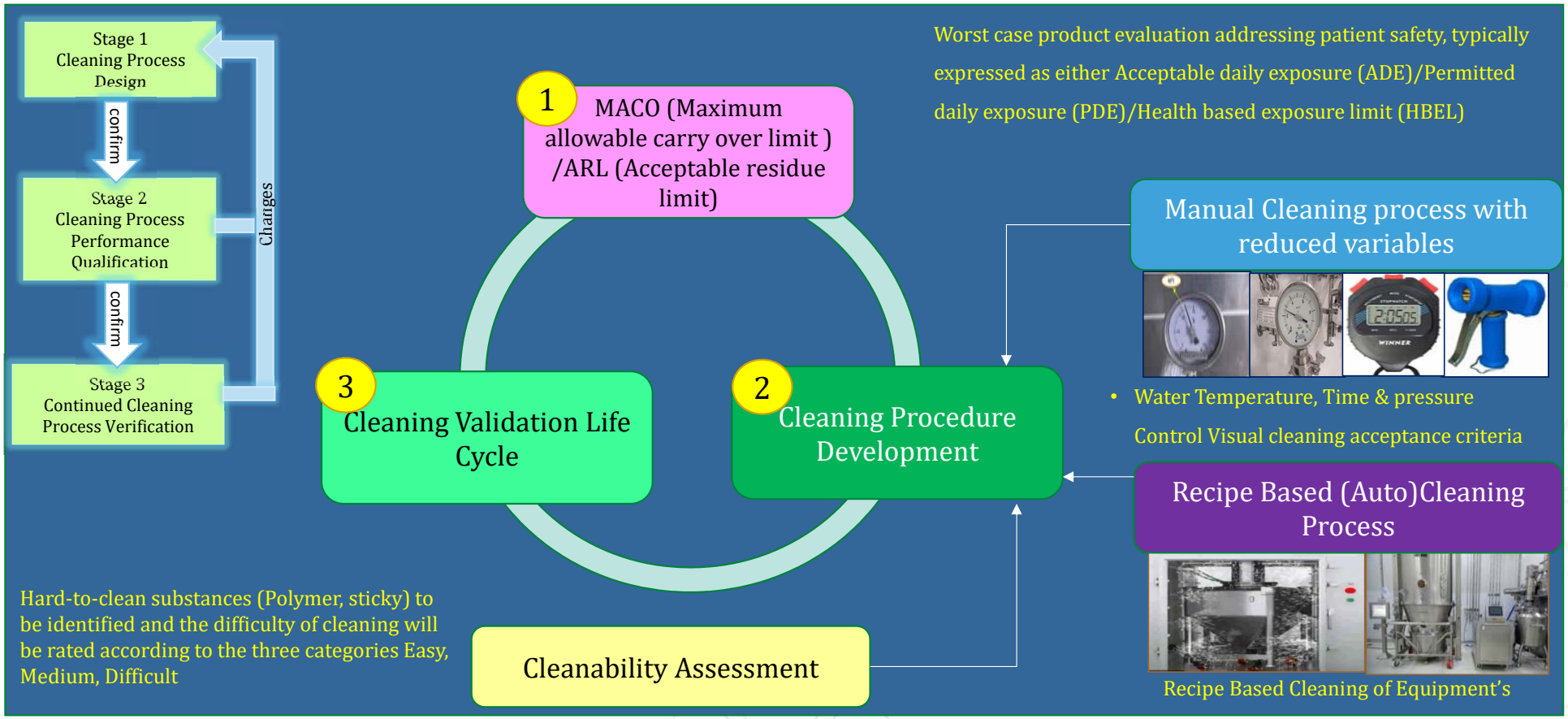
Sifting Operation

Roll Compacting Operation

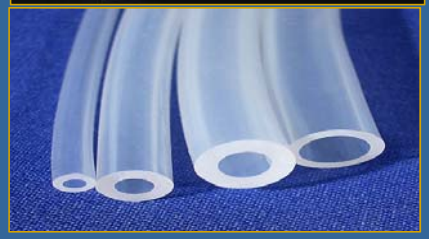
Tablet Counter

Tablet Compression

4.2 CLEANING CONTROL
4.2.2 METHODOLOGY ON EQUIPMENT CLEANING



4.2 CLEANING CONTROL
4.2.2 METHODOLOGY ON EQUIPMENT CLEANING



- ❑ Reproducibility of the cleaning process can be proved by validating the following cleaning process variables
  - Manufacturing of different batches & different products
  - Manufacturing of campaign batches
  - Using different operators for different batches
  - Using Non-dedicated equipment

- ❑ Development of Dirty Equipment /Cleaned Equipment /Campaign Run , Hold Time Study.

- ❑ Product Dedicated FBE Filter Bag / RMG Venting Bags
- ❑ API dedicated Silicone tubes/Product transfer Hose pipe

4.2 CLEANING CONTROL

4.2.2 METHODOLOGY AT STERILE FACILITY FOR MACHINE/CHANGE PARTS USED IN MULTI PRODUCT FILLING LINE/S

Filling Needles

Critical product contact surfaces (i.e., product tanks, stopper bowls, filling needles) are covered to prevent cross contamination.

Manifold

Aseptic connections and manipulations should be minimized or performed in a way to prevent contamination/ cross contamination (e.g., microbial, particulate, etc.)

Cleaned Parts

Cleaned equipment and parts should be dry and covered to avoid contamination/ cross contamination

4.2 CLEANING CONTROL

4.2.2 METHODOLOGY AT STERILE FACILITY FOR MACHINE/CHANGE PARTS USED IN MULTI PRODUCT FILLING LINE/S

Filters

Silicone Tubes

- For Filtration of product, "single use" filter shall be used in every batch
- For Product transfer during filtration, dedicated single use Silicone tubes shall be used in every batch

Liquid Filling Line

- In liquid injectable, Dedicated tubing's, filters shall be used to avoid Cross contamination
- For Change parts bowl, manifolds, connectors, needle, piston shall be cleaned using Auto process and rinse sample verification shall be evaluated to confirm traces of previous product

Powder Filling Line

- Powder filling shall be done in preferably in a closed RAB.
- Vacuum pipelines shall have NRV's
- Removal of powder traces by applying vacuum
- Cleaning of Return risers/ pre filter to remove previous product traces
- Cleaning of powder collector to remove traces of Previous product
- Verification of previous product removal by assuring swab/ rinse analysis.

4.2 CLEANING CONTROL

4.2.2 MAINTENANCE APPROACHES OF AGED EQUIPMENT

Equipment

Design

Easy to Clean

Inert

Non Reactive

Non Additive & Non Absorptive

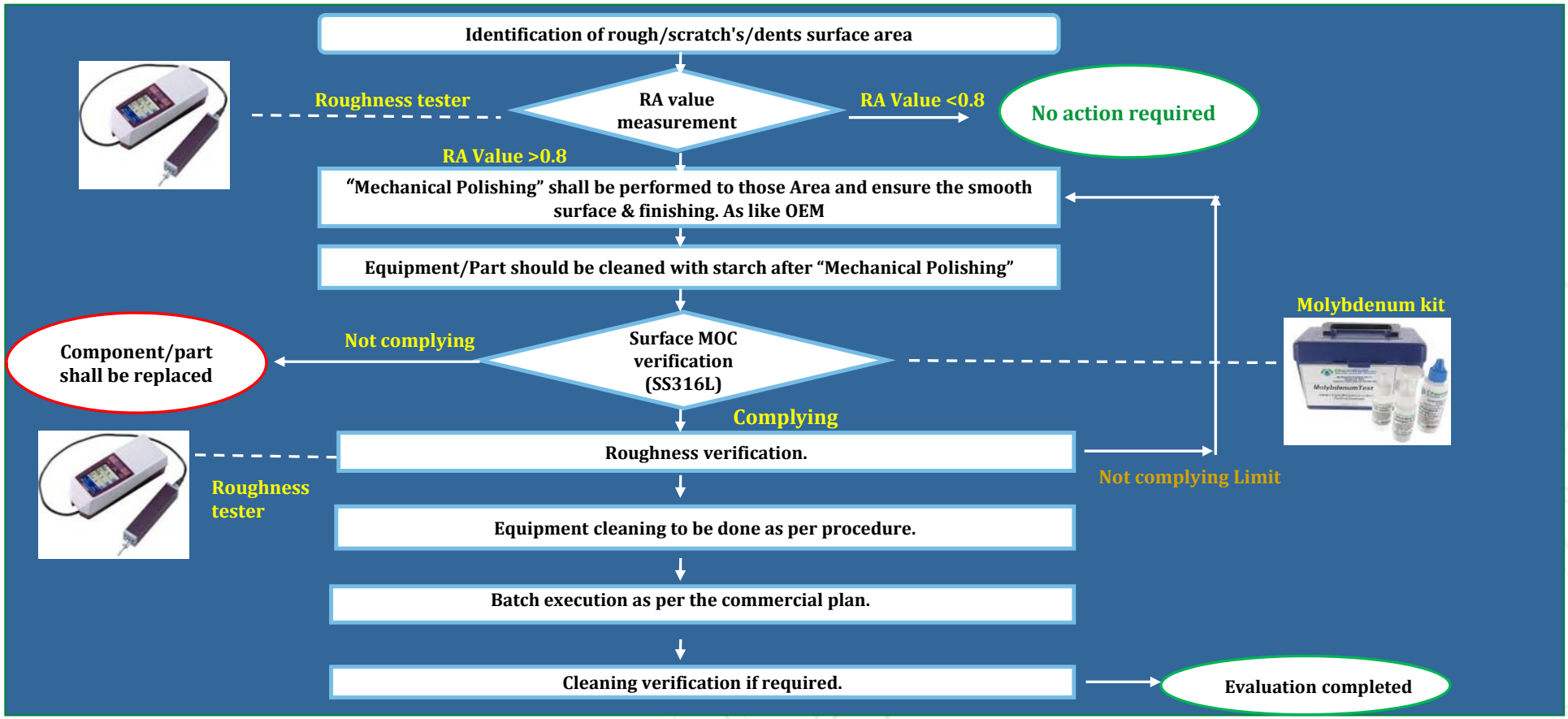
- **Material Selection** :- SS316L/Non-oxidizing
- **Periodic Maintenance :-** Electrolytic/Anodized polishing

Maintenance

Aged Equipment

(Interior surface imperfections and scratches on product contact surfaces)

4.2 CLEANING CONTROL
4.2.2 MAINTENANCE APPROACHES OF AGED EQUIPMENT



Example of Cross Contamination source

&

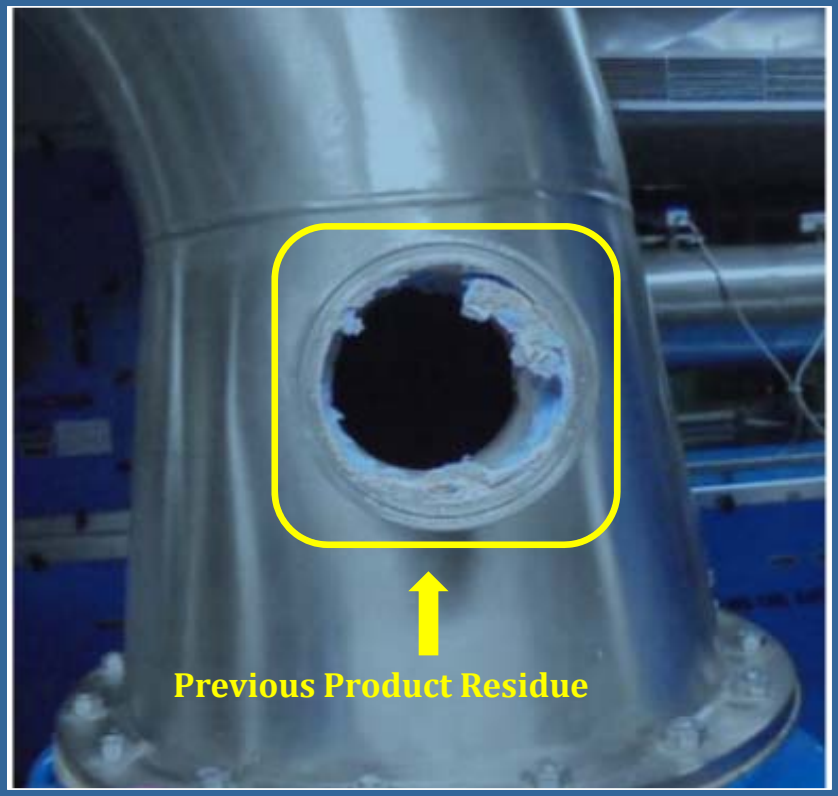
Recipe based cleaning approach for Equipment / Contact Parts

4.2 CLEANING CONTROL

4.2.2 EXAMPLE OF CROSS CONTAMINATION SOURCE FROM EQUIPMENT

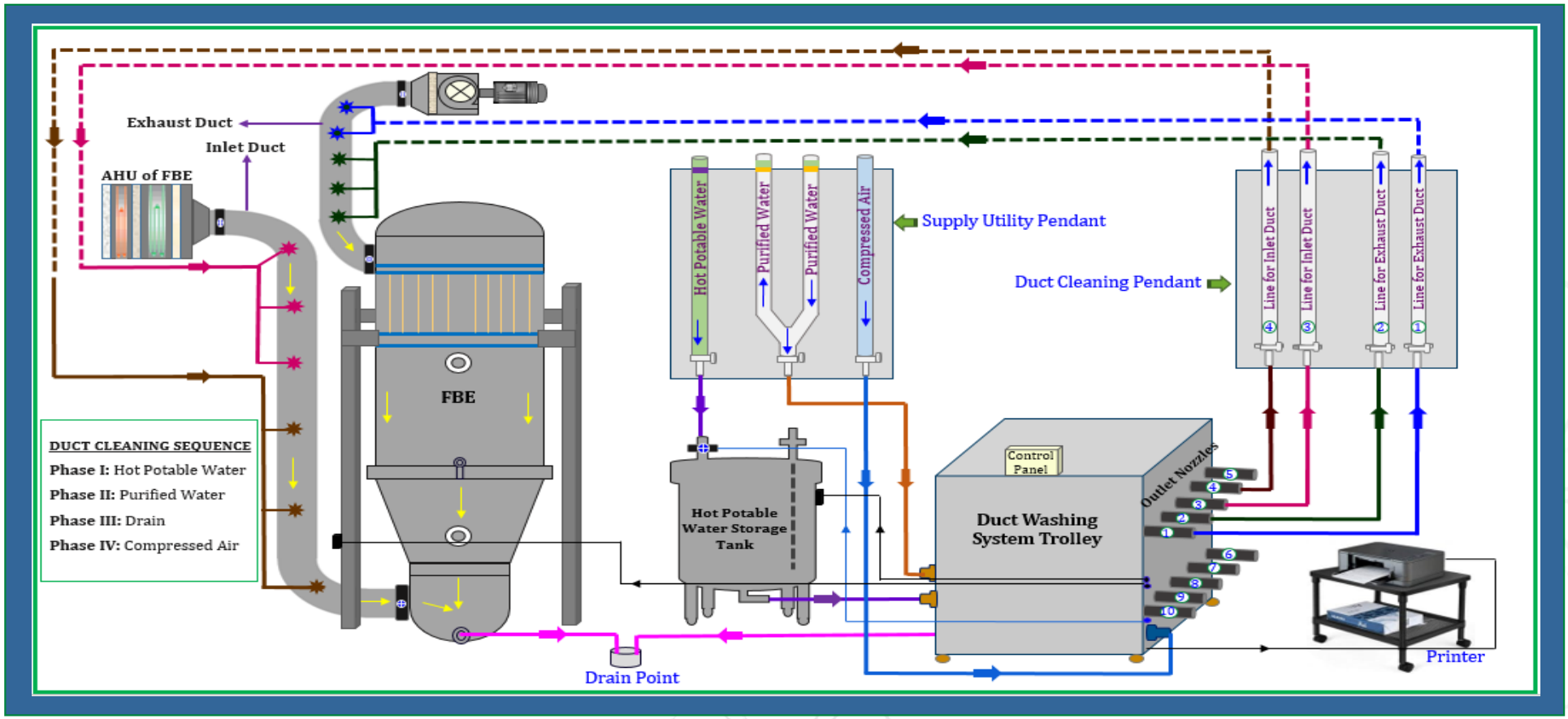
•In 2012, FDA conducted an inspection of a US Generic drug manufacturer based on field alert reports (FARs) submitted regarding an issue discovered by the firm during maintenance.

Firm manufactured multiple drugs on fluid bed dryers (including hormones) which leads to ***Cross contamination from one drug to another occurring via fluid bed ductwork****.*



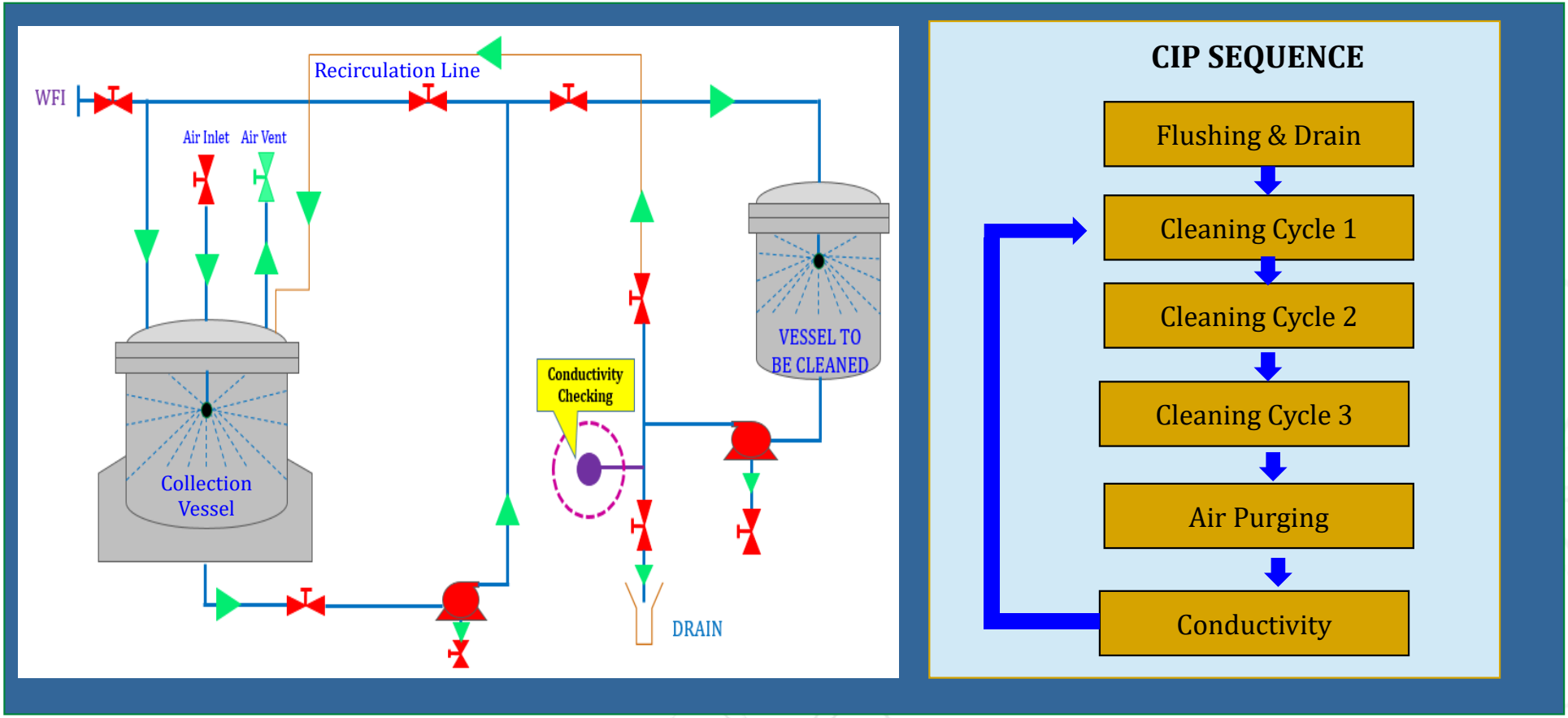
4.2 CLEANING CONTROL

EXAMPLE OF RECIPE BASED AUTOMATIC DUCT WASHING SYSTEM IN FBE/TABLET COATER

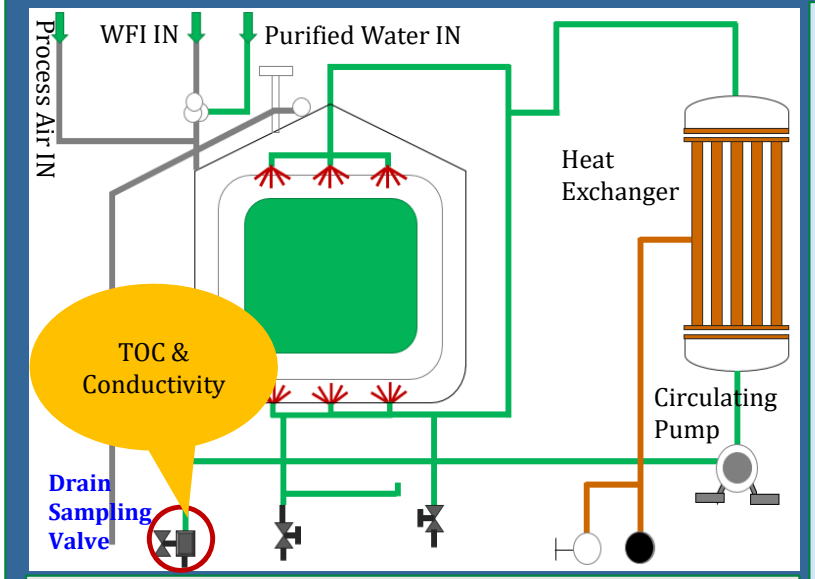


4.2 CLEANING CONTROL

EXAMPLE OF RECIPE BASED AUTOMATIC CLEANING OF VESSELS AT STERILE FACILITY

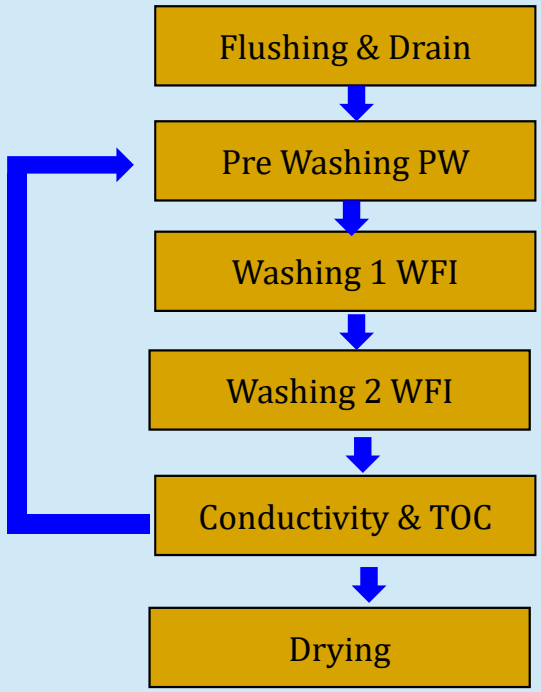


4.2 CLEANING CONTROL
EXAMPLE OF RECIPE BASED AUTOMATIC CLEANING OF CONTACT PARTS USING AUTO WASHER MODULE IN A STERILE FACILITY



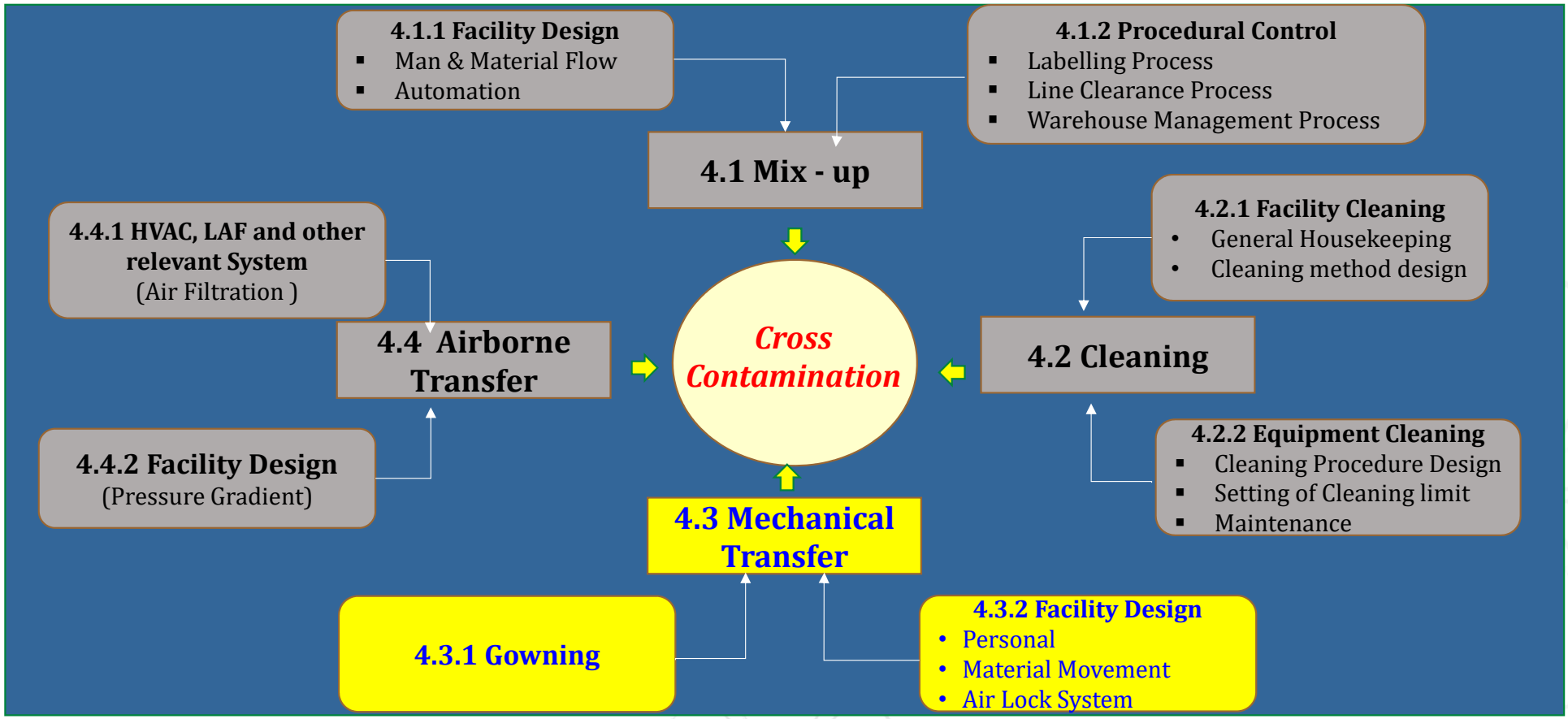
- WFI wash phase shall be repeated till TOC and Conductivity parameters are achieved as per set parameters in Contact Part Washer
- After achieving TOC & Conductivity, contact part washer shall automatically proceed for drying phase
- Visual inspection for presence of particulate matter

Contact Part Washer Operation Sequence



Carriage for Contact Part Washer

4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS



4.3 MECHANICAL TRANSFER CONTROL

4.3.1 THROUGH EFFECTIVE GOWNING PRACTICE

Over gown

- Area Dedicated
- Color coded for specific identification
- Single use /disposable
- Non-Particle shedding

Hand gloves

- Single use hand gloves
- Intactness checking of hand gloves prior to use
- Powder free hand gloves
- For sterile operation, double hand gloves shall be used

Garment Laundry

- Product dedicated Laundry (e.g., high potent Products)
- Validated Cleaning Cycle

Garment Inspection

- Visual inspection of cleaned garments includes Stains, Torn, stitched fiber defects, Ink mark etc.

4.3 MECHANICAL TRANSFER CONTROL

4.3.1 THROUGH EFFECTIVE GOWNING PRACTICE

Multi Product operational Suites at Solid Oral Facility

- Additional over gowning procedure to be followed for entry and exit from one process cubicle to another process cubicle.

Multi Product operational Suites at Sterile Facility

- Each Filling line have dedicated Entry & Exit change rooms
- Sterile disposable gown.
- Separate Laundry for washing and inspection of used garments

4.3 MECHANICAL TRANSFER CONTROL
4.3.2 FACILITY DESIGN THROUGH AIR LOCK SYSTEMS

Air Locks

Interlocking airlocks between entry points for classified areas of different grades (e.g., between ISO 8 and ISO 7).

Restricted Entry

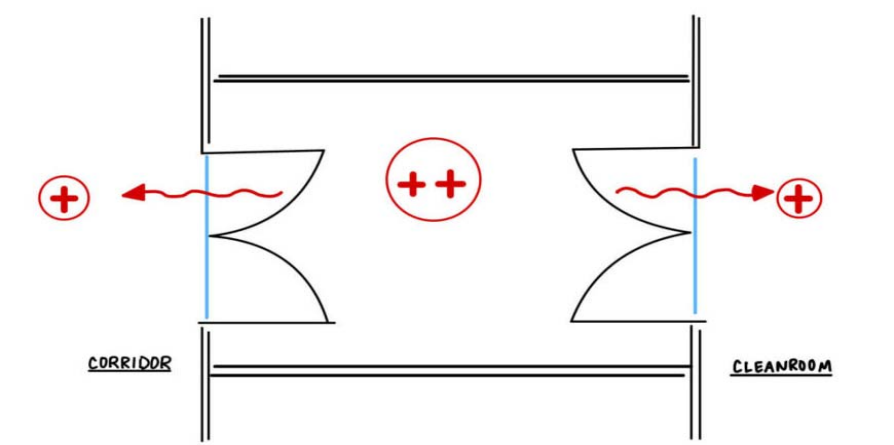
Restricted and controlled access to aseptic processing areas engaged in manufacturing of different products (e.g., card readers, biometric access).

Pass Through Procedure

- One Product material ,shall pass through at a time
- Dedicated pass box

4.3 MECHANICAL TRANSFER CONTROL
4.3.2 DIFFERENT TYPES OF AIRLOCK DESIGN

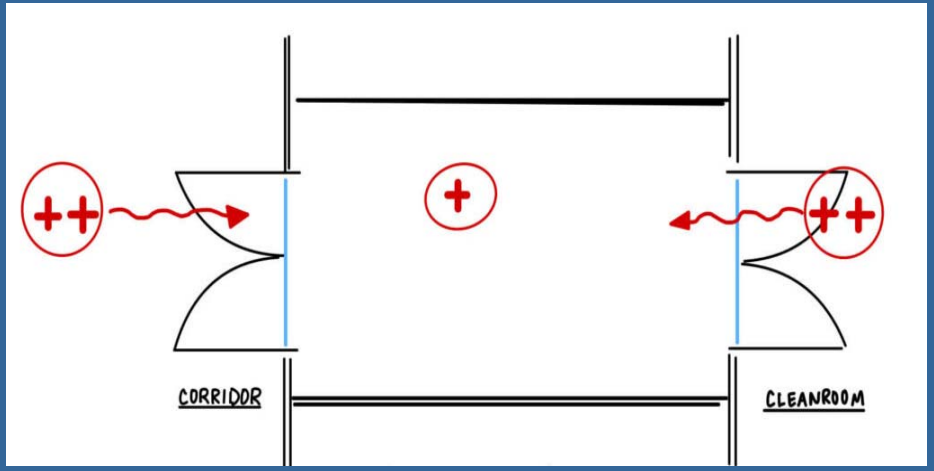
Bubble Airlock



Bubble Airlock: These types of airlocks have a higher pressure inside the airlock and lower pressure on both adjacent areas.

Application- Used in areas where the product needs protection and the people external to the clean rooms require protection from the product to reduce the possibility of particulate from entering the lesser pressure clean area

Sink Airlock

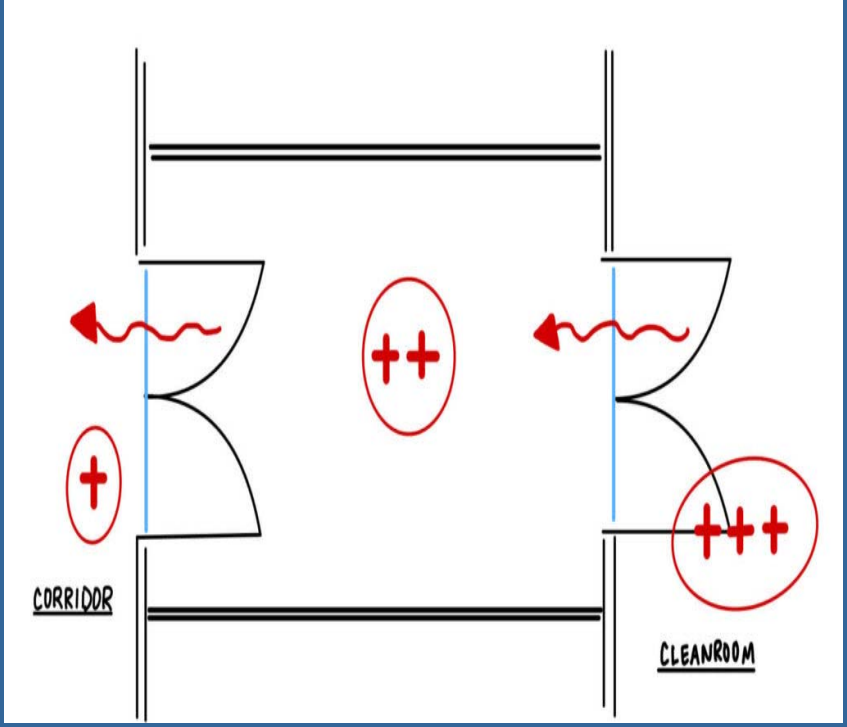


Sink Airlock:- These type of airlocks have a lower pressure inside the airlock and higher pressure on both adjacent areas.

Application- Research facility, where substances that are experimented on are highly potent products and it is essential to keep them from being exposed. In few types of production processes, in a clean room, air from contaminated area has to be contained in one place

4.3 MECHANICAL TRANSFER CONTROL
4.3.2 DIFFERENT TYPES OF AIRLOCK DESIGN

Cascade Airlock

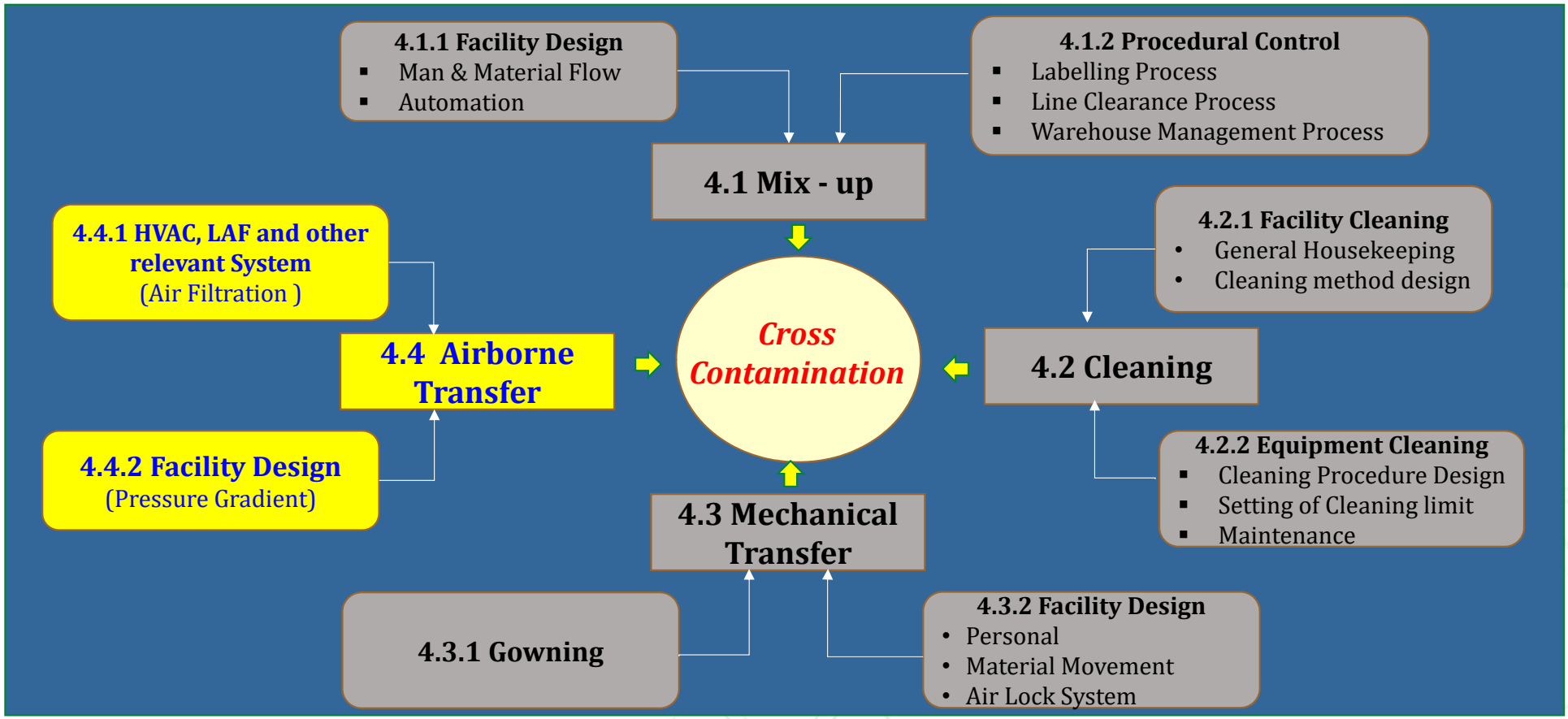


Cascade Airlock:- Airlocks having a higher pressure on one side and lower pressure on another side. This prevents entry dust and contamination from outside to airlock and from air lock to inner side

-Application-

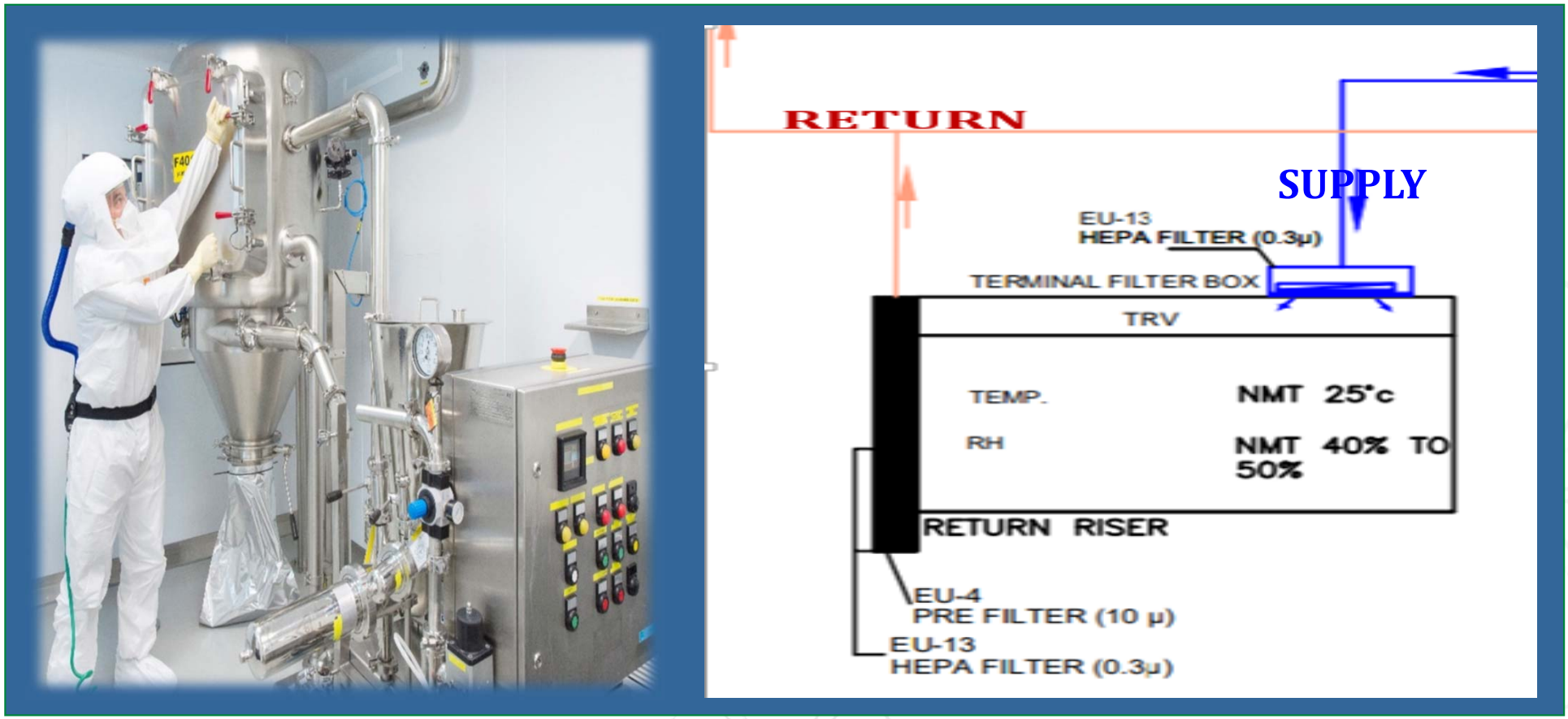
Any manufacturing facility where the product requires protection from particulate matter but the people outside the clean room don't need protection from the product in the clean room

4. ROUTES OF CROSS CONTAMINATION & IT'S CONTROLS



4.4 AIRBORNE TRANSFER CONTROL

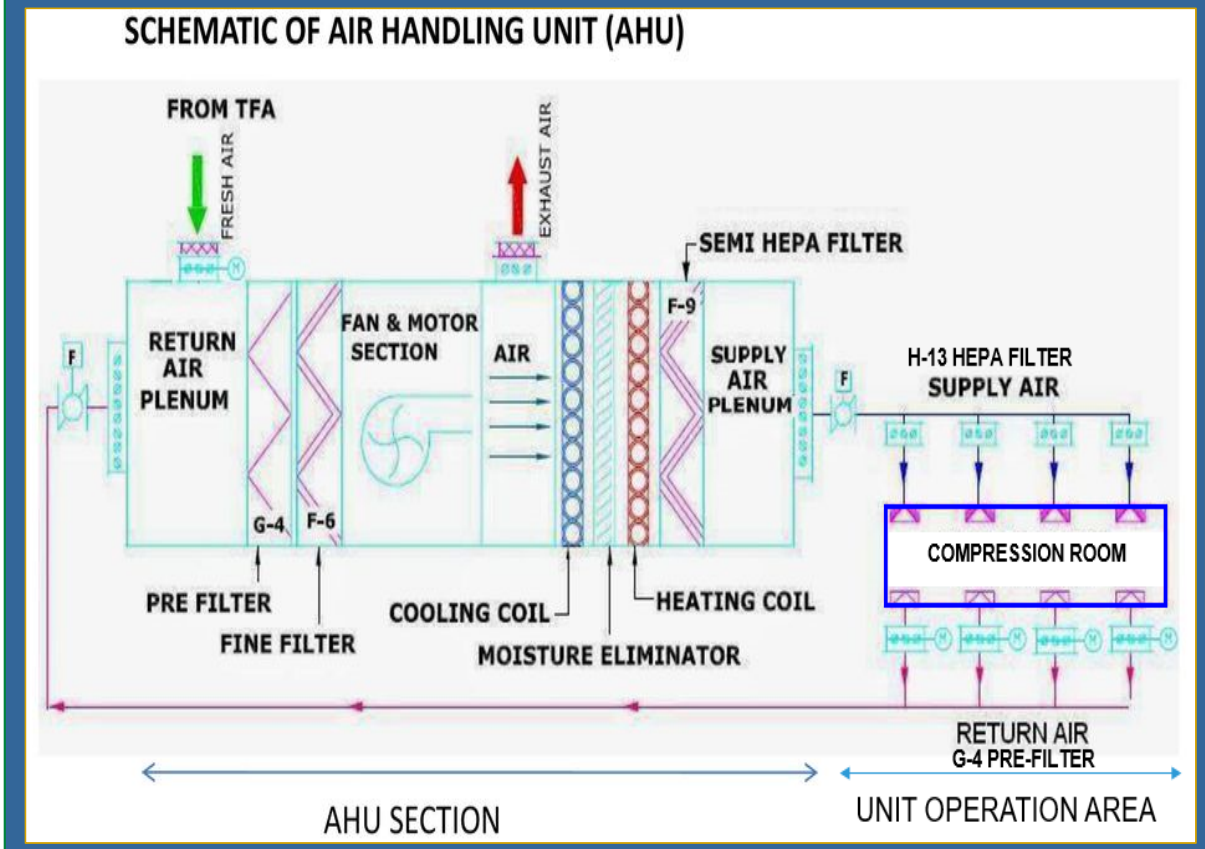
4.4.1 CONTROL VIA HEPA IN RETURN FOR HIGH POTENT MOLECULE FACILITY



4.4 AIRBORNE TRANSFER CONTROL
4.4.1 ISOLATORS

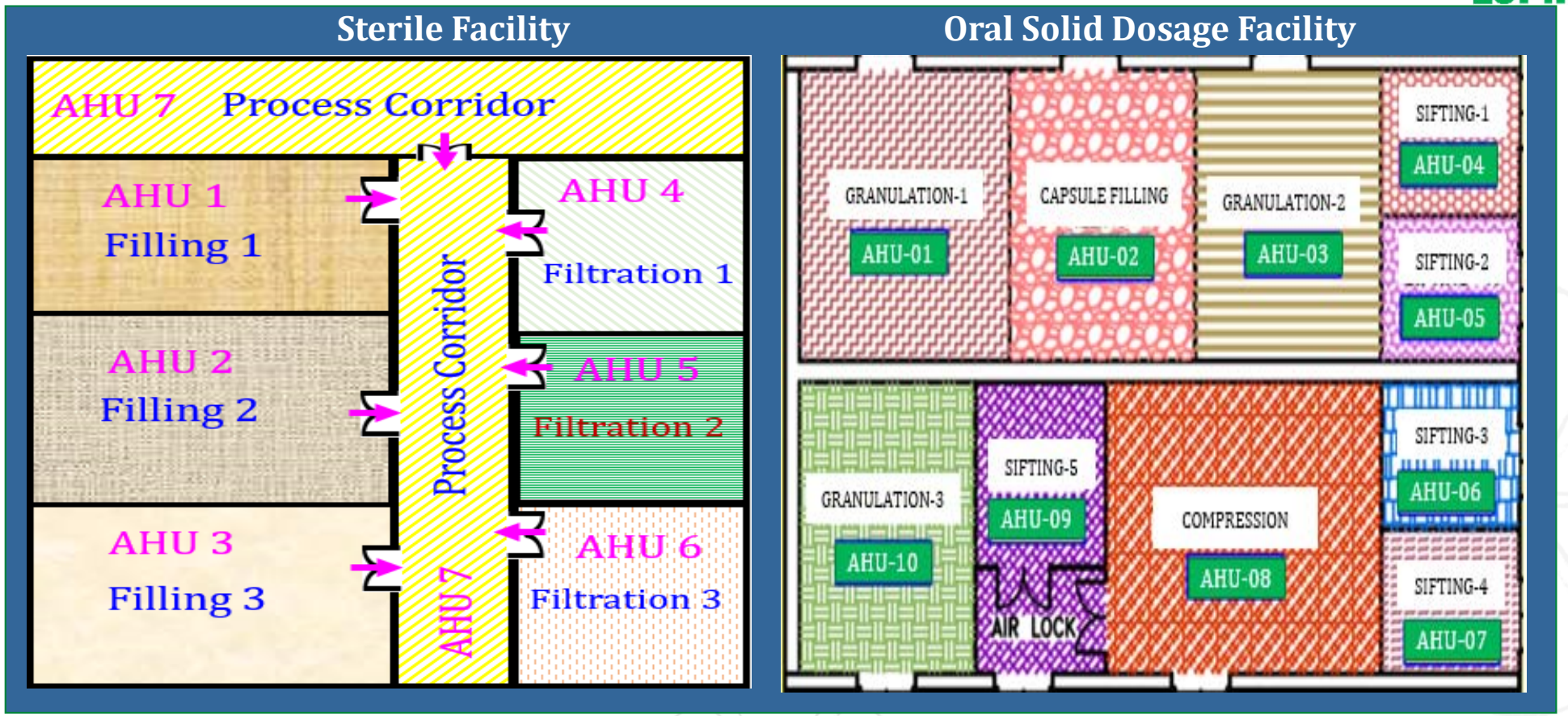
- Pharmaceutical **Isolator** provides for both barrier protection from cross-contamination as well as a clean air system.
- **RABS and cRABS** aim is to provide a controlled environment with high level of protection to transfer and process materials or devices through small openings (called “mouse holes”)

4.4 AIRBORNE TRANSFER CONTROL
4.4.1 DEDICATED AIR HANDLING UNIT FOR UNIT OPERATION IN MULTI PRODUCT PROCESS FACILITY



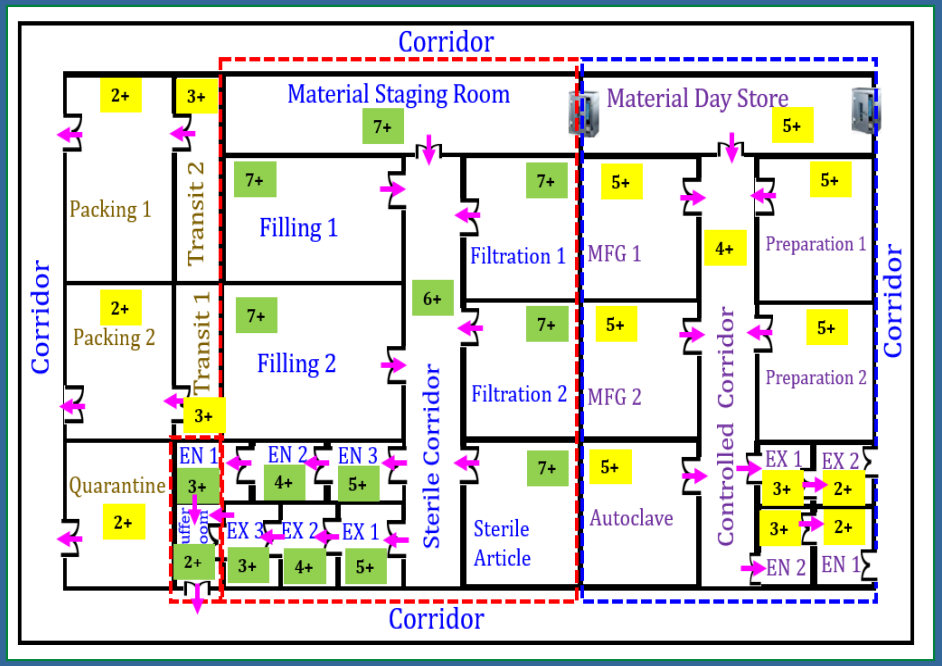
- Preferably area dedicated AHU's for a unit operation in multi product processing facility.

4.4 AIRBORNE TRANSFER CONTROL
4.4.1 DEDICATED AIR HANDLING UNIT FOR UNIT OPERATION IN MULTI PRODUCT PROCESS FACILITY

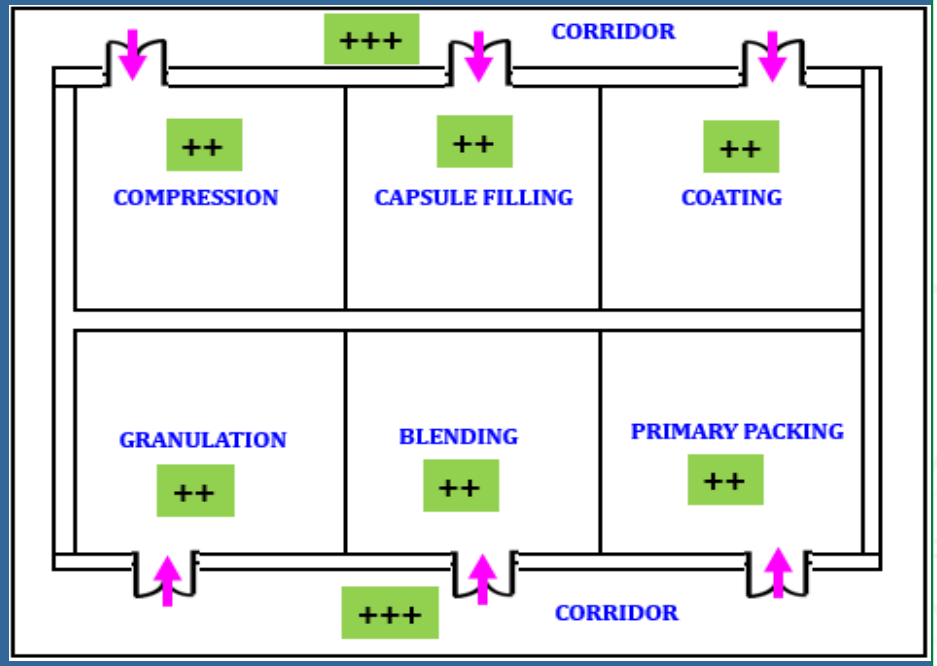


4.4 AIRBORNE TRANSFER CONTROL
4.4.2 PRESSURE ZONING IN FACILITY DESIGN

Sterile Facility



Oral Solid Dosage Facility



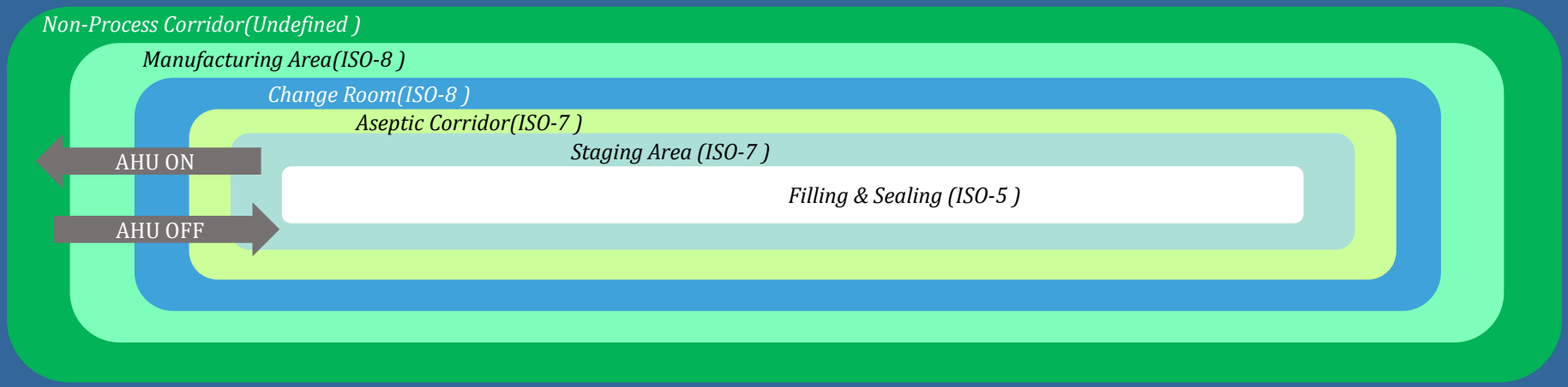
Legends:-
+ Pressure symbol
→ Air flow

- Pressure differential between same class NLT 6 Pascal
- Pressure differential between different class NLT 12 Pascal

4.4 AIRBORNE TRANSFER CONTROL
4.4.2 THROUGH AHU OPERATION SEQUENCE AT STERILE FACILITY

- **Cascading AHU ON / OFF sequence**

In Dynamic Condition



- **AHU interlocking System**
- **UPS supply available to AHUs** during power failure

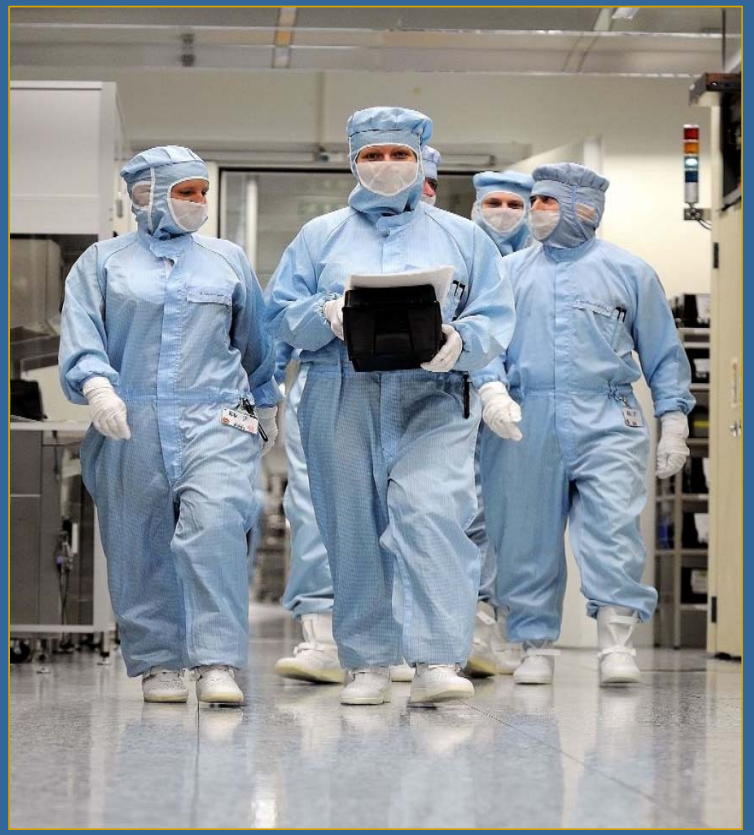
CONTROLS ON MULTI PRODUCT OPERATIONAL LINE IN STERILE FACILITY

- For multi product operations, dedicated vessels, filling lines, filters, S2S connectors, tubing's with coding and identification.
- Gown coding (with different colors).
- Each filling line must have dedicated exit change rooms
- Separate laundry facility for washing the dresses
- Demarcation for dedicated transfer lines
- Disposable gowns/gloves

5.0 CONCLUSION

Contamination Control is NOT a Paper Exercise!

It is a Mindset !!



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Lupin Limited,

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