8TH ADVANCED GMP WORKSHOP 2023

Cross Contamination Control Strategy with Case Study and Regulatory Expectations

Rahul Songire

Zydus Lifesciences Limited

03rd October 2023

The desired state: A mutual goal of industry, society and the regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight

- Failing to change to a more flexible and agile system may lead to being seen as old, aging or obsolete
- The inclusion of the terms “maximally efficient”, “agile” and “flexible” suggests that the facilities of yesterday will not fare well going forward
- Flexibility is key factor in the facility approach decision – “characterized by a ready capability to adapt to new, different, or changing requirements”
- **In order to be “reliable”, absence of unacceptable adulteration in drug products due to cross-contamination with other products produced in a shared facility is must**

Consequences due to the Cross Contamination

Product Quality and Safety Implications

- Impact on product efficacy and potency
- Potential adverse effects on patients
- Increased risk of recalls and market withdrawals

Financial Losses

- Cost of product recalls and disposal
- Expenses for facility shutdowns, investigations, and corrective actions
- Loss of sales and market share

Regulatory Consequences

- Violations of Good Manufacturing Practice (GMP) regulations
- Potential fines or legal actions
- Damage to company reputation and trust

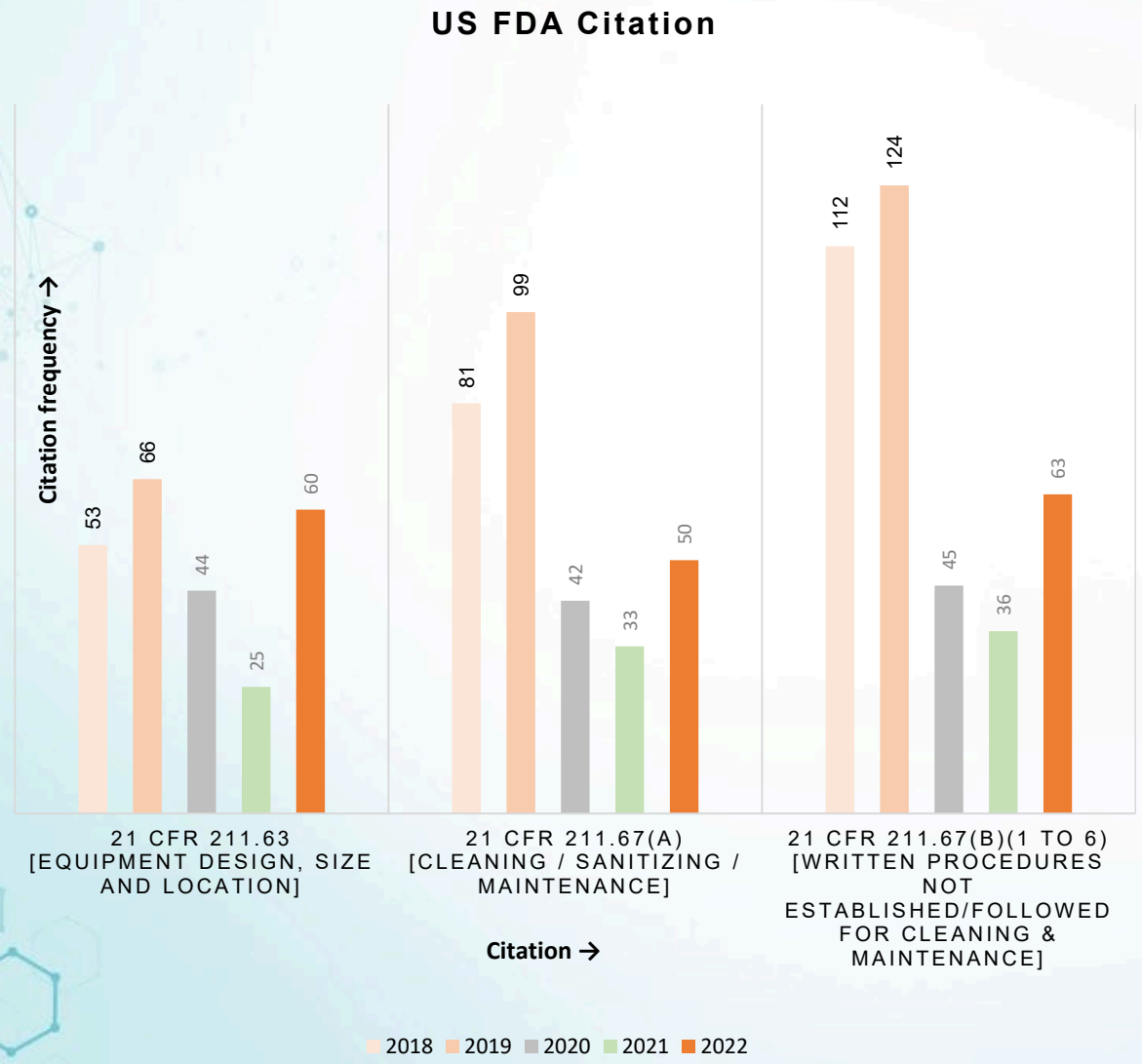
Operational Disruptions

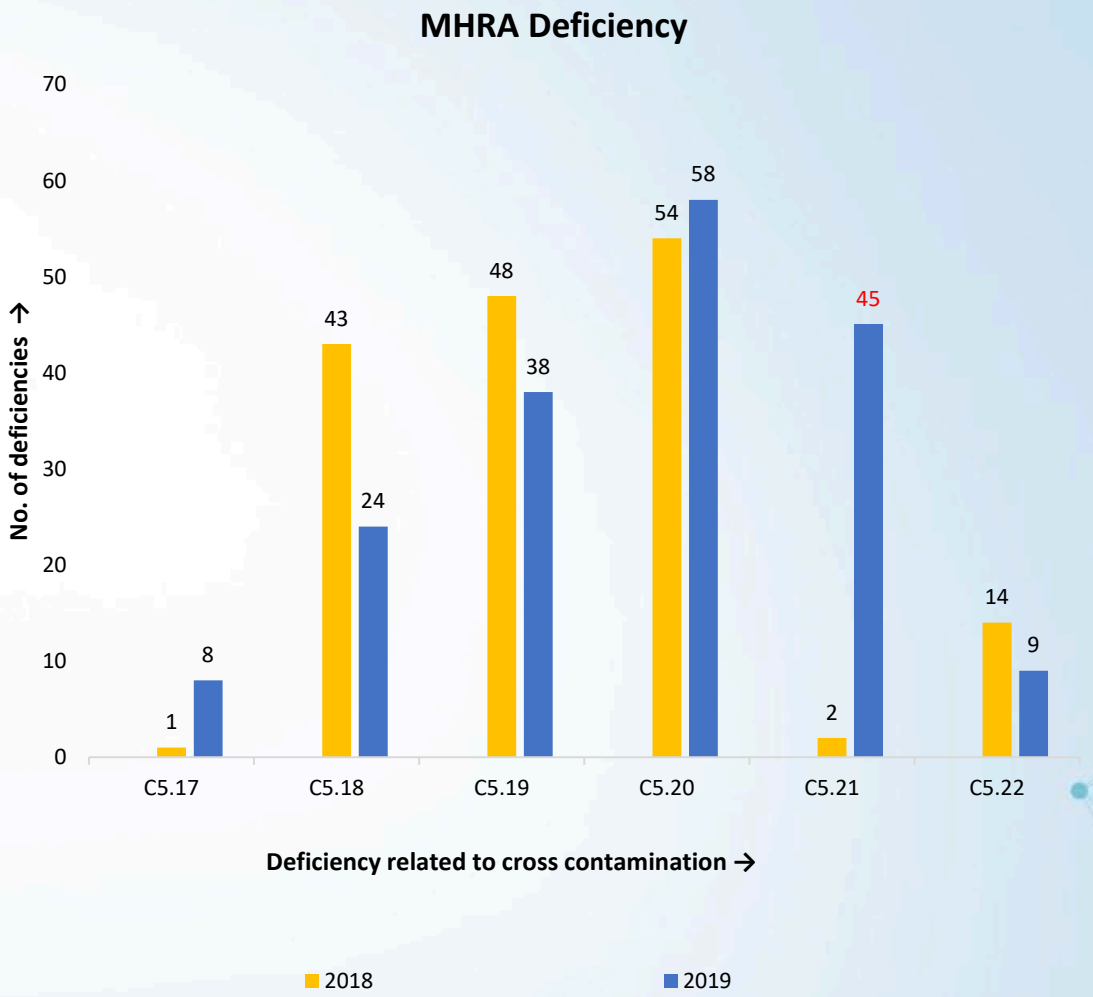
- Production delays and downtime
- Disruption of supply chain and distribution
- Potential impacts on meeting market demands

Investigation and Remediation Costs

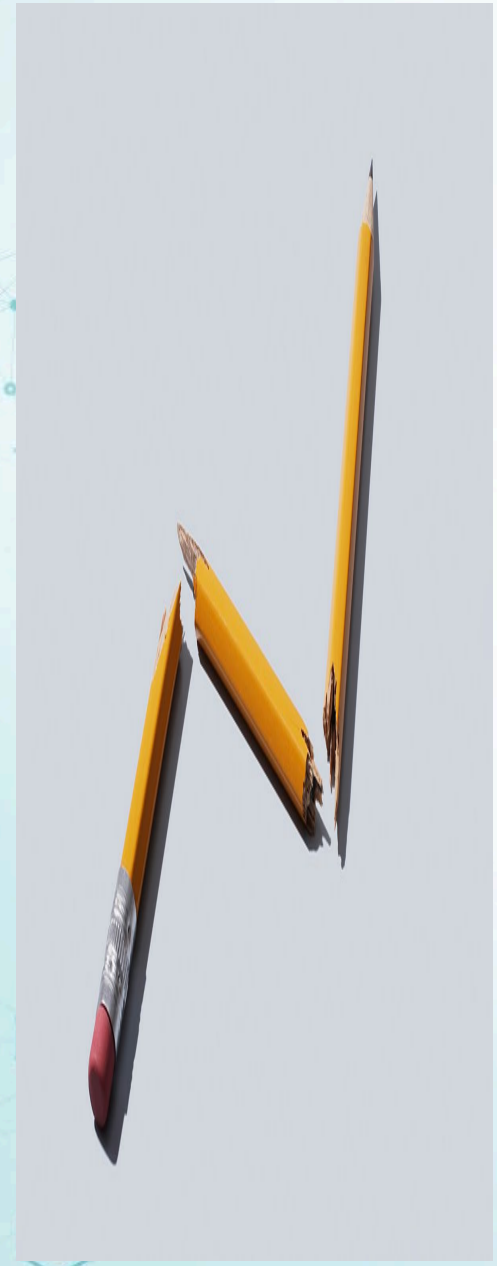
- Resources required for identifying the source of contamination
- Training and retraining to staff to prevent future occurrences

US FDA/MHRA inspection trend and concern on contamination





US FDA Inspection Trend and Regulatory Concern



"Your firm failed to follow the procedure"

WL to Sterile facility (07/2023)

An FDA investigator observed **white spots at the bottom** of a **……** bulk **solution holding tank** used to supply a non-dedicated filling machine despite the vessel being documented as clean

WL to Sterile facility (07/2023)

You also **did not propose a systemic assessment of your equipment cleaning program**

483 to OSD facility (09/2022)

We observed **residues of white powder** [e.g., flakes] **on different surfaces of cleaned**

WL to Sterile facility (12/2022)

Our investigators observed **numerous scratches** and **dents** on product contact surfaces of the …….**rubber stopper bowl-II**.

WL to OSD facility (02/2020)

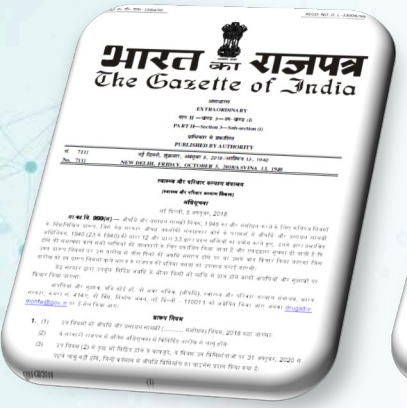
Our investigators observed multiple….and……containing residues of what appeared to be different products **inside the exhaust ducts**

WL to API facility (11/2019)

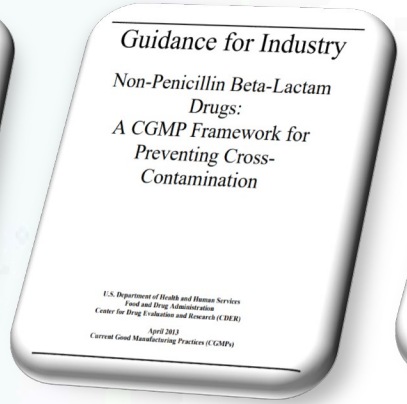
Interior surfaces of the……**chutes were wiped with lint-free cloths**,….**stains were observed**. Testing you conducted later determined the… stains were **residual API observed**

References

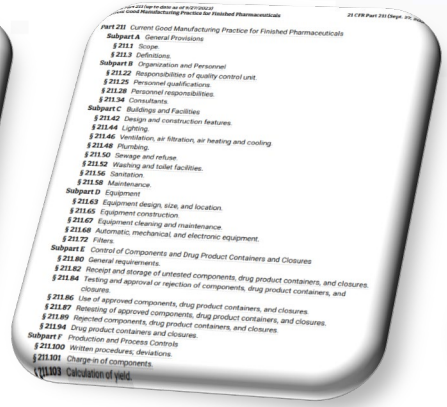
Revised Schedule M



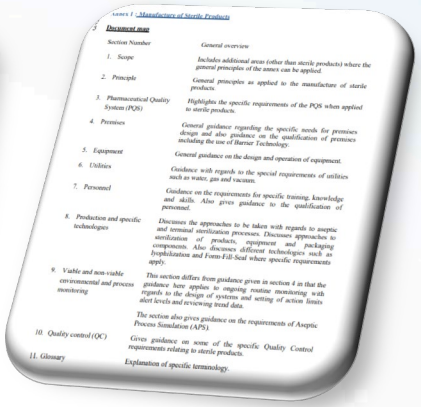
USFDA



21 CFR part 211



EU annex 1



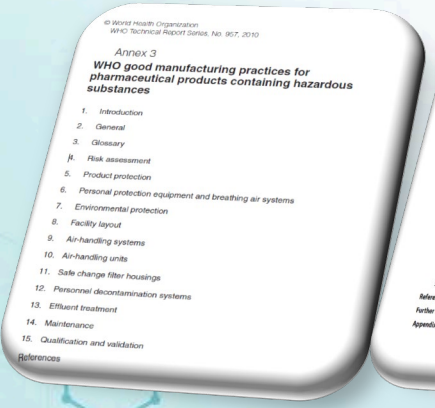
EMA shared facility

EMA Q& A

On health-based exposure limits

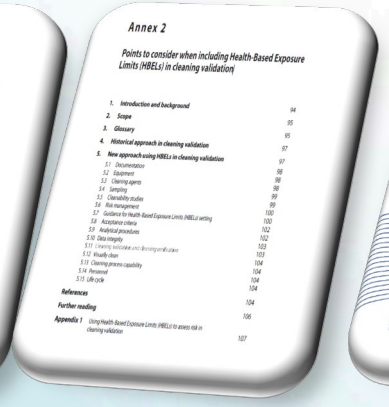
WHO

Containing hazardous substances



WHO

HBELs in cleaning validation



PDA TR 29

PDA TR 90

ISPE

ISPE

ISPE

Dedicated facility

Substances classes which may not be produced in the same facilities used in the production of other APIs include;

- **Scientific data from the toxicological evaluation does not support a controllable risk e.g. Highly potent allergens such as beta-lactams e.g. Penicillins or Cephalosporins**
- **The risk can't be adequately controlled by operational and/or technical measures e.g. Cytotoxic compounds, Certain hormones**
- **Radiopharmaceuticals**
- **Ectoparasiticides e.g. substances for the treatment of lice**
- **Relevant residue limits, derived from the toxicological evaluation, can not be satisfactorily determined by a validated analytical method**

Safety limit Vs LOQ

Relevant residue limits, derived from the toxicological evaluation, can not be satisfactorily determined by a validated analytical method

$$\text{MACO (µg)} = \text{PDE (µg)} \times \frac{\text{B.Size (In units)}}{\text{LRDD (In units)}}$$

$$\text{MACO (µg)} = 10\ (\text{µg}) \times \frac{50000\ (\text{In units})}{20\ (\text{In units})} = 25000\ (\text{µg})$$

Example 1: Swab sample (OSD)	
MACO (µg)	25000
Total product contact surface area (cm^2)	33000
MACO (µg) per cm^2 area	25000/33000= 0.757
MACO (µg) per 100 cm^2 sample surface area	0.757× 100= 75.7
Dilution volume (in mL) per swab (100 cm^2 area)	25
MACO (µg) per 25 mL	75.7
MACO (PPM)	75.7/25=3.028
Safety limit (PPM)	**3.028**

LOQ > Safety limit

LOQ (PPM) | 4

LOQ < Safety limit

LOQ (PPM) | 1.5

Example 2: Rinse sample (Injectable)	
MACO (µg)	25000
Total product contact surface area (cm^2)	33000
MACO (µg) per cm^2 area	25000/33000= 0.757
MACO (µg) per 1000 cm^2 rinse area	0.757× 1000= 757
Rinse volume (in mL) for 1000 cm^2	200
MACO (µg) per 200 mL	757
MACO (PPM)	757/200=3.785
Safety limit (PPM)	**3.785**

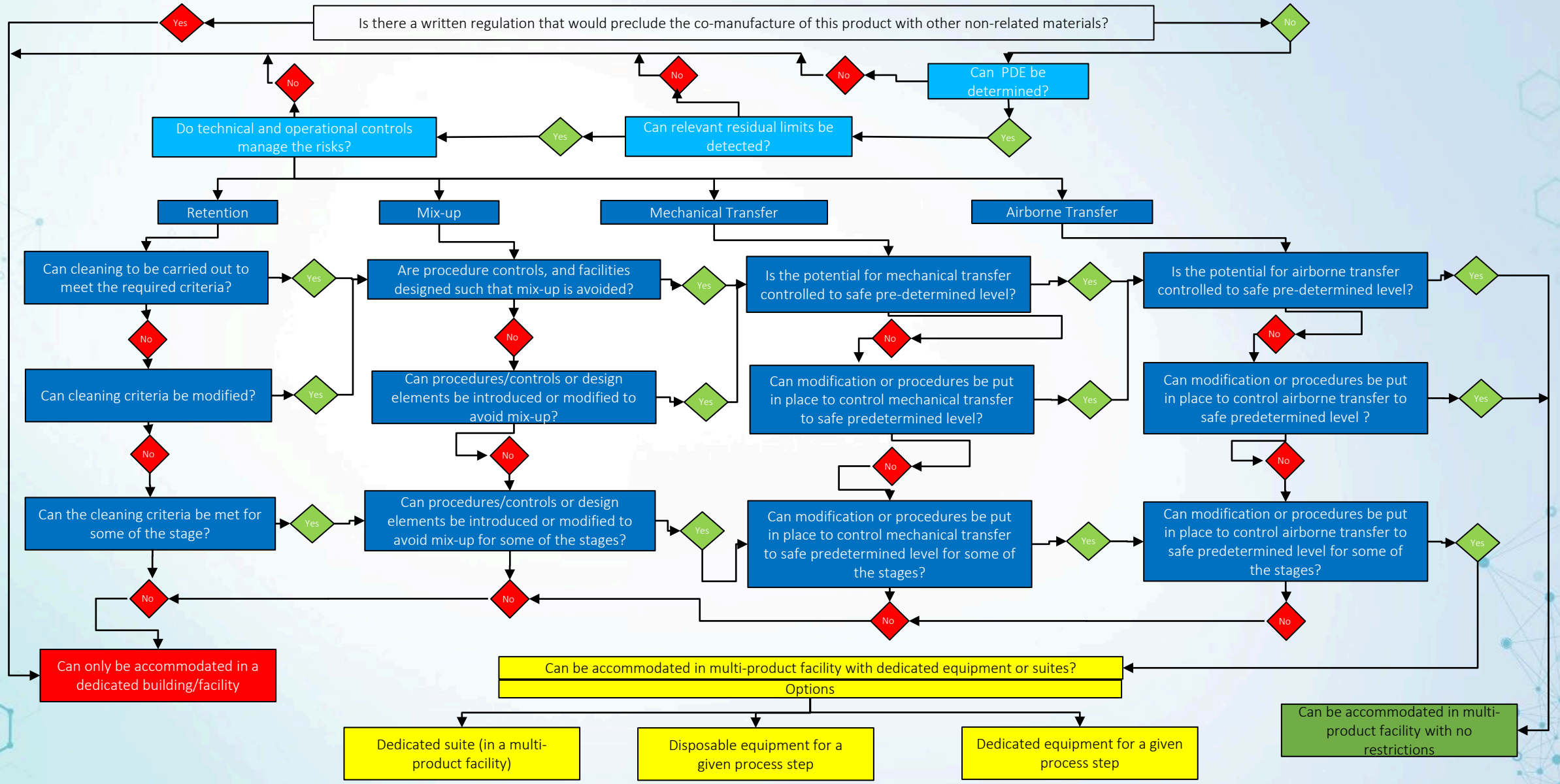
LOQ > Safety limit

LOQ (PPM) | 4.5

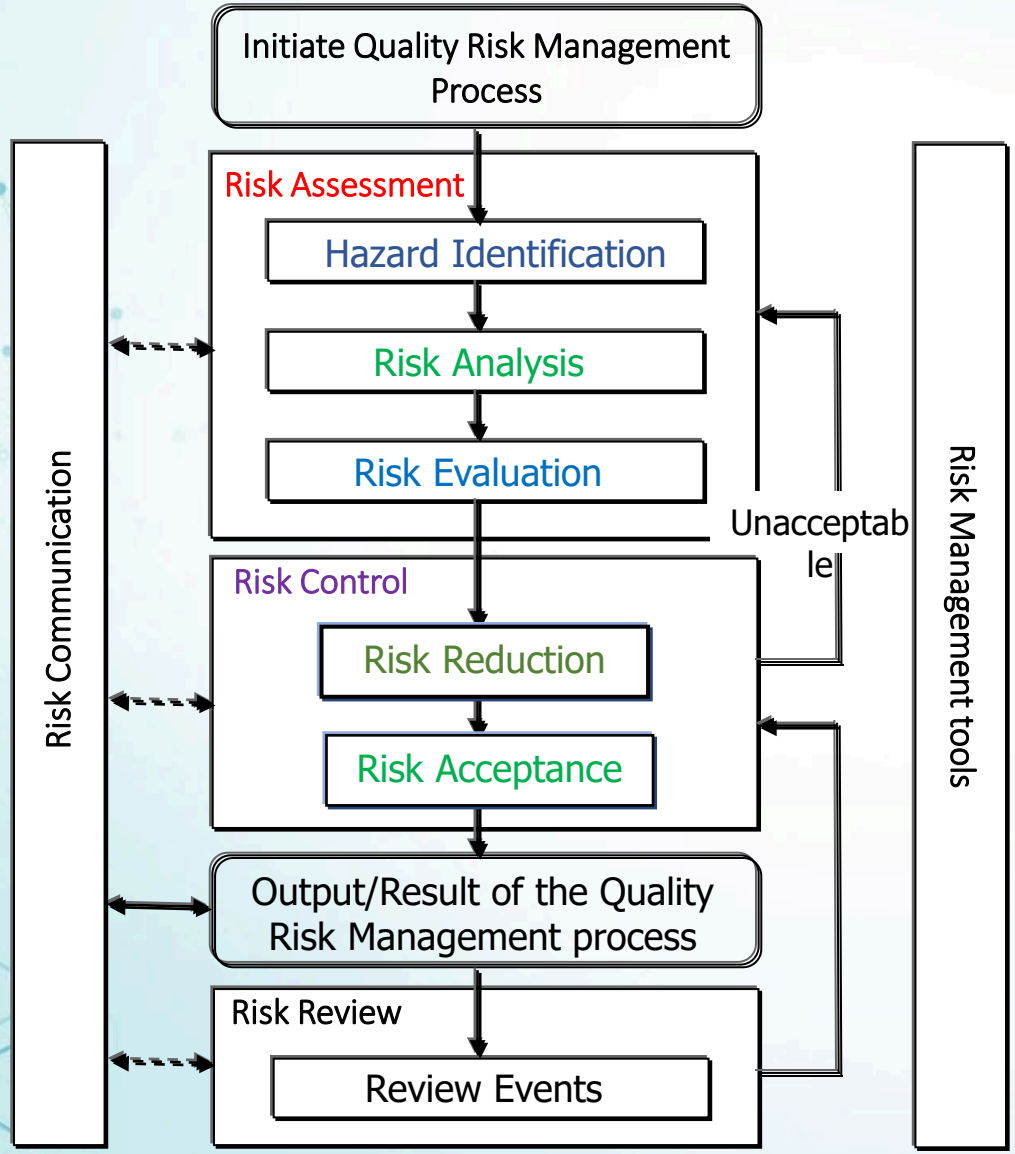
LOQ < Safety limit

LOQ (PPM) | 1.5

Logic diagram: To decide facility/separation category



Risk Assessment



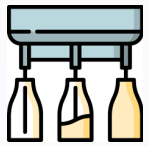
All risk assessments shall be a "**live document**" and reviewed on a regular basis to ensure that the existing control measures remain appropriate and effective

List of Elements

Material and Infrastructure:
Flow, design, maintenance, filtration, equipment etc.

Qualification:
Supplier, Personnel, equipment, process etc.

Personnel:
Personnel flow, gowning, handling, training etc.



Simulations:
Media fill, smoke study, gowning simulation, material handling simulation etc.

Risk assessment is **more than** FMEA

Human factors

Quality Policies Standards for Managing the Risk of cross contamination

Subject Matter Experts:

- Toxicologists
- Industrial hygienists
- Engineers
- Quality managers
- Users or operating personnel
- Subject Matter Experts

Technology transfer (New Product Introduction)

- Mechanism that triggers an assessment of potential cross contamination risks prior to bringing the product/compound into the facility
- ADE monograph
- Cleaning Process
- Sensitivity of analytical method

Risk Management

- Policy describing understanding of risk and how to assess it and mitigate/control

Cleaning validation master plan/policy

- Describing selection of drug product for cleaning validation, maximum allowable carryover limits
- Bracketing approach
- New product introduction
- New equipment introduction

Change Control

- Includes triggers for risk review – new product introduction, new equipment introduction, facility changes, formulation changes etc.

Product Quality Review

- Results from the risk management process may become part of the product quality review as appropriate. This review shall provide an indication that the risk of cross contamination is in a controlled state

Corrective and Preventive Action

- Risk reduction controls tracking and implementation

Competency of staff

- Staff involved in managing the risk of cross contamination should have training on how to avoid cross contamination and quality risk management

Routes of Cross-Contamination

MIX-UP

Cross contamination is caused by human error (incorrect API, use of contaminated equipment)

- Facility design
- Equipment design
- Proper line clearance procedure
- Physical segregation

e.g.: Mix up of API, Inadequate identification or no label of any material and product

RETENTION

Material which is left from the previous process due to failure or inadequate cleaning

- Dedicated equipment/ facilities
- Self contained processing modules
- Disposable technologies
- Cleaning considerations

e.g.: Carryover on product contact parts, failure to clean to limits

Contamination due to sticky nature of the previous product

MECHANICAL TRANSFER

Transfer by mechanical means of contaminants from non-product contacts part, transfer system etc.

- Incorporation of process related design elements
- RABS/Isolator
- Personnel and material flows
- Closed processes/automation

e.g.: Contamination due to previous product powder deposited on loading/unloading system for lyo.

AIRBORNE TRANSFER

Sedimentation of Aerosols from one product into another. The risk of one product in airborne suspension contaminating another product

- Dedicated/self contained facilities
- Closed processing systems
- HVAC design – pressure gradient
- Gowning/decontamination of people and materials passing in and out

e.g.: OEL band 6 product manufactured in general product equipment

Containment

Limitation of the spreading of the substance or an agent is containment

01 Containment is always relative i.e. it doesn't always refer to a “closed” system. In practice, normally the question is not **“Is containment necessary?”,** but **“How much containment is necessary?”**

02 The needed level of containment depends on the degree of biological activity of the contaminating substance

03 Zero risk is considered scientifically unachievable and not necessary

04 Primary containment refers to those measures that reduce the spread of a substance from the actual production equipment

e.g.:

- Housing for tablet presses and the attached devices such as metal detectors, IPC samplers, de-dusting unit,
- Isolators used for weighing APIs

The focus should always be on the optimization of the primary containment

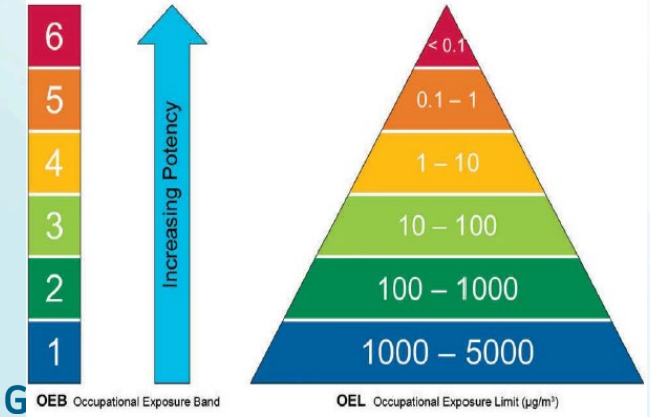
05 Secondary containment refers to the measures that reduce the spread of the substance that escaped beyond the primary containment

e.g.:

- Cleanrooms,
- Airlock systems and pressure gradients between the corridors and the production room

Thresholds and hazard categories: ADE/PDE and OEL

- OELs are defined as eight-hour time weighted averages (8-Hrs. TWA)
- Generally if OEL is more than 100 µg/m^3 then it is permissible for a person to be exposed to concentrations higher than 100 µg/m^3 for a limited period of time
- For substances such as irritants Short term Exposure Limits (STEL) or Short-Term Time Weighted Averages (STTWA) shall be set
- Modern facilities shall be planned such that they can operate without the need for organization measures and personnel can be employed in an entirely flexible manner
- To ensure that it is not possible to exceed the OEL during the normal operations most companies define Design Exposure Limits (DEL) or Containment Reference Targets (CRT)
- Employee must be protected primarily by technical measures and that PPE may only be used as a primary protection against overexposure if technical measures do not exist



Effect
Very high pharmacologic and toxic effect
High pharmacologic and toxic effect
Medium pharmacologic and toxic effect
low pharmacologic and toxic effect
Very low pharmacologic and toxic effect

Containment Strategy

Material Info
- Toxicity
- Physical Form
- Other HSE Factors
- Process
- Dosage Form

External Factors
- GMP Regulations
- HSE Regulations
- Available Space
- Location
- Ergometric

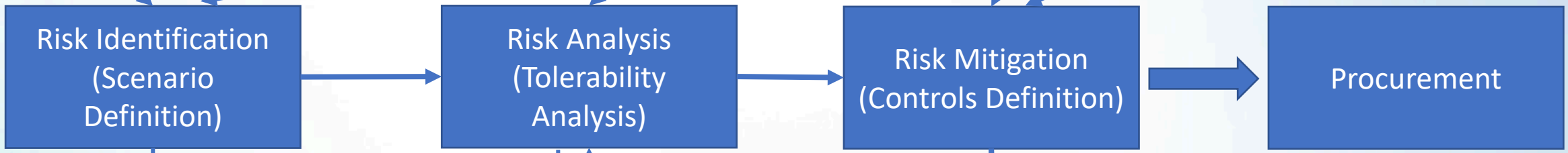
Process Info
- How much?
- How?
- Where?
- When?
- By Who?
- With What?
- Cleaning etc.

Tolerability Criteria
- OELs
- STELs
- MACO
- Microbial Limits

Control Options
- Elimination
- Substitution
- Process Flexibility
- Engineering Control

Control Knowledge
- Process Constraints
- Physical Constraints
- Human Factors Impact

Inputs



Outputs

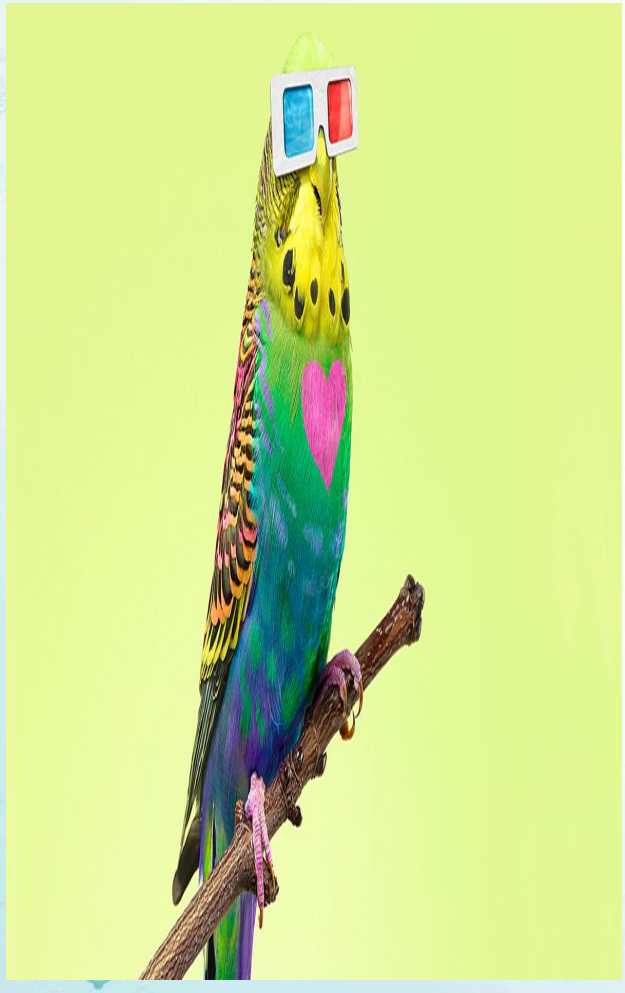
Containment Strategy Document

Defined Containment Approach

HSE: Health, Safety and Environment
STEL: Short-Term Exposure Limit

Other Industries: Statistics related to Human Factors

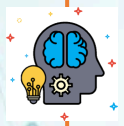
To change the way we think, change the way we see



- Root cause of the vast majority of deviations are quality system weaknesses
- The third highest cause of death in the United States is medical error
- The global coast associated with medication errors has been established at 42 billion USD annually
- The worst period for human errors is 2 am to 5 am
- Human error accounts for 90% of road accidents
- The rate of error and mistakes for most procedure-based tasks is 1/100
- The average worker is interrupted every 11 minutes and then spends almost a third of his/her day recovering from these distractions
- Most of the pieces of manufacturing equipment and utilities are designed for right-handers
- Best operator make biggest mistake
- 17 hours of work without a break is operationally the same as being legally drunk
- Latent errors are underestimated

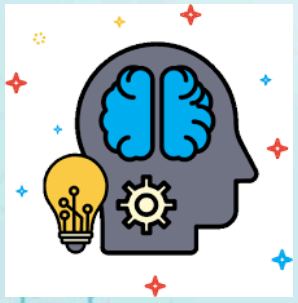
Design of Cleaning Checklist

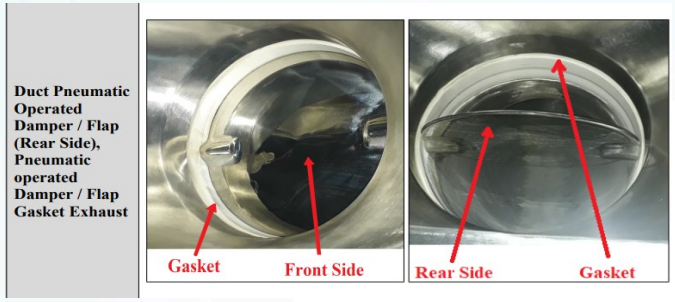
Tweo

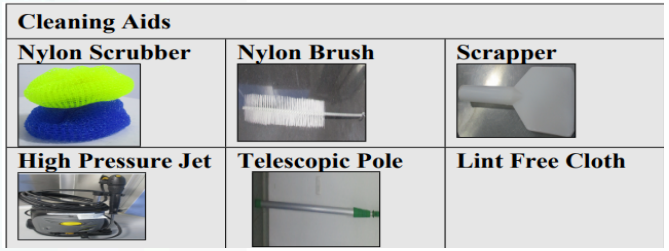


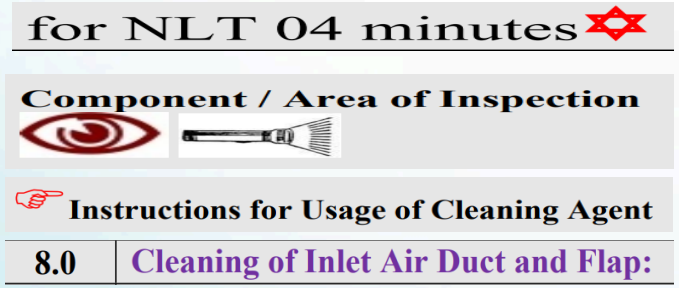
Two

02









- Spelling mistakes – Write numeric “01” instead of word “One”
- Serif font is for readability and sans serif for legibility hence header shall be sans serif and paragraphs shall be serif font
- Attention actuators/visual aids :
  - A picture is worth a thousand words
  - 83% information of the surrounding is acquired by site.
  - Graphical procedure with colour images, symbol to be used
- Poor instructions:
  - Verify all parameters
  - Mix for at least one hour
  - Take approx. 100 mL solution and mix
- NLT – NMT: In cleaning validation CPPs followed shall be “NMT” and for routine cleaning “NLT”
- Picture to the left, text on the right
  - The left hand sight field is analysed by right hemispehere of our brain and the right sight field by left brain
  - Right side of our brain is responsible for the perception of visual information, while the left hand side is primarily responsible for speech and abstract thinking
- Write actions in the order in which they need to be carried out
  - Add detergent ABC. Mix for 10 minutes
  - After adding detergent ABC, start mixing for 10 minutes

Human Factors in Cleaning : Automation Digital Control

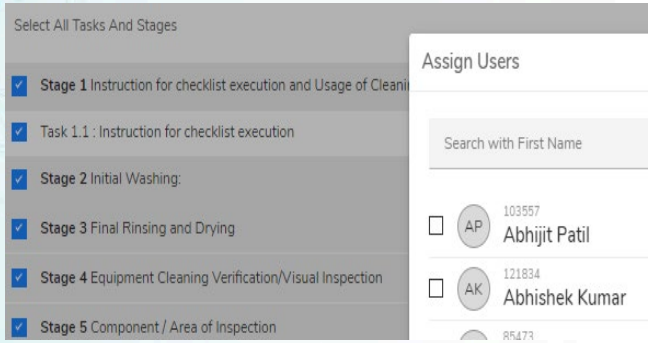
01

- **Operation excellence and compliance:** System shall allow the daily work allocation based on qualification for manual cleaning of the specific equipment
- **Attention actuator:** To **enable sequential** or parallel cleaning steps according to the equipment cleaning flow

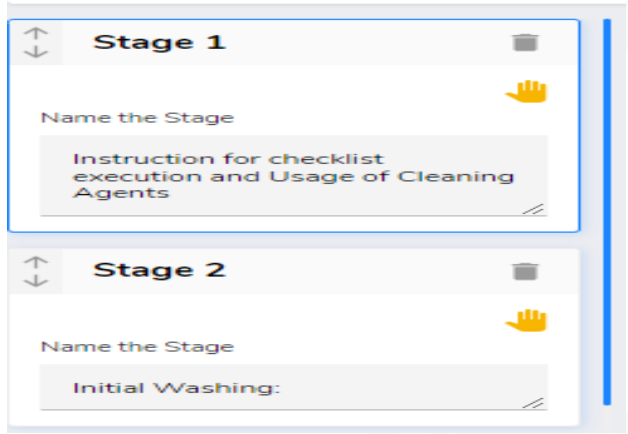
02

- **CPP:** The system **permits CPP parameters** within the **specified cleaning range**. E.g. if the Pressure Parameter **must be between 45-50 pa** then any deviation, only acceptance is obtained from supervisor/QA.
- Same control can established for other CPPs i.e. **temperature, cleaning time, flow rate** etc.

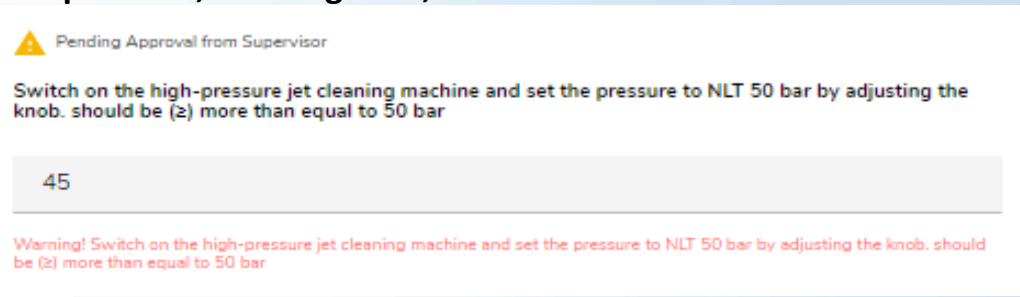
Task



Attention actuator



CPP



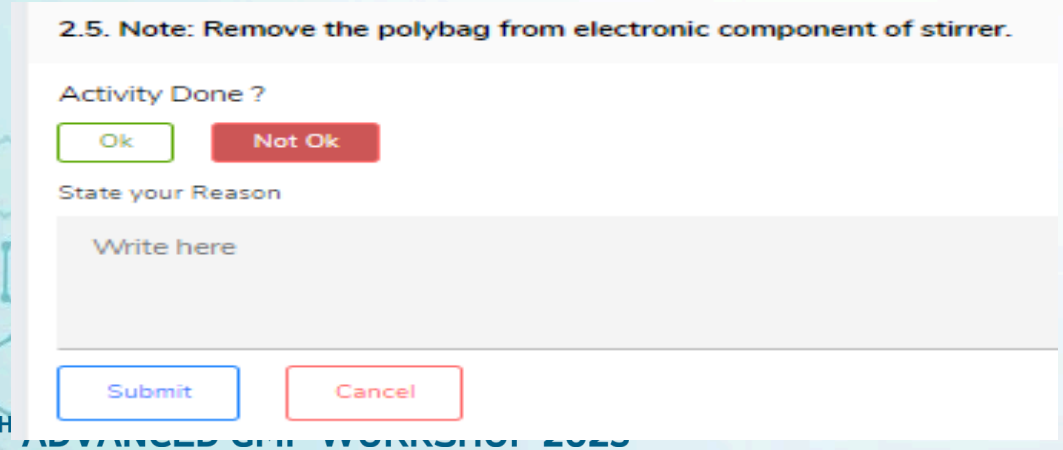
03

- **Interlock:** The system also controls the **interlinking of cleaning rules.**
- **E.g.** Campaign length exceeded, DEHT and CEHT exceeded

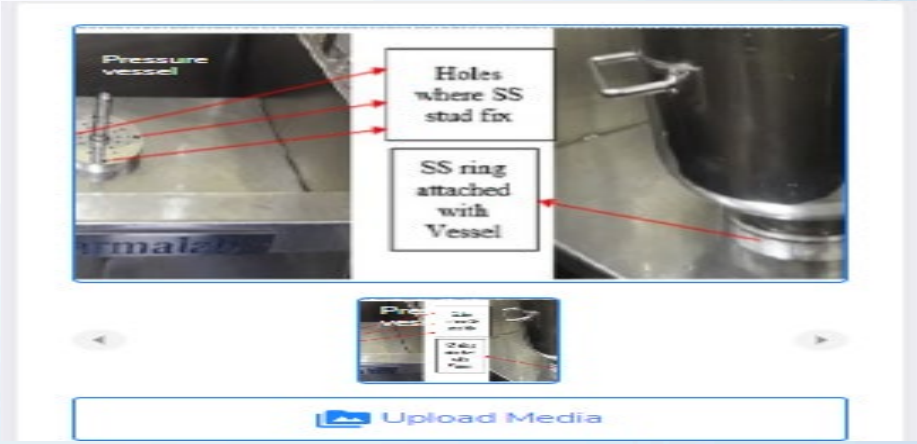
04

- **Paperless:** Ready availability of **cleaning checklist, photographs** of **hard to clean** equipment parts, assembling/disassembling steps, previous product details, **DEHT, CEHT** etc.
- **Eliminate:** Offline checklist issuance and GDP error

Interlock

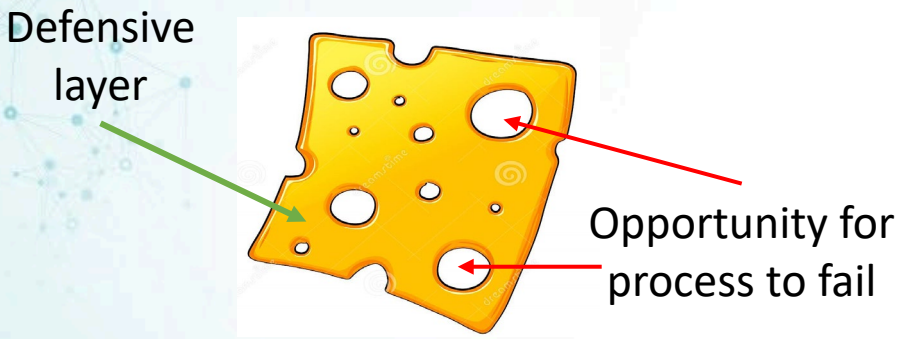


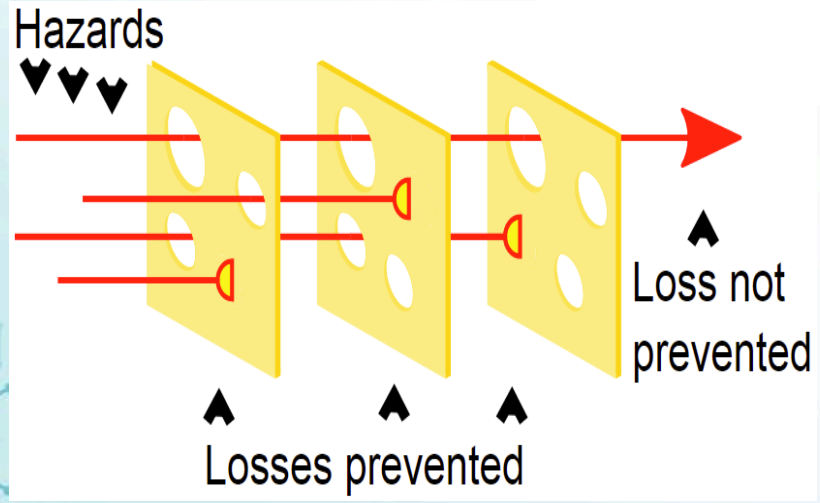
Photographs



Elimination of human errors is almost impossible without first eliminating human beings from the system

Swiss cheese model





- **NVPC monitoring:**
  - NVPC alarm in the clean room
  - Automatic machine stoppage
  - Alarm display in BMS room

- **Dual system shall be established for calculations i.e. Software based MACO calculation vs manual MACO calculation**

  E.g.

  Software calculated MACO: 30 mg

  Manual calculated MACO: 26 mg

  Root cause: Wrong SRDD entered in manual calculation

Human Competency

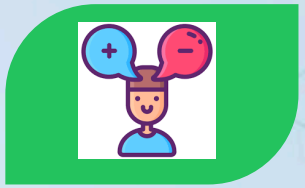

Education


Experience


Training


Skills


Behaviour


Attitude

Competency:

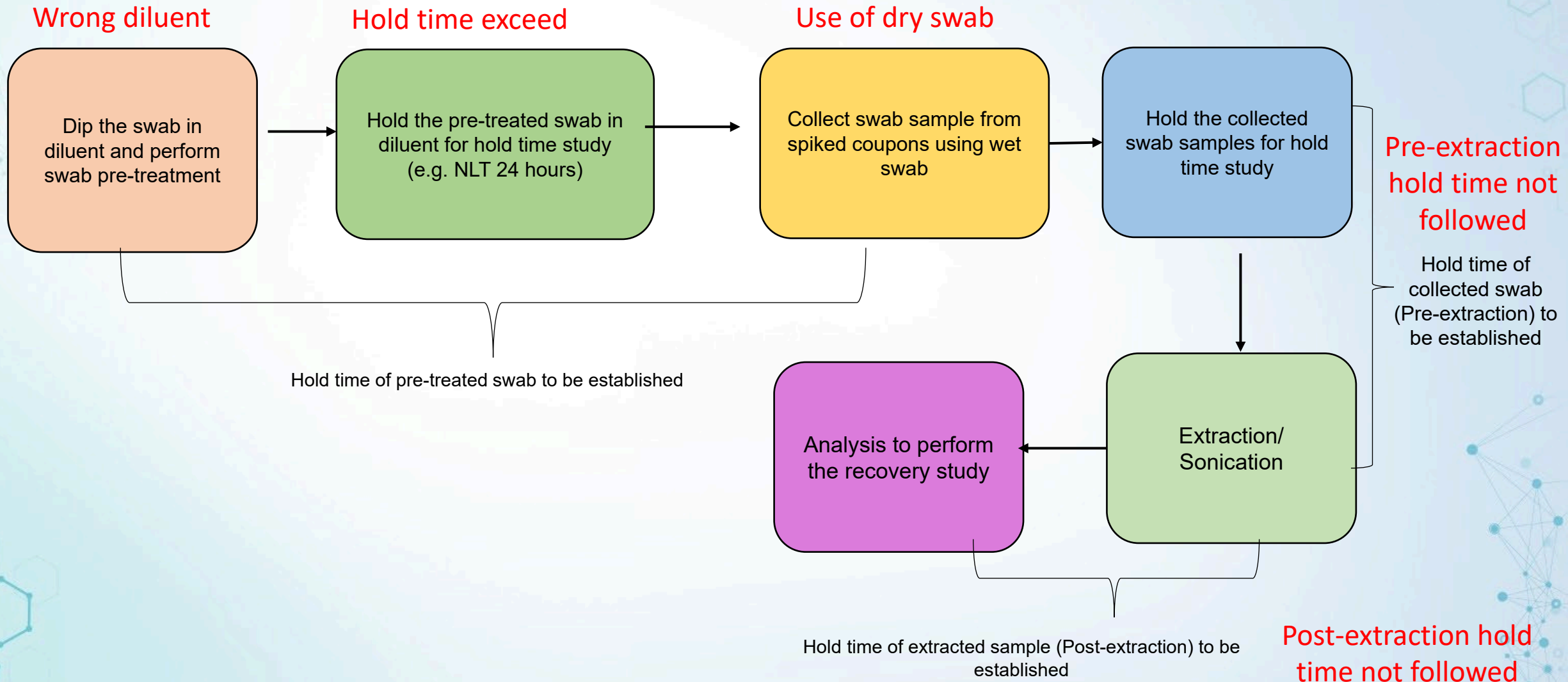
- **It is much more than training.**
- **It implies appropriate education, experience, training, skills, behaviour, attitude and physical and mental capabilities.**

EU Annex 1 2022:

- **Personnel should have adequate qualifications and experience, training and behaviour with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.**

Selection and Handling of Swab Samples

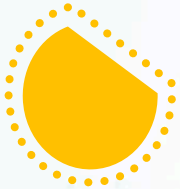
Process flow of Swab sampling and Analytical Method Validation (AMV)



Unknown Impurity in Product

Unknown impurity observed in 03 different drug product samples

Case study



Identified Unknown Impurity of Previous Product - **Preservative** (Excipient)

Root cause: Multiple hypothesis and a 6M investigation identified the root cause as **inadequate CIP parameters**, which were **unable** to effectively **remove traces** of the preservative **which was not considered during cleaning validation**

CAPA: CIP parameters **modification**, increasing Purified Water temperature from **55 ^{o}C to 80 ^{o}C** and Water for Injection quantity from **100 kg to 300 kg**.

Case study

Identified Unknown Impurity in **Previous Product (Impurity-A)** which is **generated during bulk** manufacturing

Root cause: It is known impurity of drug product which is cleaned. Multiple hypotheses and 6M analysis identified the root cause as **ineffective CIP parameters** in the existing **filling machine**, unable to completely remove traces of **the newly introduced product**

CAPA: Revised filling machine CIP.

Case study

Identified unknown impurity of previous **product API**

Root cause: After extensive trials and investigation, the unknown impurity in the previous product's API was attributed to its **inherent sticky nature**, making thorough removal from product contact surfaces **challenging**

CAPA: Efforts were made to enhance the cleaning process, including **modifying CIP parameters** and introducing specialized **cleaning agents**.

Overlooking latent errors

Contamination

Micro contamination in the drug product

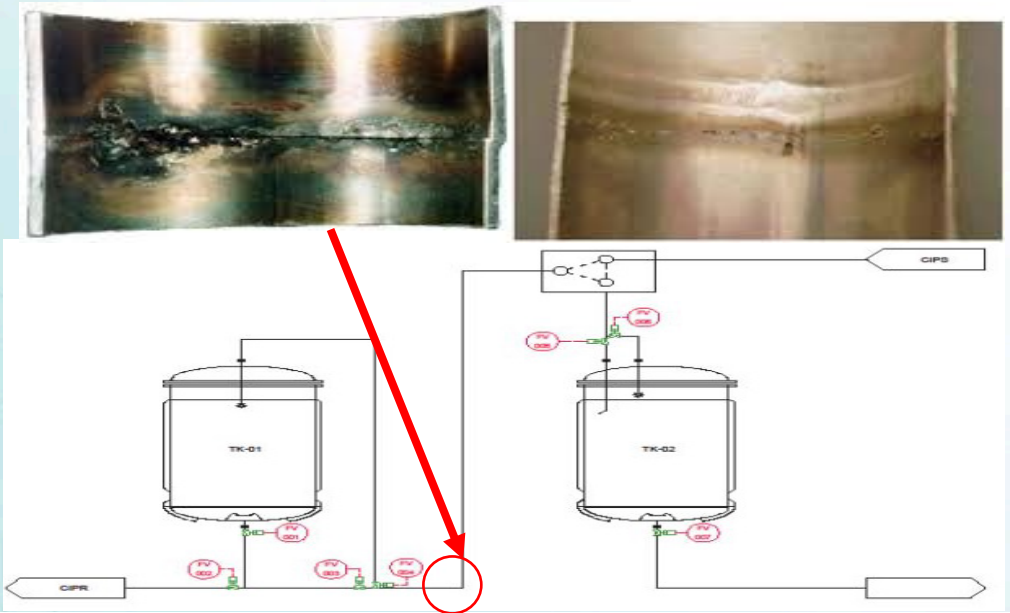
Case study

Aseptic process simulation study (Media fill) failure in “Stainless steel sterile filter holding tank with stainless steel product transfer line”

Root cause: **Inadequate orbital welding joint** of product transfer pipes

CAPA: New orbital welding done, cleaning and passivation performed.

03 consecutive **media fill** study performed



Case study

Drug product failed in **BET test**

Root cause: Excipient is natural source of contamination

CAPA: Impacted batch and **materials rejected** and vendor disqualified

Manufacturing Skid

Case Study 11: Common Pitfalls during Implementation of Cleaning Validation

- **Method development with incorrect LOQ and LOD**
  e.g.: MACO limit is 01 mg however method developed at 0.9 mg

- **01 Manufacturing skid but 02 MACO calculated**
  e.g.: MACO calculated for general products and scaleup/exhibit products

- **Lack of traceability of dedicated equipment in the production area**
  e.g.: In cleaning validation filling pumps (N1, N2) concluded dedicated however in production it is used as shared equipment

- **Actual simulation not performed during rinse recovery study**
  e.g.: Rinse recovery study performed with known concentrated samples instead of spiking on coupons of different MOC

- **Non-adherence to qualified Dirty Equipment Hold Time (DEHT) and Clean Equipment Hold Time (CEHT)**
  e.g.: DEHT validated as 24 hours however in routine batch manufacturing CIP is performed beyond the 24 hours. After completion of the batch only initial rinse performed and final CIP is performed whenever next batch planned

- **Not handling of swab samples as per analytical method validation (AMV)**
  e.g.: Swab pretreatment not performed even though it is recommended in AMV

THE CULTURE EATS STRATEGY INTO BREAKFAST

- As automation gains momentum, there will be a premium placed on people who have high ability in emotional intelligence
  - Self awareness
  - Agility
  - Team work
  - Influence

- Word supervise originated from latin word super + videre (to see)

  Thus original definition includes the need for physical contact between supervisor and supervisees.

  Supervisors must be prepared with technical and non technical competencies

- Trusting teams :

  Informal, unintimidating environment in which no one is afraid of making mistakes

- GEMBA walk to build a positive Quality Culture
  - Night shift by supervisors

Anyone can make things bigger and more complex. What requires real effort and courage is to move in the opposite direction to make things as simple as possible.

Albert Einstein

Thank you

rahul.songire@zyduslife.com