QUALITY CONNECT

Enhancing Digital and Operational Excellence in Life Science Quality

First Edition

Milan

May 14th, 2024

Powered by LifeBee — DIGITALIZING LIFE SCIENCES — A ProductLifeGroup Company

Supported by AFTI

Mirka Broccato

QP&GMP Compliance Executive Consultant

20 years of experience in Pharmaceutical sector:

- Currently in LifeBee as QP&GMP Compliance Executive Consultant
- Risk Analysis of process&product
- GMP Impact of digitalization project
- Data Integrity Project
- Mapping of processes to improve efficiency and GMP compliance
- Training GMP
- 9 years working in a pharmaceutical manufacturing company as QP and Quality Unit Director
- 10 years in a pharmaceutical manufacturing company as deputy QP and Quality Control Manager

Benedetta Ligabò

Senior Consultant

With a background in Pharmaceutical Chemistry, she has gained 6 years of experience in Pharmaceutical sector.

- Currently in LifeBee as Senior Consultant.
- Previous experience in Fresenius Kabi Italia, where she deepened
  - Risk Assessment (QC and production area),
  - Data Integrity Project (QC and production area),
  - Contamination Control Strategy Project,
  - Batch Record review,
  - Root cause analysis for deviation and OOS,
  - Change Control Management.

AGENDA

Regulatory aspects of Contamination Control Strategy

- *Regulatory*
- *Fundamental concepts*

CCS Methodology

- *Analytical approach*
- *Document*
- *Benefits*

Case Studies

Cleaning Validation process

- *Challenges*
- *Improvement Journey*
  - *Mapping*
  - *Measurement*
  - *Criticality Identification*
  - *Action Plan*
  - *Benefits*

Conclusions

Regulatory aspects of Contamination Control Strategy

- Regulatory
- Fundamental concepts

QUALITY BY DESIGN VS CONTROL STRATEGY

Quality by Design (QbD):
A systematic approach to development that begins with predefined objectives and emphasizes product
and process understanding and process control, based on sound science and quality risk management.

Control Strategy:
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

3.2.1 Process performance and product quality monitoring system
Use **quality risk management** to establish the control strategy. (...)
The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action;

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 June 2017
EMA/CHMP/ICH/167068/2004
Committee for Human Medicinal Products

ICH guideline Q8 (R2) on pharmaceutical development
Step 5

Transmission to CHMP	December 2004
Transmission to interested parties	December 2004

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

September 2015
EMA/CHMP/ICH/214732/2007
Committee for Human Medicinal Products

ICH guideline Q10 on pharmaceutical quality system
Step 5

Transmission to CHMP	May 2007
Transmission to interested parties	May 2007

ICH Member

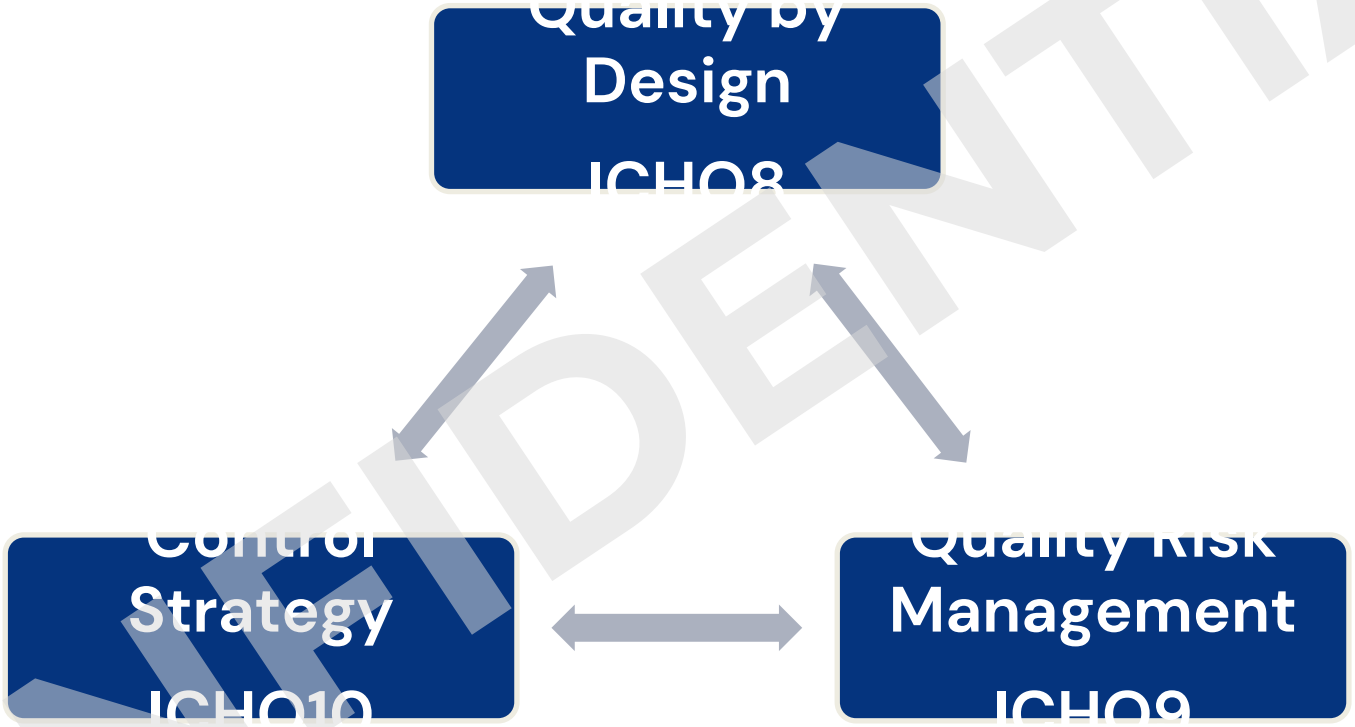
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 February 2023
EMA/CHMP/ICH/24235/2006
Committee for Medicinal Products for Human Use

2005

ICH guideline Q9 (R1) on quality risk management
Step 5

FUNDAMENTAL CONCEPTS



To adequately design products and processes by analyzing all patient risks and defining a control strategy that reduces these risks

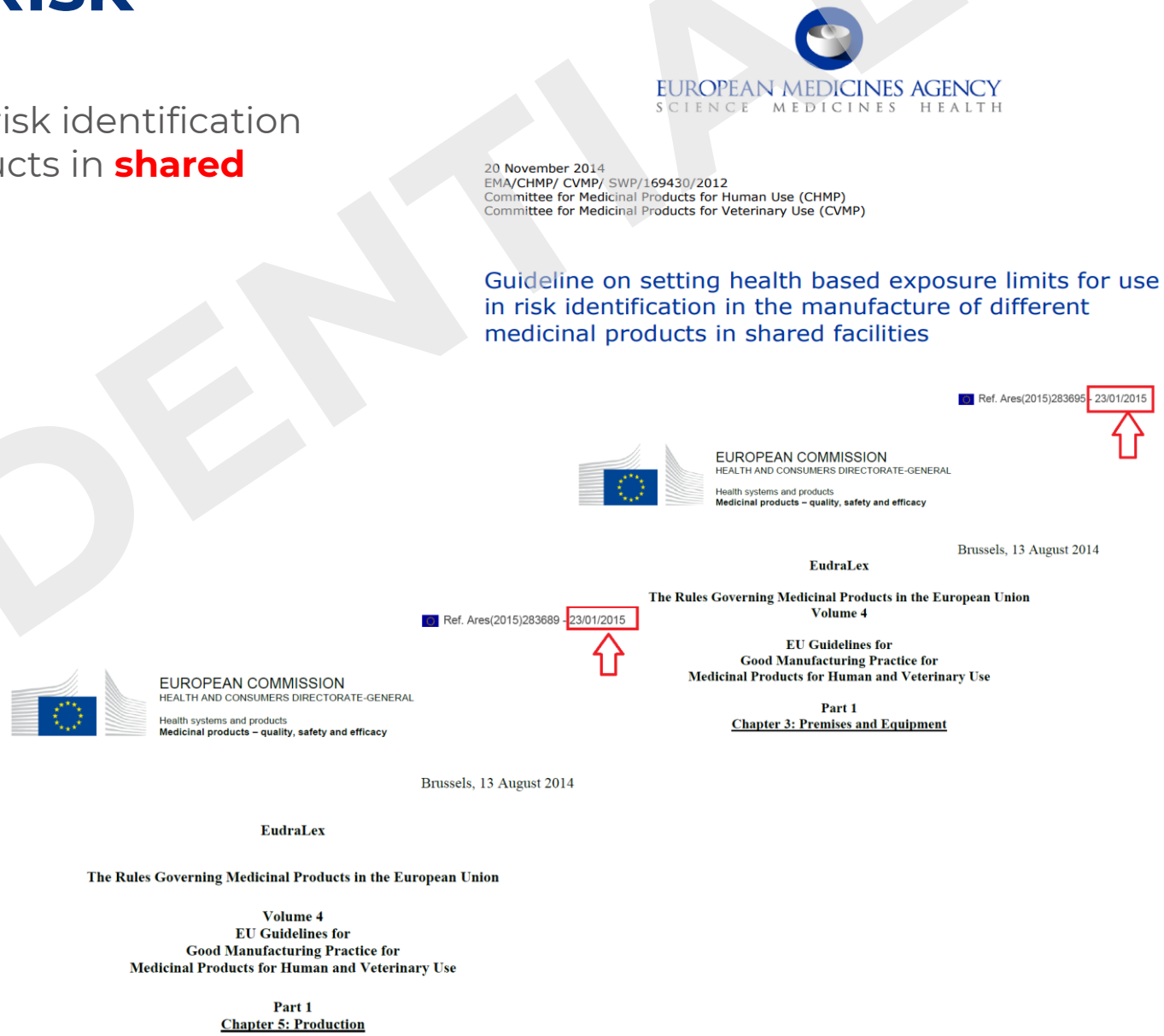
Contamination Control Risk

QUALITY

Setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in **shared facilities**

3.6 Cross-contamination should be prevented for all products by **appropriate design and operation of manufacturing facilities**. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks**.**

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of **technical and organisational measures** required to control risks for cross-contamination.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/ CVMP/ SWP/169430/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

Ref. Ares(2015)283695 - 23/01/2015

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 3: Premises and Equipment

Ref. Ares(2015)283689 - 23/01/2015

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 13 August 2014

EudraLex

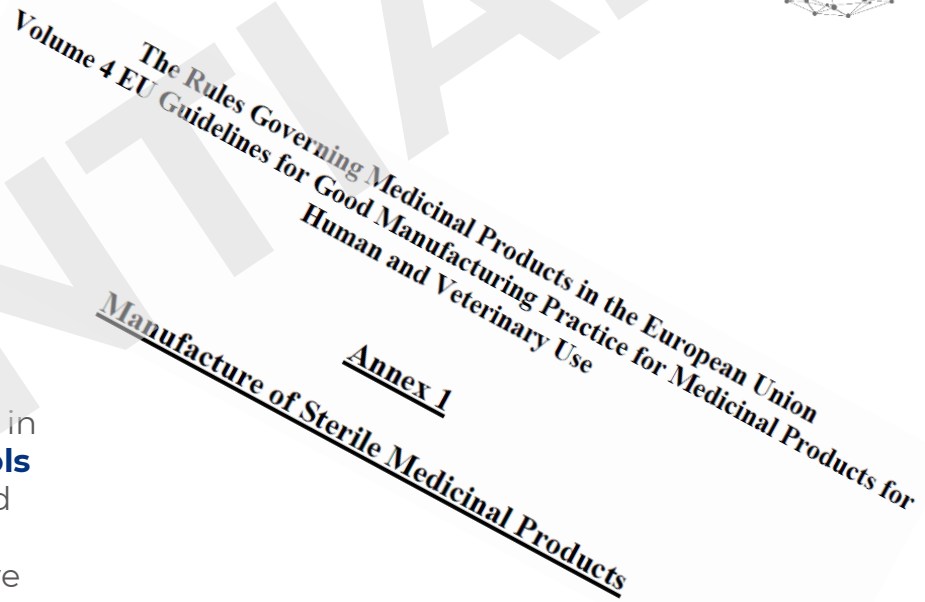
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Part 1
Chapter 5: Production

Contamination Control Risk

Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.



2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all **critical control points** and assess the effectiveness of **all the controls** (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. (…)
The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review.

However, some of the principles and guidance, such as **contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning**, may be used to support the manufacture of **other products** that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

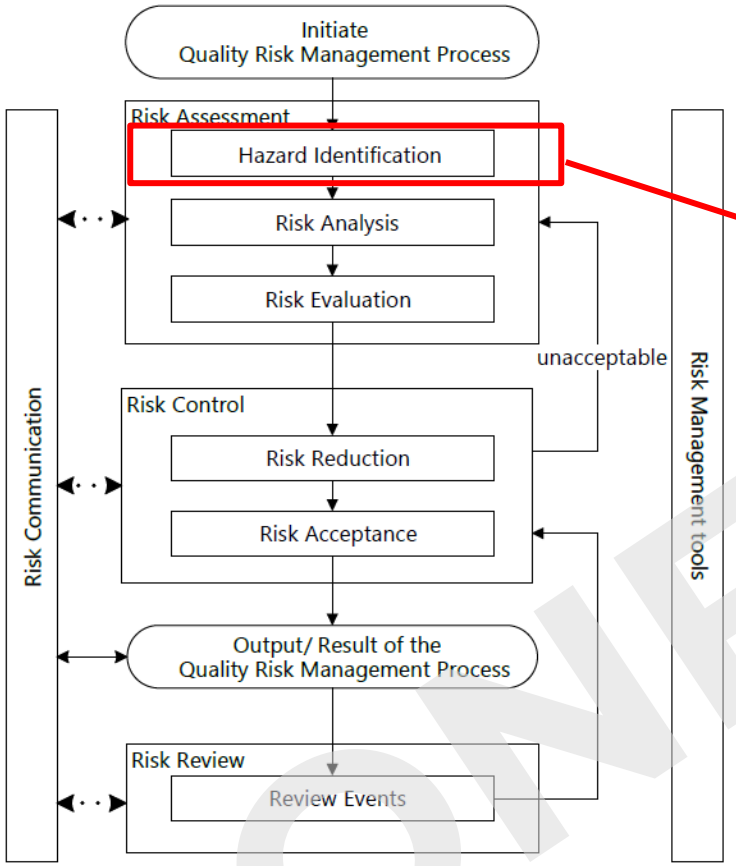
CCS Methodology

- Analytical approach
- Document
- Benefits

Analytical Approach

- Identifying the departments involved
- Hazard Identification
- Risk Analysis
- Risk Evaluation
- Results
- Key elements, methods and organizational strategy
- Conclusion

Quality Risk management process



MORE OBJECTIVITY

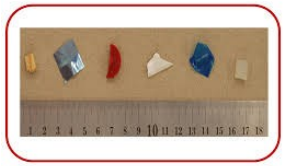
144 ***Hazard identification*** is a systematic use of information to identify hazards referring to the risk
145 question or problem description. Information can include historical data, theoretical analysis,
146 informed opinions, and the concerns of stakeholders. Hazard identification addresses the "What
147 might go wrong?" question, including identifying the possible consequences. This provides the
148 basis for further steps in the quality risk management process.

new version ICHQ9

Hazard identification – Type of contamination

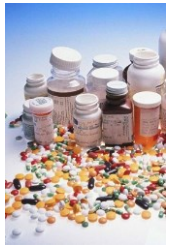
- **Chemical contamination**: undesired introduction of impurities of a chemical nature into or onto a raw material, intermediate, API or bulk product during production, sampling, packaging, storage

- **Physical contamination:** undesired introduction of foreign matter into or onto a raw material, intermediate, API or bulk product during production, sampling, packaging, storage



- **Microbiological contamination**: undesired introduction of impurities of a microbiological nature into or onto a raw material, intermediate, API or bulk product during production, sampling, packaging, storage

- **Mix-up:** contamination of one product with another via inadequate plan and process design or human error



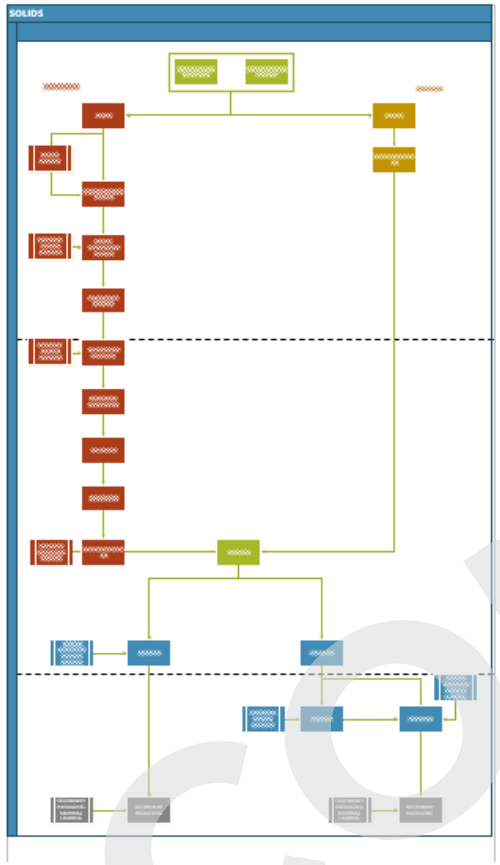
Hazard identification – Routes of contamination

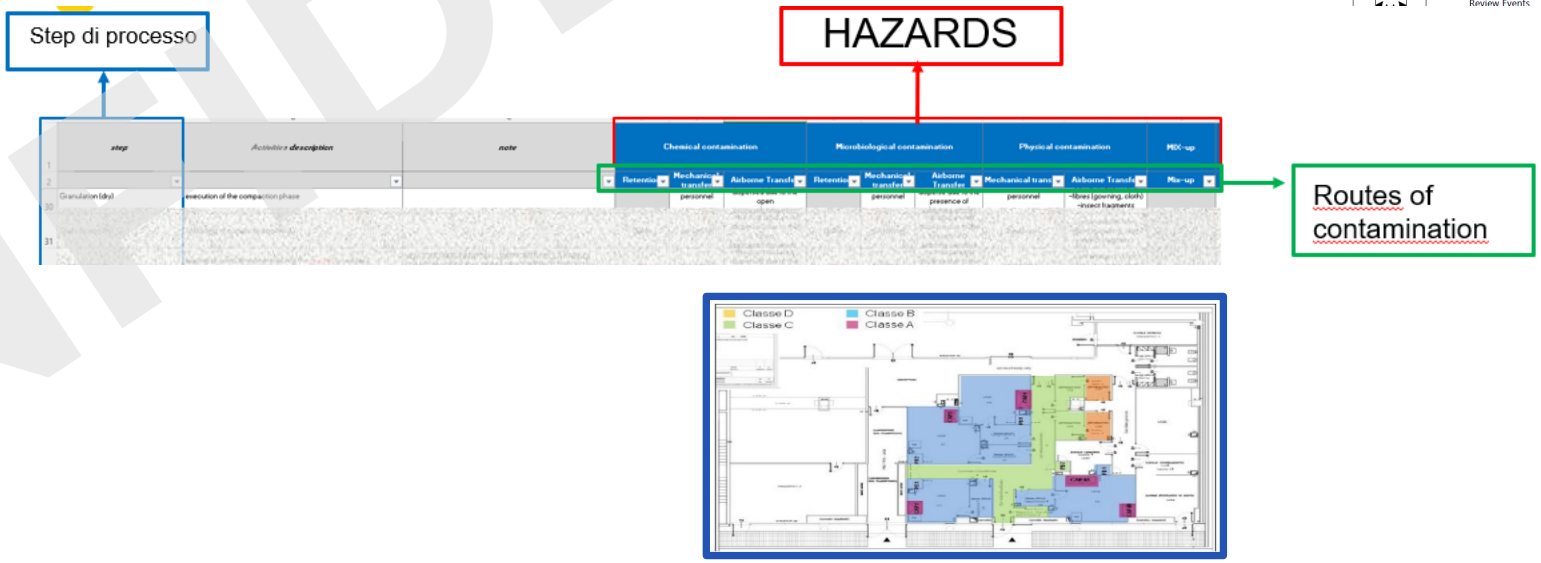
- **Retention:** the microbiological contamination on product contact surface
- **Mechanical Transfer:** transfer of microbiological contamination to the product from contaminated indirect contact surface (gowning, material, equipment)
- **Airborne Transfer:** sedimentation of aerosols (stable suspension of fine solid or liquid particle in air) from one product/area into another
- **Material:** contamination due to the inherent characteristics of the material constituting the product

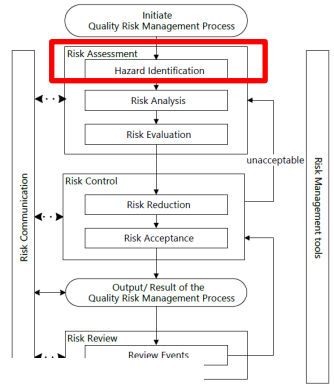
(rif. Linea guida ISPE)

Quality Risk management - Hazard identification

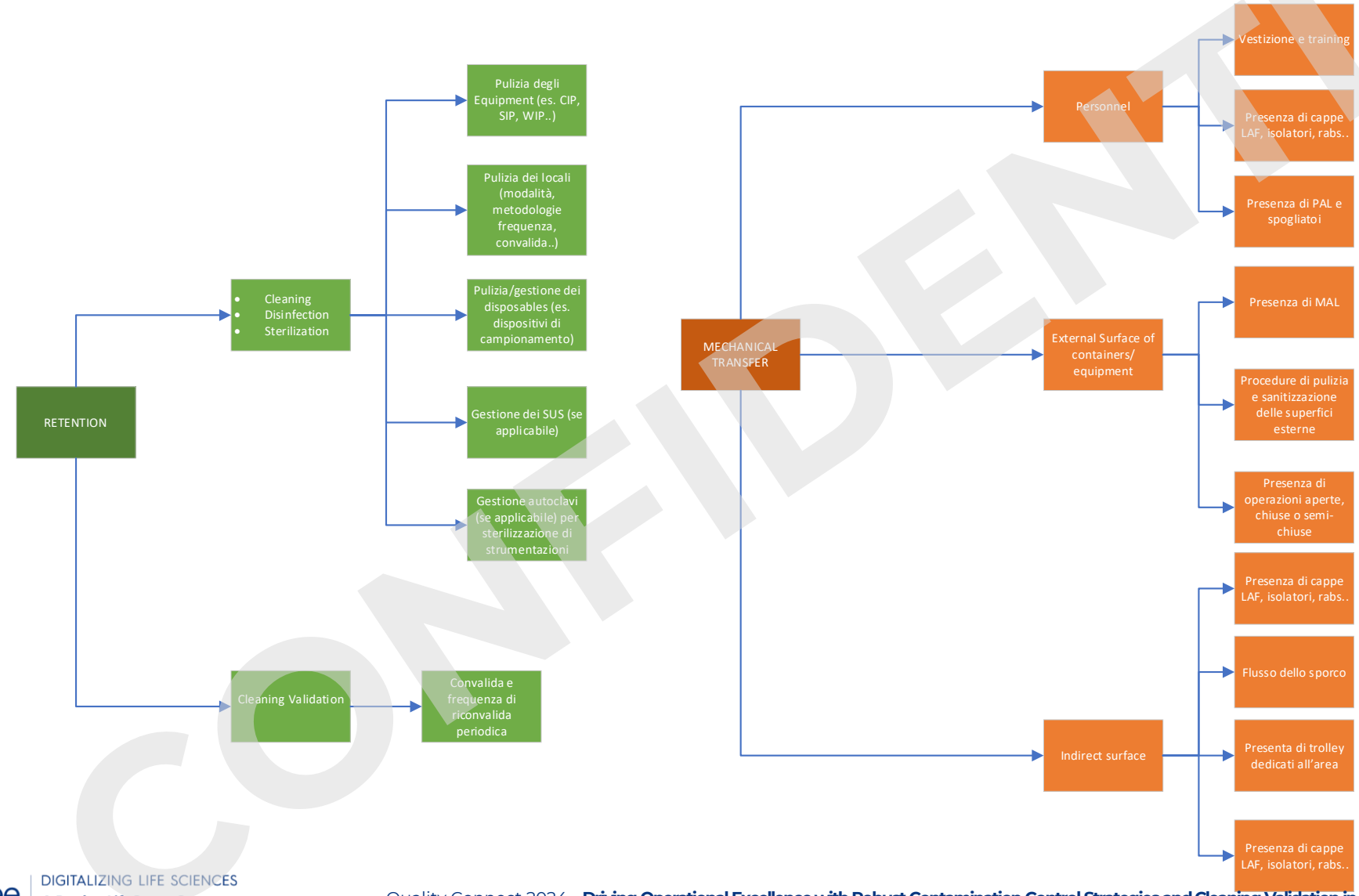
Process mapping

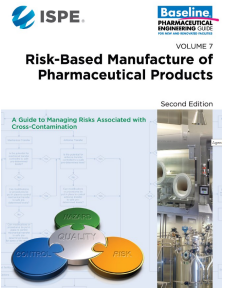




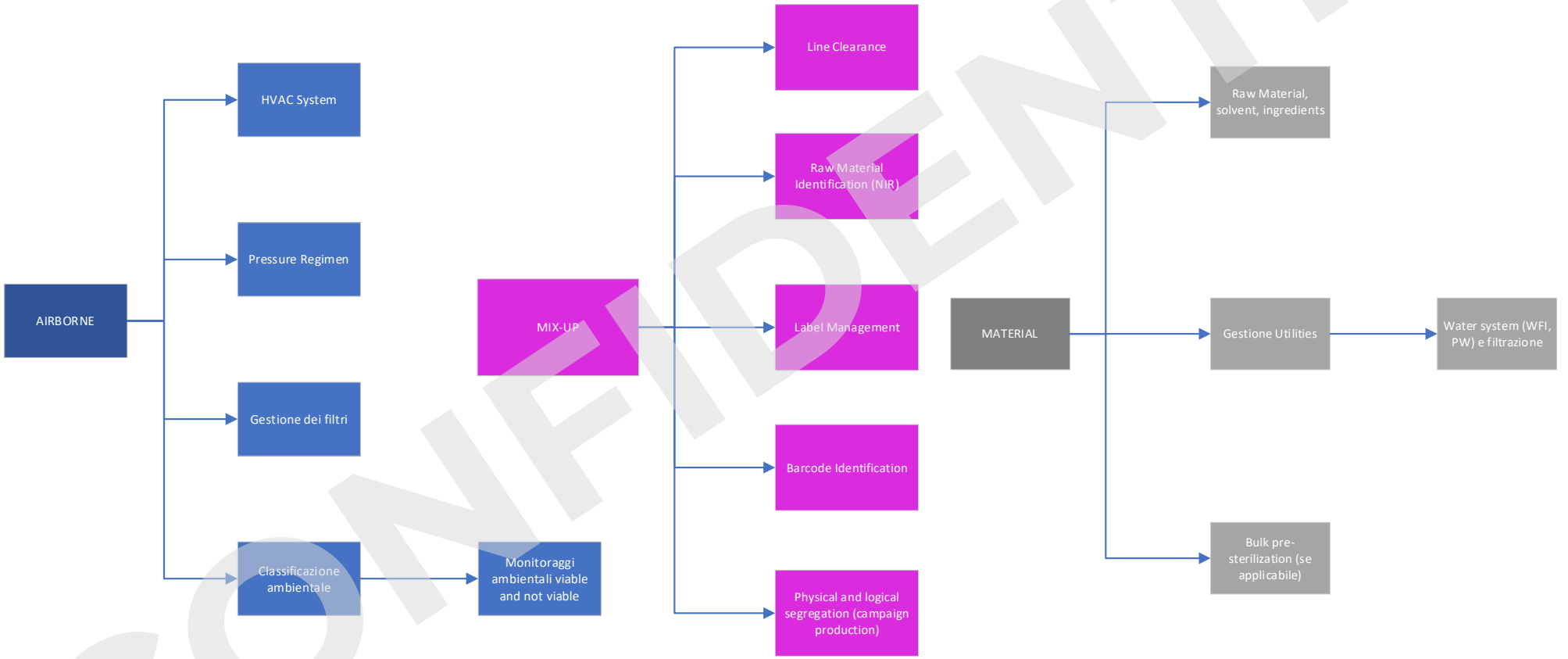


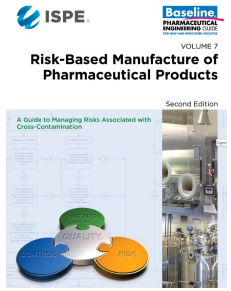
Routes of contamination – elements to be considered



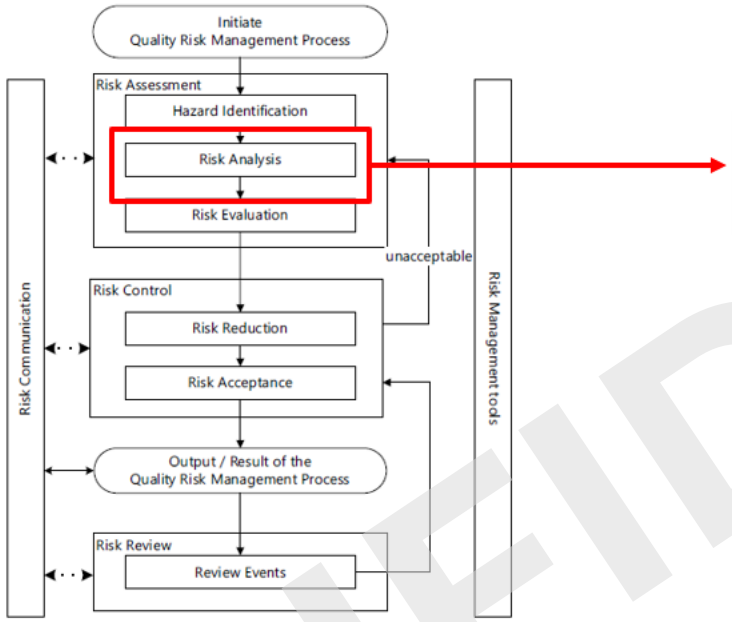


Routes of contamination – elements to be considered





Quality Risk management – Risk Analysis



Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

SEVERITY, OCCURRENCE, DETECTABILITY DEFINITION

For define risk ranking, the FMECA technique is applied, and a quantitative factor is calculated (RPN) based on definition of Severity, Occurrence and Detectability Scale according to the fallowing paragraphs.

RPN = Severity (S) x Occurrence (O) x Detectability (D)

Risk Analysis – Detectability definition

For define risk ranking, the FMECA technique is applied, and a quantitative factor is calculated (RPN) based on definition of Severity, Occurrence and Detectability Scale according to the fallowing paragraphs.

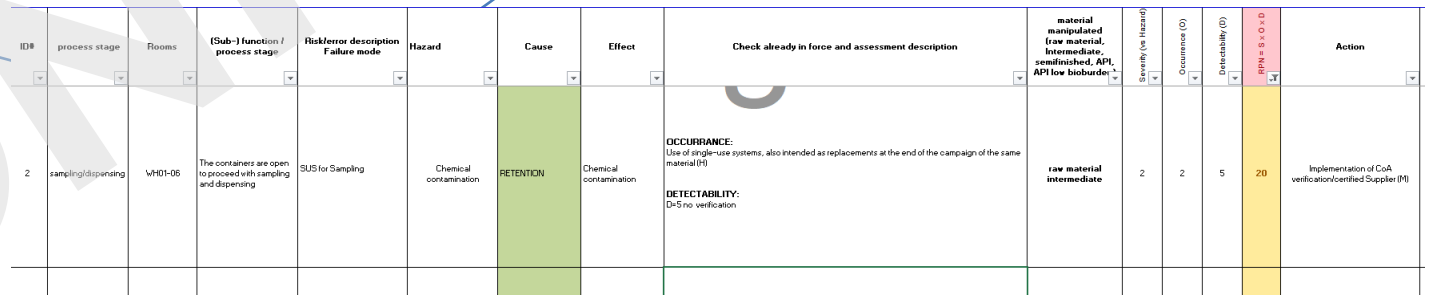
RPN = Severity (S) x Occurrence (O) x Detectability (D)

Chemical contamination
Micro contamination
Physical contamination
Mix-up

Routes contamination:
Mechanical transfer
Airborse transfer
Retention
Mix-up

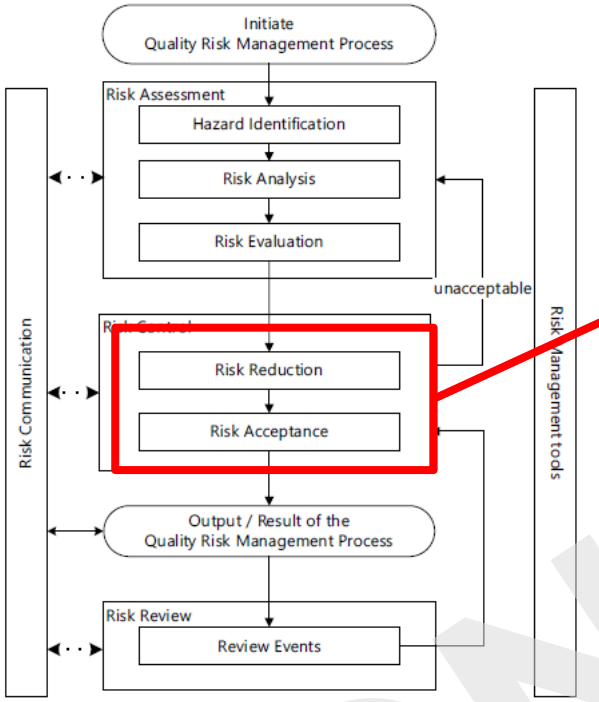
Quality Attributes (QA/CQA)

Failure mode



ID#	process stage	Rooms	(Sub-) function / process stage	Risk/error description Failure mode	Hazard	Cause	Effect	Check already in force and assessment description	material manipulated (raw material, intermediate, semifinished, API, API low bioburden	Severity (vs Hazard)	Occurrence (O)	Detectability (D)	RPN = S x O x D	Action
2	sampling/dispensing	WH01-06	The containers are open to proceed with sampling and dispensing	SUS for Sampling	Chemical contamination	RETENTION	Chemical contamination	OCCURRANCE: Use of single-use systems, also intended as replacements at the end of the campaign of the same material (H) DETECTABILITY: D=5 no verification	raw material intermediate	2	2	5	20	Implementation of CoA verification/certified Supplier (M)

Quality Risk management – Risk control

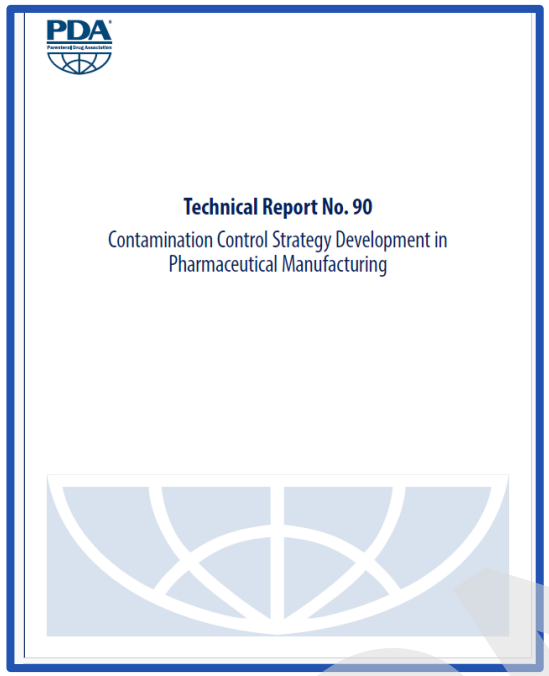


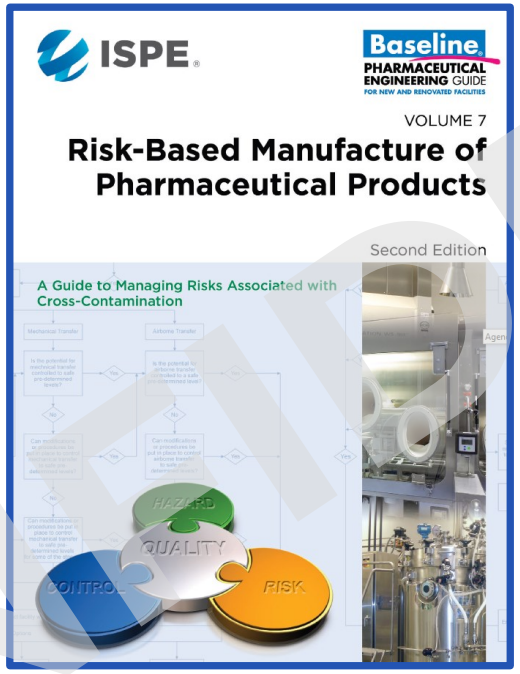
Risk control includes decision-making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

CAPA Plan definition

- **Tecnical Measures**
- **Organizational Measures**

Contamination Control Strategy Document





Contamination Control Strategy Document

Benefits of an analytical approach

- Evaluate objectively the effectiveness of the mitigation actions already in place in the facilities.
- Implement a tool capable of supporting the needs of production sites characterized by frequent integration of new products.
- Have a tool to support investigation activities for deviations, out-of-specifications (OOS), and out-of-trend (OOT).
- Have a tool capable of identifying impacts following changes.

Case Studies

Case study 1: new product information

Predictive approach to assessing the impact on facilities of introducing a new product or new pharmaceutical form

- Evaluation of the adequacy of current departments for the production of a new product -> change control management
- Verification of the impact on Severity for all 4 contamination routes

- Inclusion of the new Severity in the Risk Assessment (RA) and recalculation of the Risk Priority Number (RPN)
- Identification of any areas for improvement by introducing measures already used in similar situations in the same facility.

Case study 2: root cause analysis

Root cause analysis in case of complaints, deviation, out of specification or out of trend

- Identification of the defect involved -> e.g. physical contamination
- Select the process steps that may have an impact on physical contamination.
- Identify the elements that can lead to physical contamination in that specific process step.
- Verification of the compliance with all prescribed measures for that process step

Case study 3: change of department layout

Predictive approach of a layout change involving manufacturing department

- Analysis of the impact of a layout change in manufacturing department on the risk of contamination
  -> Change control management
- Identification of the rooms involved
- Verification of the impact of the change on contamination routes (equipment, material, personnel…).
- Verification of the impact of the change on the measures currently in place in the affected steps of the change.

Recalculation of the RPN to assess if the modification has introduced new risks to be controlled through specific mitigation actions

Main criticity resulting from CCS

- Risks associated with the **aging** of structures/facilities (material and personnel flow).
- Lack of **detectability** tools (field/equipment data collection, continuous monitoring of environmental conditions…).
- High complexity of **cleaning validation** processes.

Cleaning Validation process

- Challenges
- Improvement journey
  - Mapping
  - Measure
  - Criticality Identification
  - Action Plan
  - Benefits

Cleaning Validation Process - Challenges

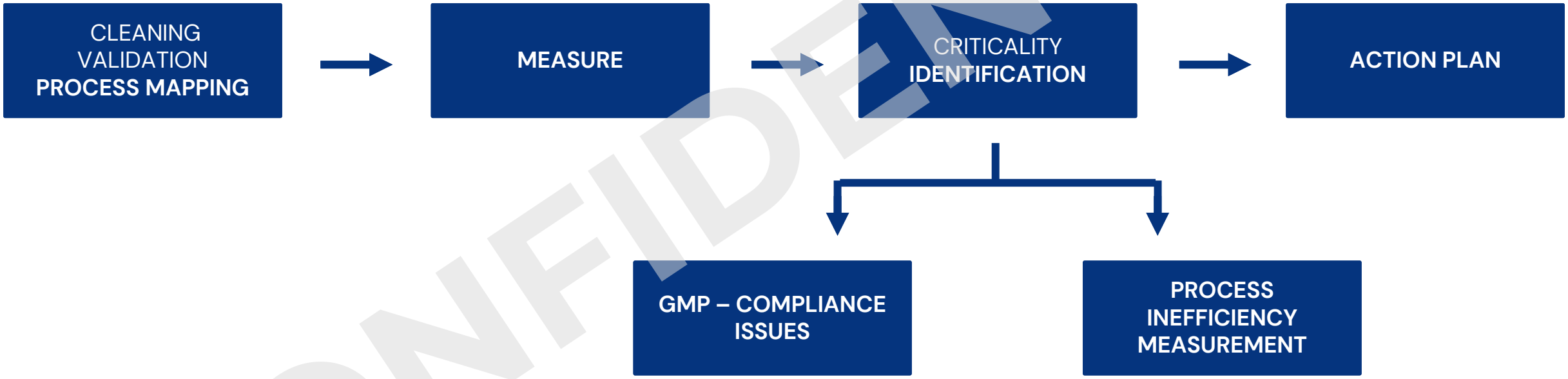
Which are the main challenges to built a proper Cleaning Validation Process?

- **Outdated procedures and antiquated protocols** hinder the timely identification of contamination problems.
- **Complex methodologies** lead to confusion and human errors, compromising the CCS effectiveness.
- **Variable approach** that may lead to inefficiencies in QC analysis and increased time dedicated to cleaning tasks
- Lots of Equipment data (different geometry, surface, materials etc..) and different Products data (different batch size, PDE etc..) that increasingly complicate the development of a **worst-case approach**
- **Anticipating unfavorable combinations** between outgoing and incoming products in equipment

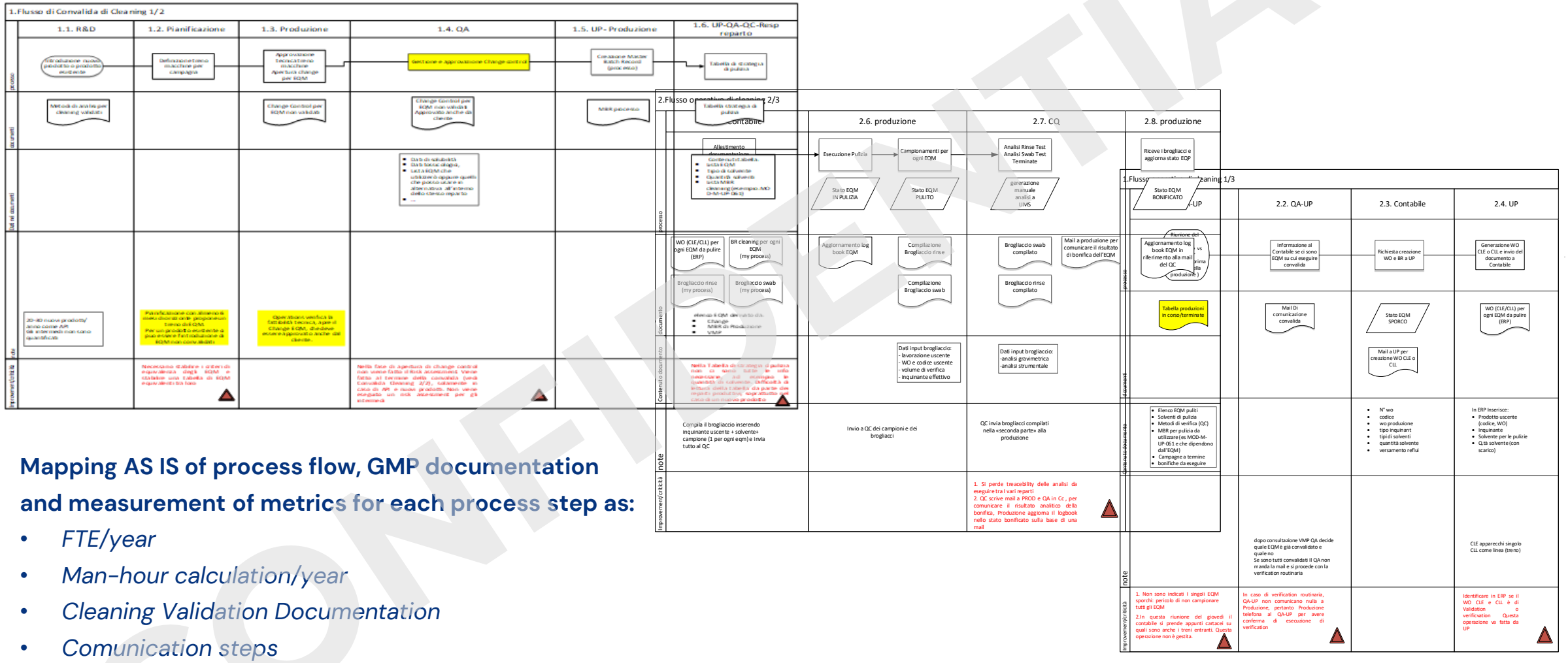
Consequences:
Bad Cleaning Process Verification:
- *Choose the worst case approach*
- *Choose the frequency*
- *Choose the right product*

Cleaning Validation Process – Improvement Journey

How to deal with Cleaning Validation Process to gain a robust and efficient flow of Cleaning Validation?



Cleaning Validation Process – Process Mapping & Measure

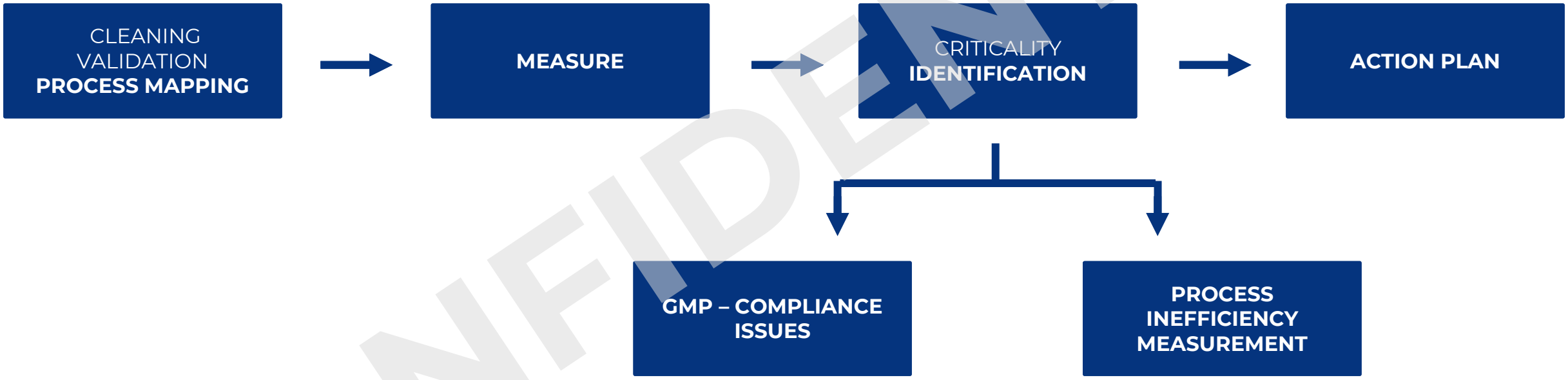


Mapping AS IS of process flow, GMP documentation and measurement of metrics for each process step as:

- *FTE/year*
- *Man-hour calculation/year*
- *Cleaning Validation Documentation*
- *Comunication steps*

Cleaning Validation Process – Improvement Journey

How to deal with Cleaning Validation Process to gain a robust and efficient flow of Cleaning Validation?



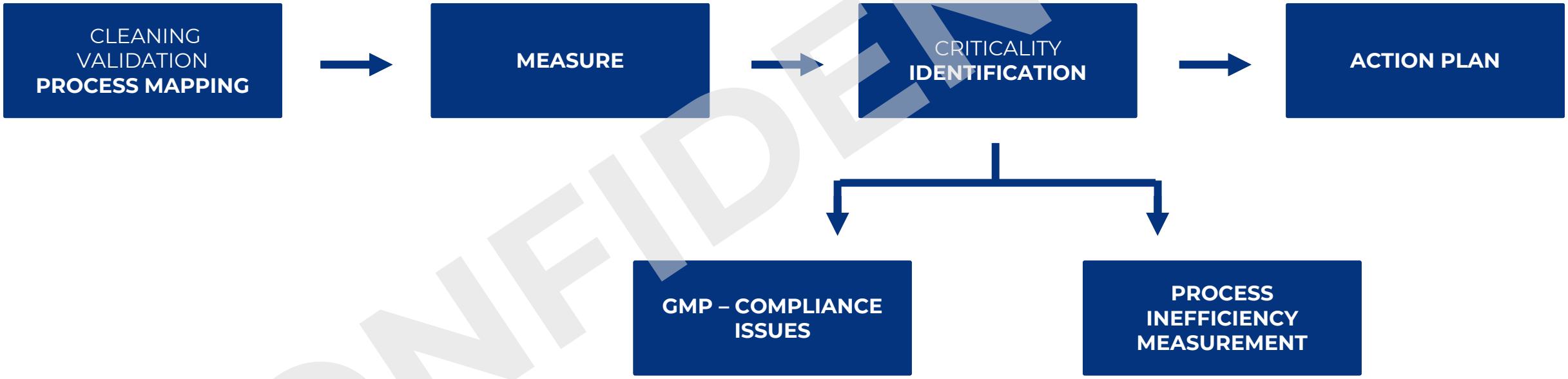
Cleaning Validation Process – Criticality Identification (from a Case study)

Main GMP and Operational Excellence Criticality funded

FLOW STEPS	GMP IMPACT	OPERATIONAL EXCELLENCE IMPACT
Weekly Production Planning Meeting		x
Drafting and emission of Cleaning Validation Protocol	x	
Manual completion of cleaning documentation for each department	x	x
Documentation collection and delivery to QA for batch record review	x	x
Calculation of acceptance limits for each equipment	x	x
Preparation and distribution of documentation for cleaning validation by the QA department	x	x
The time elapsed between sample receipt and QC approval		x

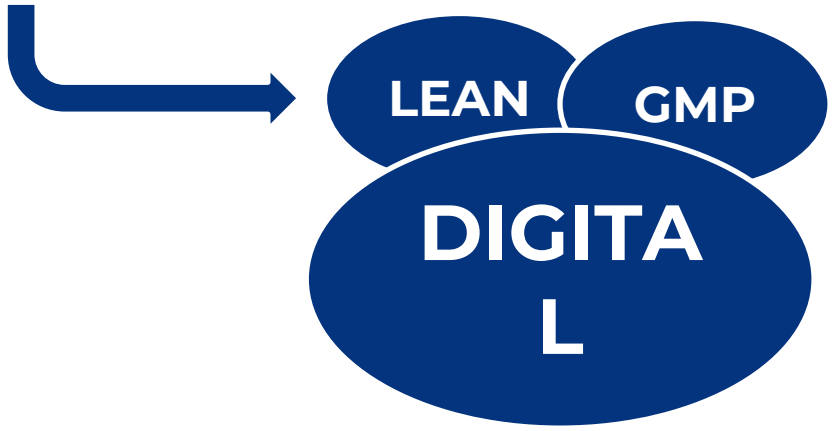
Cleaning Validation Process – Improvement Journey

How to deal with Cleaning Validation Process to gain a robust and efficient flow of Cleaning Validation?



Cleaning Validation Process – Action Plan

Action	Priority	Status
Harmonization and standardization of validation protocols	MEDIUM	Open
Flow review for re-loop elimination	MEDIUM	Open
standardization of fillable forms per department	MEDIUM	Open
Production planning tool	LOW	Open
Reviewing SOPs for implementing the worst-case approach	HIGH	On-going
Reviewing and defining specification limits	HIGH	On-going
Assigning and cataloging missing data for PDE , toxicity, and solubility	HIGH	On-going
Defining criteria for grouping equipment and products	MEDIUM	Open



Cleaning Validation Process – Improvement Journey Benefits

Precision and Reliability: more **accurate, robust, and objective** assessment of cleaning validation process efficacy, minimizing the risk of human errors and providing more reliable results. Sharing and centralization of available information on cleaning processes for both historical analysis and daily management of cleaning activities. Structured organization of historical data and cleaning processes.

Cost and Time Reduction: processes optimization of cleaning validation process reduce operational costs and downtime associated with cleaning validation, improving overall process efficiency and **enabling agile scheduling of activities**.

Regulatory Compliance: maintain high standards of regulatory compliance by ensuring **traceability, GMP compliant and comprehensive documentation** of cleaning validation process.

Continuous Improvement: Continuous data analysis quickly **identifies any cleaning issues and enables timely corrective measures** to constantly improve process effectiveness.

Conclusions

The future challenge: analysis of collected data

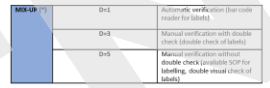
Annex 1

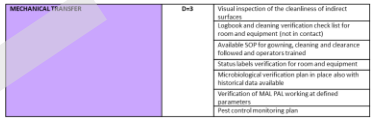
9.14 A total particle monitoring program should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.

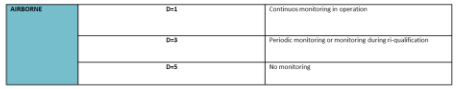
9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 µm)

9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing

Contamination control Strategy







Availability of large quantities of data

CPP, total particle, viable particles, ΔP, filter Integrity test, Airflow volume, Air velocity test, recovery test, T, RH%..

How can we use this data with a predictive approach?

Artificial Intelligence: predictive data analysis

2.2.6. Manufacturing

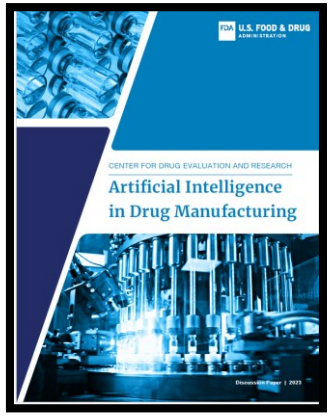
The use of AI/ML in the manufacturing of medicinal products including process design and scale up, in-process quality control and batch release is expected to increase in the coming years. Model development, performance assessment and life-cycle management should follow the quality risk management principles, taking patient safety, data integrity and product quality into account. For human medicines the principles of ICH Q8, Q9 and Q10 should be considered, awaiting revision of current regulatory requirements and GMP standards. The EMA Quality Innovation Group is engaging actively with stakeholders in this field to come up with relevant recommendations for human and veterinary medicines.

- **Trend Monitoring:** AI can be used to examine consumer complaints and deviation reports containing large volumes of text to identify cluster problem areas and prioritize areas for continual improvement. This offers the advantage of identifying trends in manufacturing-related deviations to support a more comprehensive root cause identification. AI methods integrated with process performance and process capability metrics can be used to proactively monitor manufacturing operations for trends. These methods can also predict thresholds for triggering corrective and preventive action effectiveness evaluations.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle
Draft



Thanks

Mirka Broccato
QP&GMP Compliance Executive
Consultant
m.broccato@lifebee.it

Benedetta Ligabò
Senior Consultant
b.ligabo@lifebee.it

LifeBee
DIGITALIZING LIFE SCIENCES
A ProductLifeGroup Company