Total Contamination Control in Clean and Sterile areas

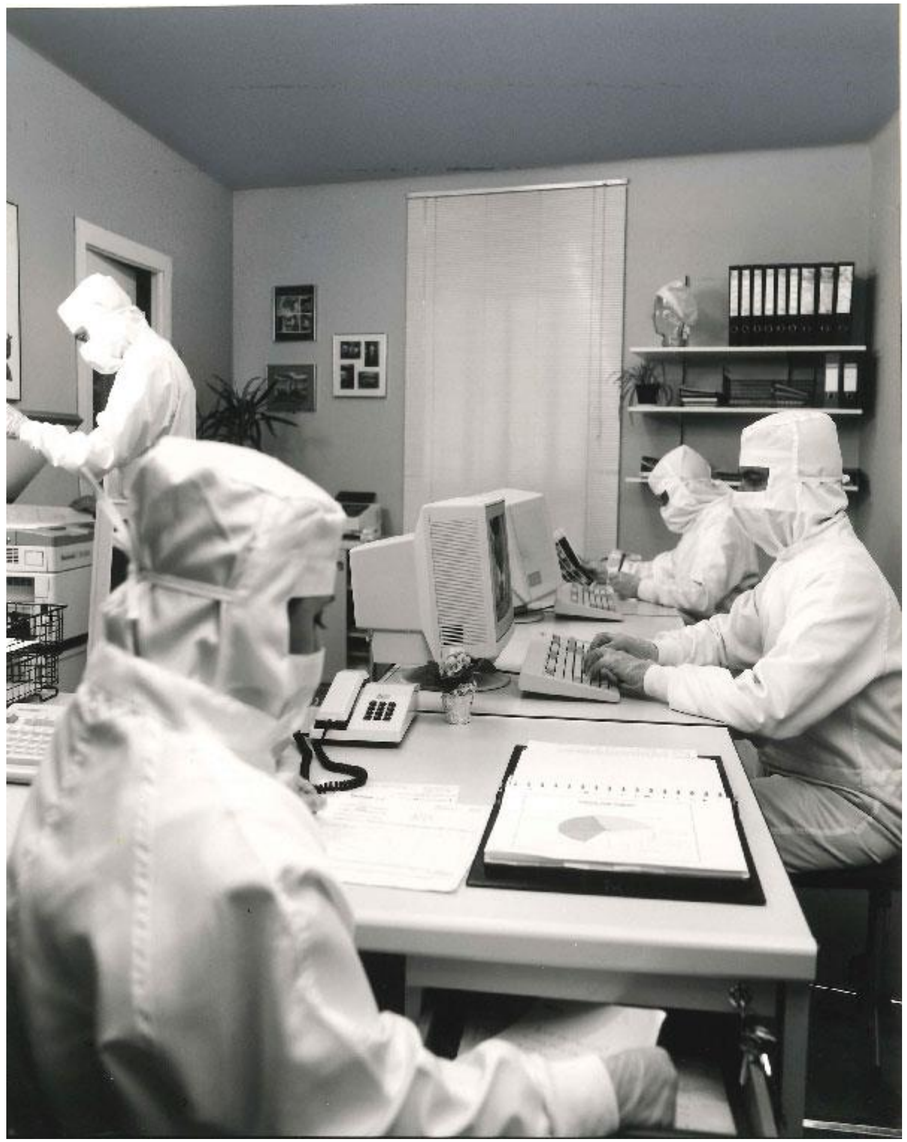
vestilab
clean room control

35 years in the Cleanroom sector

CRC Vestilab® Clean Room Control → vestilab clean room control

- Founded in 1983.
- In 2011, Vestilab became part of the **Alsico** group and became part of its High Tech division, while also entering the workwear sector with the Vestilab **Workwear** brand
- **72** people
- **Factory and offices** in Sant Quirze del Vallés (**Barcelona**). Commercial Delegation in **Madrid**
- **40 % is export and 60% is Iberia market**

Our philosophy is to help customers minimize the risk of contamination



APPROACHES & IMPLICATIONS OF THE EU GMP ANNEX 1

GMP EU ANNEX 1: GUIDE FOR THE MANUFACTURE OF STERILE MEDICINAL PRODUCTS

1989	1996	2003	2008	2019
Annex 1 is published, associated to Vol. 4: GMP of EU	Annex 1 first review	Second review	Third review	Draft

Annex 1 has never been completely reviewed from the moment in was published in 1989

GMP EU ANNEX 1: MANUFACTURE OF STERILE MEDICINAL PRODUCTS

NEW CONCEPTS:

PHARMACEUTICAL QUALITY SYSTEM (ICH-Q9)

QUALITY RISK MANAGMENT (ICH-Q10)

CONTAMINATION CONTROL STRATEGY (CCS)

The importance of risk in the revision of the new Annex 1 compared to Annex 1 of 2008.

Content extension: from 16 to 50 pages

Introduction of the word "Risk"	Current version of Annex 1 (Nov 2008)	Draft Annex 1 (Dec 2017) *2019*
Risk	20 times	92 times
Quality Risk Management (QRM)	1 time	15 times
Risk analysis	0 times	21 times
Risk assessment	0 times	1 times

In recent years, numerous weaknesses within the manufacture of sterile injectable drugs have been identified. As a result, nearly one-third of the industry's sterile injectable manufacturing capacity is off line because of quality issues, according to a congressional report.

*Source: **Aseptic Manufacturing. A Roadmap to Excellence***
Sponsored by DPT.www.pharmamanufacturing.com

What does it really means in Practice?

GMP ANNEX 1

BE PROACTIVE

RISK IDENTIFICATION

RISK ASSESSMENT

GENERAL OVERVIEW

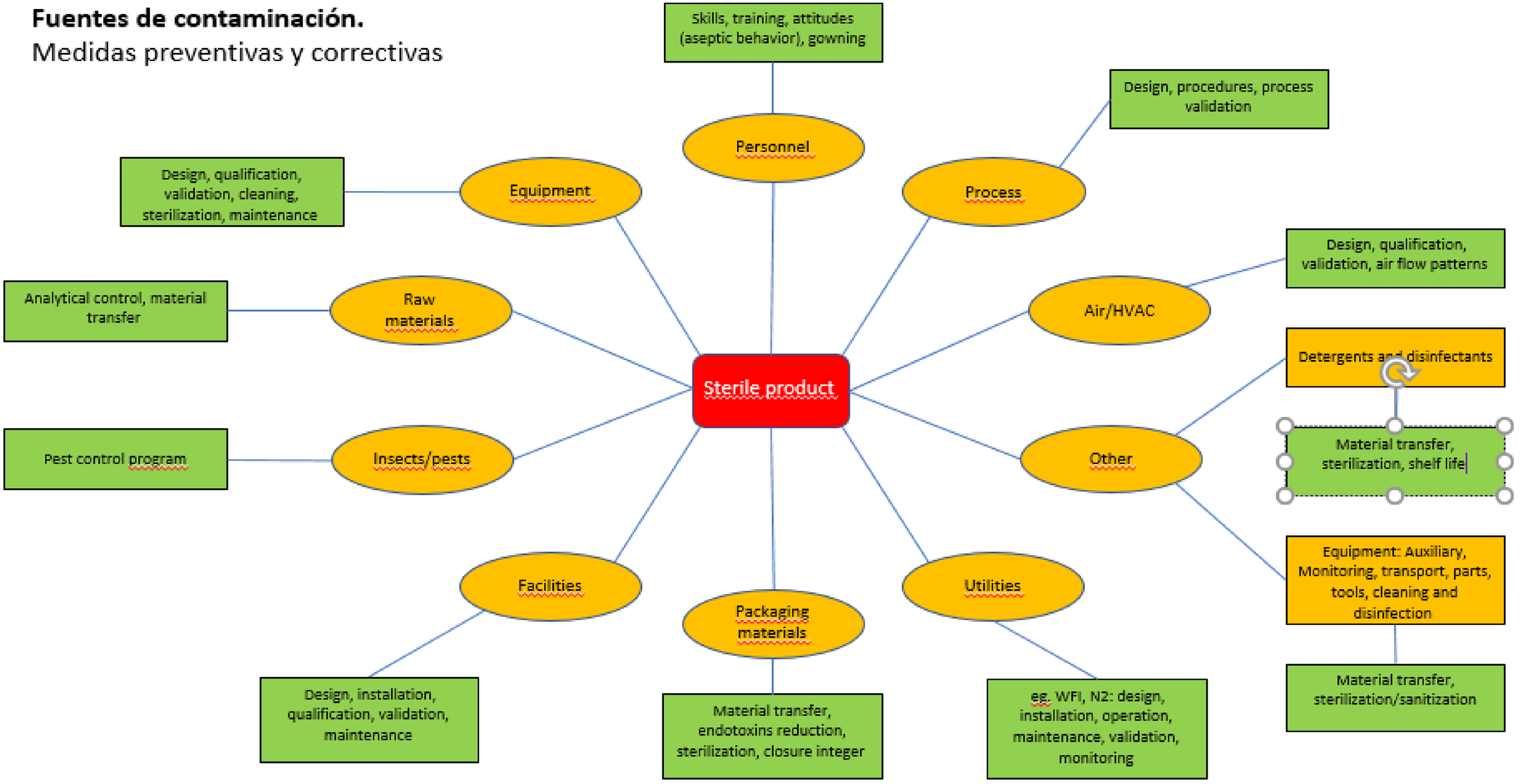
1. Scope
2. Principle
3. Pharmaceutical Quality System (PQS)
4. **Personnel**
5. **Premises**
6. Equipment
7. Utilities.
8. Production and specific technologies
9. Viable and non-viable environmental and process monitoring
10. Quality control (QC)
11. Glossary

1. Scope

The intent of the Annex is to provide guidance for **sterile medicinal products**. However **some of the principles and guidance**, such as **contamination control strategy**, room qualification, classification, monitoring and 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 of microbial, particulate and pyrogen contamination, to reduce it as far** as possible, is considered important. **Where to Control de Contamination is important.**

CONTAMINATION CONTROL STRATEGY: HOLISTIC VIEW

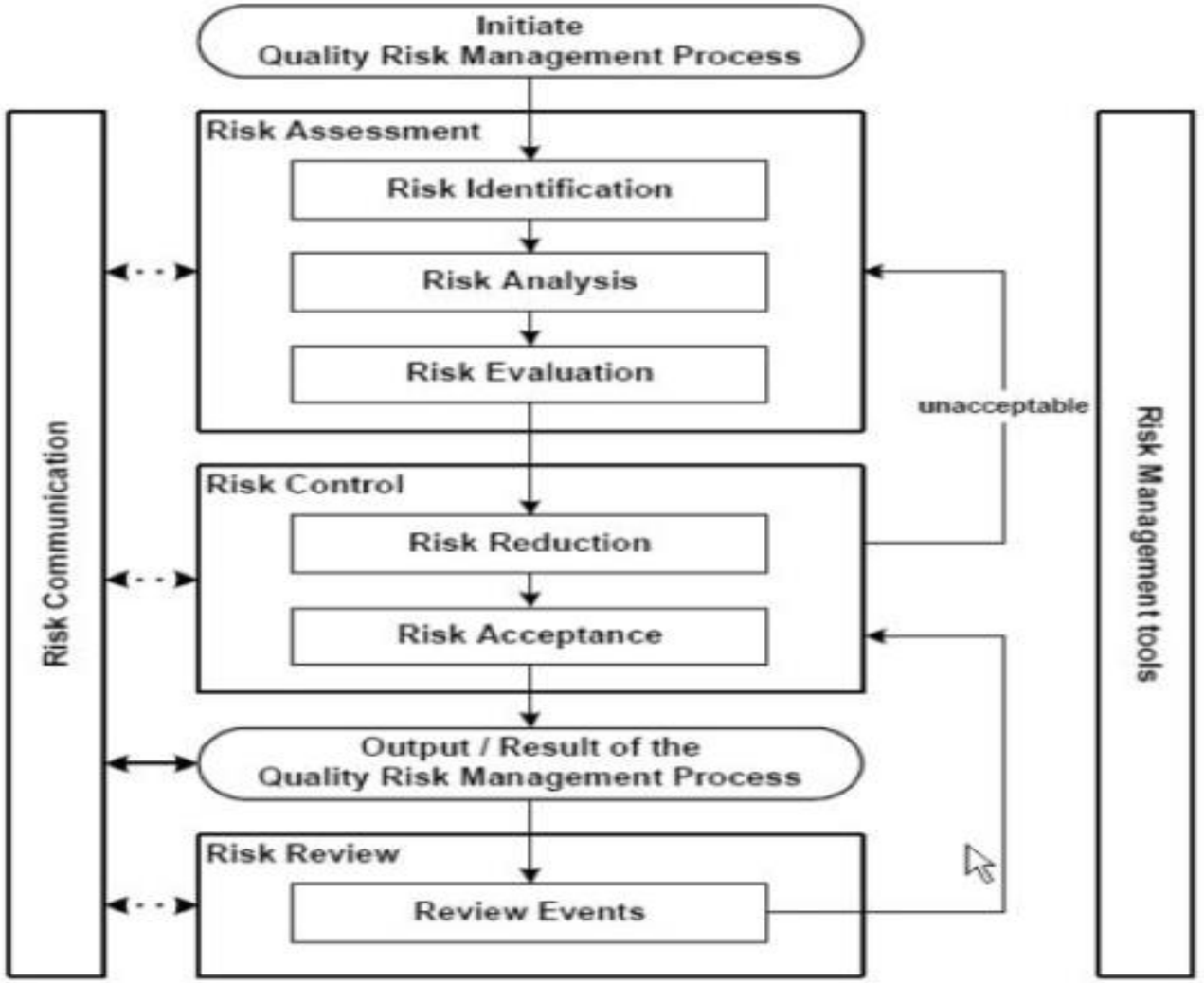
Fuentes de contaminación.
Medidas preventivas y correctivas



QUALITY RISK MANAGMENT (Q9)

Evaluation the risk to patient and product quality

- Effective Risk Management:
    - Identify
    - Evaluate
    - Eliminate (if possible)
    - Control and risk priority
- Characteristics:
    - Documented
    - Should include rational of decision taken
    - Revised regularly
- Root Case Analysis and CAPAS

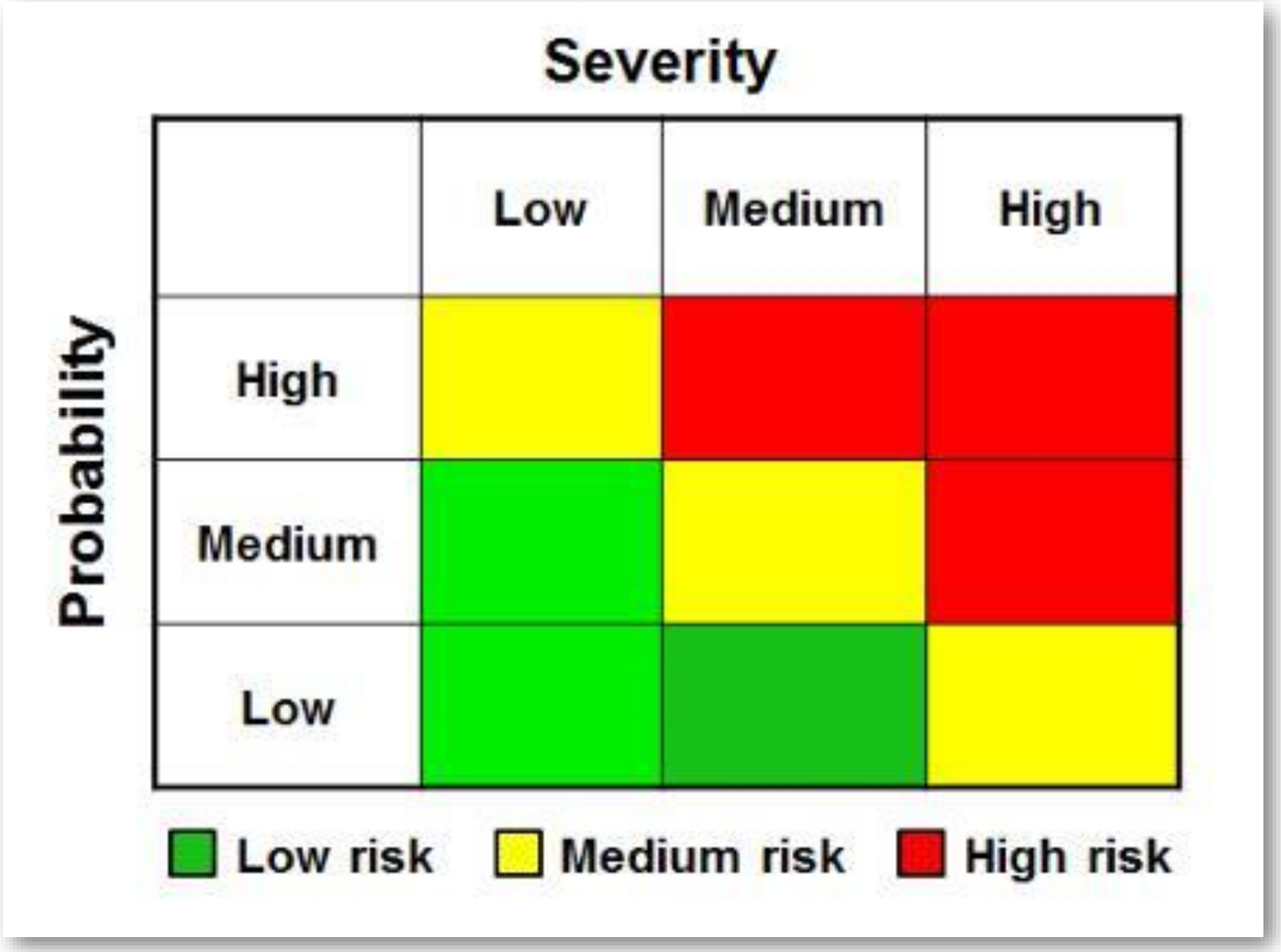


QUALITY RISK MANAGMENT (Q9)

How I evaluate the risk?

- Severity
- Probability
- Detectability

- Impact in patients health?
- What is the probability to occur?
- Is the detectability difficult or easy?



QUALITY RISK MANAGMENT (Q9)

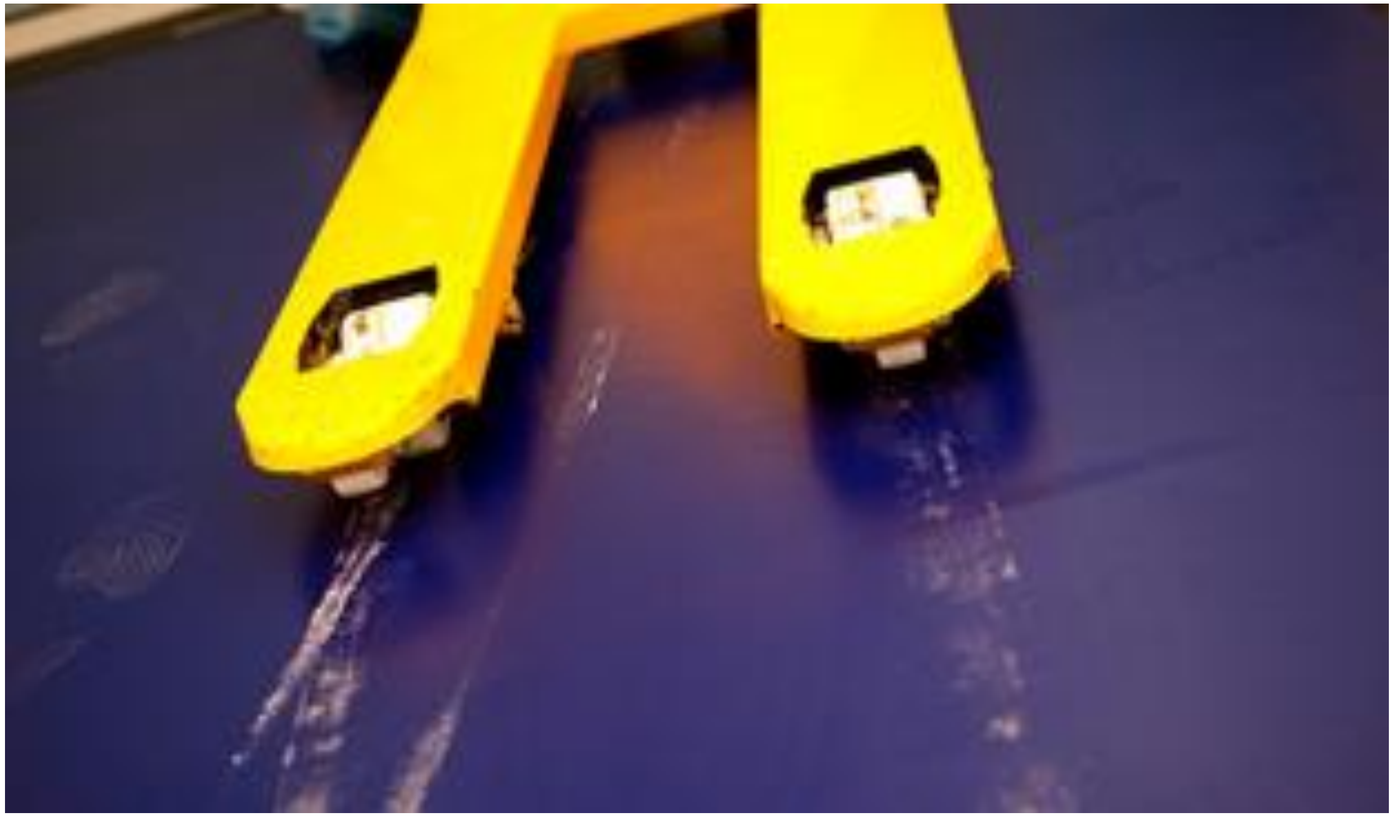
KEY RISK: Visual Inspection in Vials, Synergies, non transparent emulsions or Lyophilized

Injectable
Subjected to EU GMP Annex 1
Aseptic conditions
Foreign particle detection

Can it be treated equally considering the risk assessment?

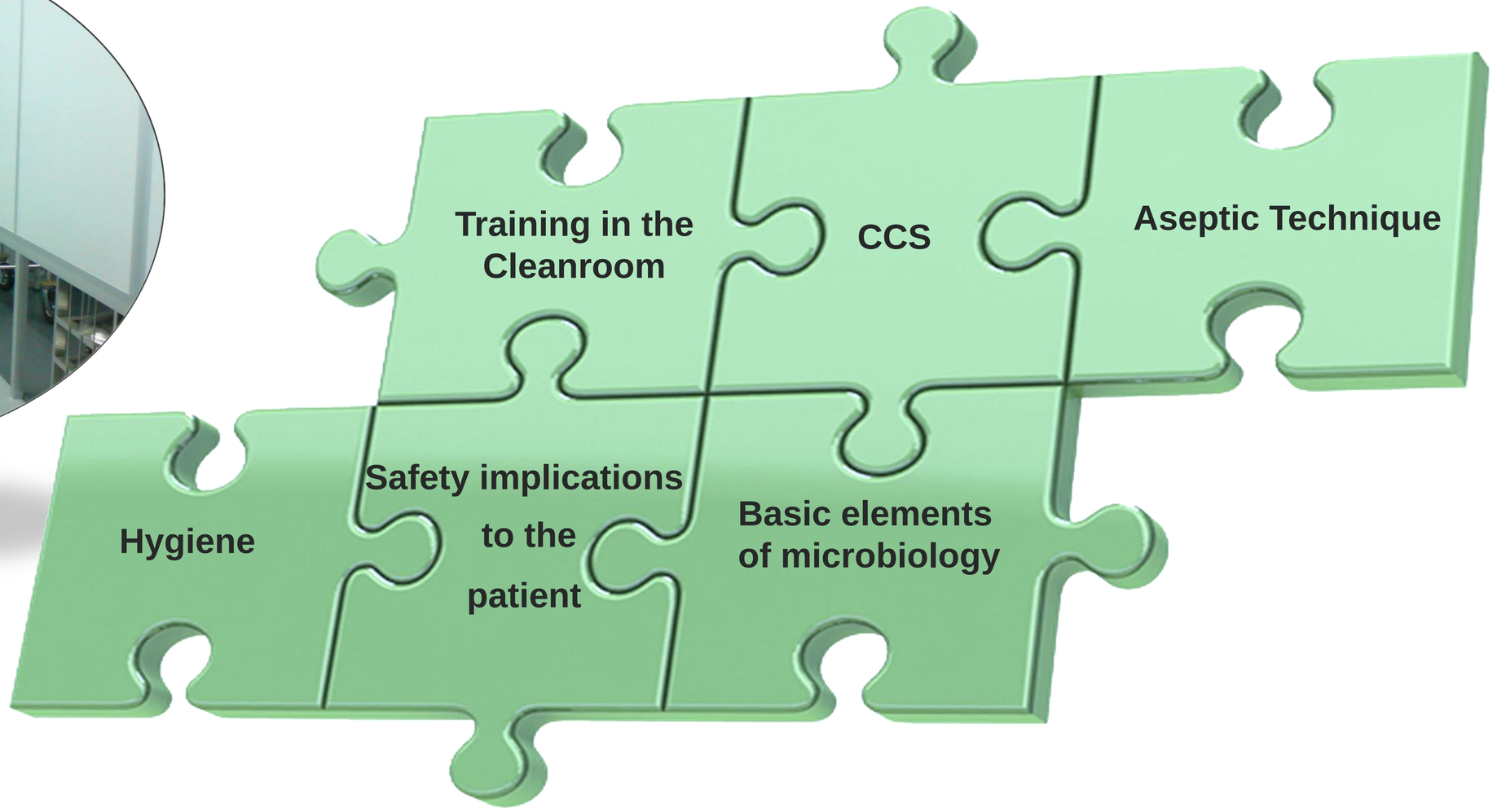
KEY RISK: CROSS CONTAMINATION: WHEELS

QRM: Preventing **cross-contamination** is a significant challenge that must be addressed for **pharmaceutical** manufacturers during manufacturing, packaging and inventory management operations to ensure the quality of supply to patients



How I clean the wheels?

GMP ANNEX 1 IMPLICATIONS: PERSONNEL (4)



GMP ANNEX 1 IMPLICATIONS: PERSONNEL (4)

The personnel working in a grade A/B cleanroom should be **trained for aseptic gowning and aseptic practices. (…) a sterile face mask and sterile eye coverings should be worn** to cover all facial skin and prevent the shedding of droplets and particles.

This training should include reference to hygiene, cleanroom practices, contamination control, **aseptic techniques,** and potential **safety implications to the patient of a loss of product sterility** and in the basic elements of microbiology.

The **microbial monitoring** of personnel in the grade A/B area should be performed to assess their aseptic behavior.

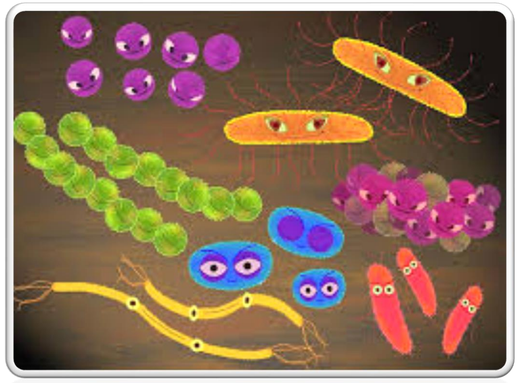
Personnel present in cleanrooms A/B during manufacturing **shall be trained during the aseptic process simulation** (APS) execution / Media fill

All personnel (**including those concerned with cleaning and maintenance)** employed in such areas should receive **regular training** in disciplines relevant to the correct manufacture of sterile products.

Garments should be **packed and folded** in such a way as to allow operators to change into the garments **with contact to the outer surfaces of the garment reduced to a minimum**.

GMP ANNEX 1 IMPLICATIONS: DISINFECTION (5.31)

5.31 The disinfection of clean areas is particularly important.
They should be cleaned and disinfected thoroughly in accordance with a written program (***for disinfection to be effective, cleaning to remove surface contamination must be performed first***). More than one type of disinfecting agent should be employed, and should include the periodic use of **an sporicidal agent.**



Cleaning programs should be effective in the removal of disinfectant residues.

5.32 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods.
Disinfectants and detergents used in grade A and B areas **should be sterile prior to use**.

5.33 Disinfectants should be shown to be effective when used on the specific facilities, equipment and processes that they are used in.
Disinfectants should be shown to be effective for the duration of their in use shelf-life taking into **consideration appropriate contact time** and the manner in and surfaces on which they are utilized.
Monitoring should be undertaken regularly in order to show the effectiveness of the disinfection program and to detect the development of resistant and/or spore forming strains.

ISHIKAWA- HOW TO ANALYSE THE RISK?

Integrity and stability packaging

Transfer

Entry of air in the bottle

Inviolability of the container

Training / education

Complex Preparation

Integrity filter

Concentration disinfectants

Sterility in use

Residues

Failures in disinfection

GMP ANNEX 1 IMPLICATIONS: DISINFECTION (5.31)

Ready To Use with inner-bag

Satisfactory Validation

Fully certificated lot by lot

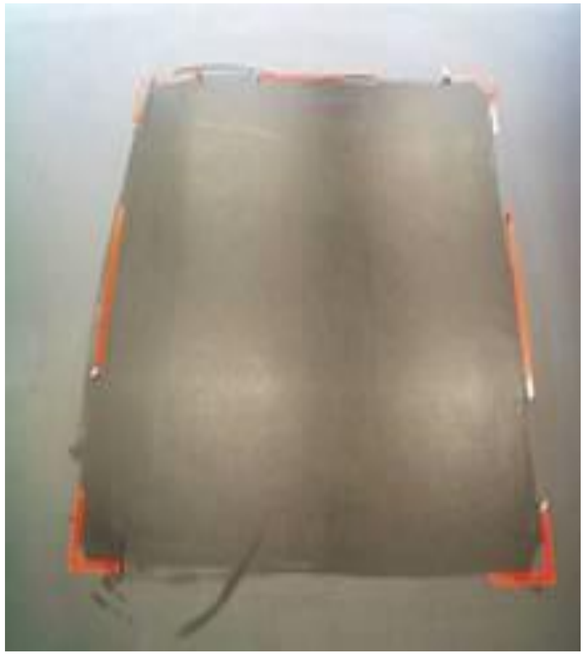
ater For Injection (WFI) quality water

EM excursions / deviations

Irradiated

Micro filtered 0,22µ

KEY RISK: ACHIEVE PROPER DISINFECT CONTACT TIMES



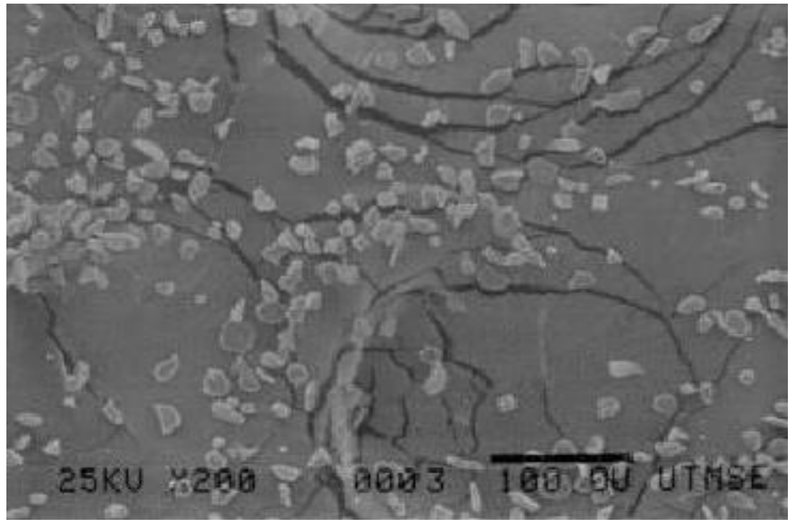
0 min

1 min

3 min

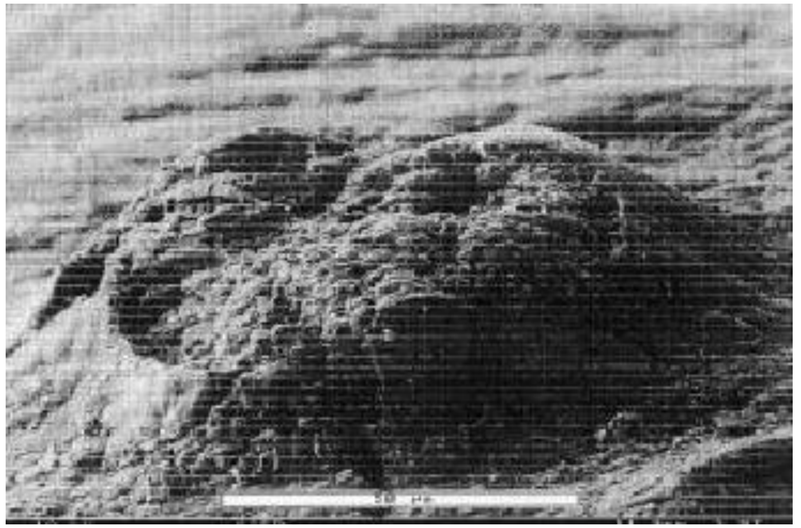
5 min

CLEANING PROGRAMS SHOULD BE EFFECTIVE IN THE REMOVAL OF DISINFECTANT RESIDUES.



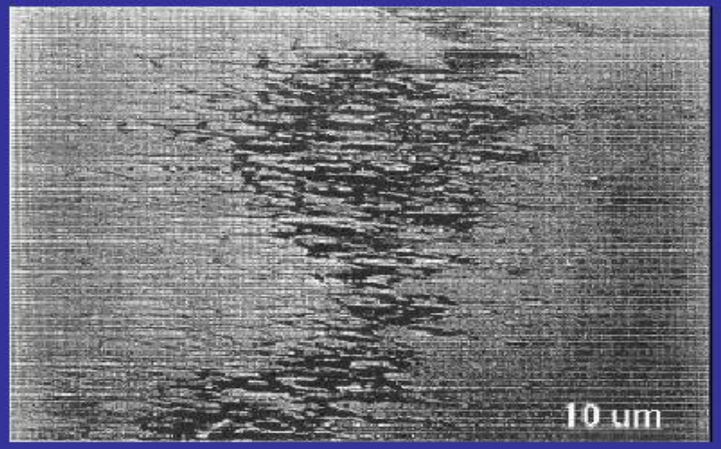
Sodium hypochlorite

Phenolic

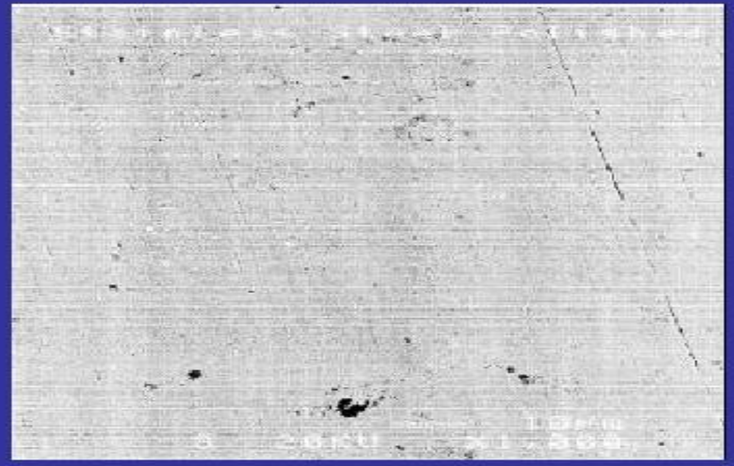


Quaternary Ammonium

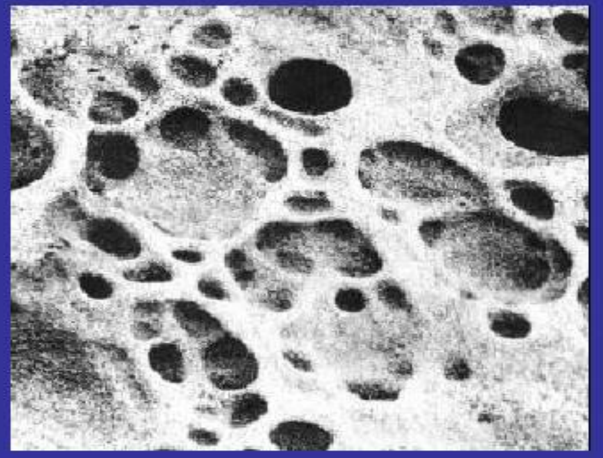
Epoxy Surface



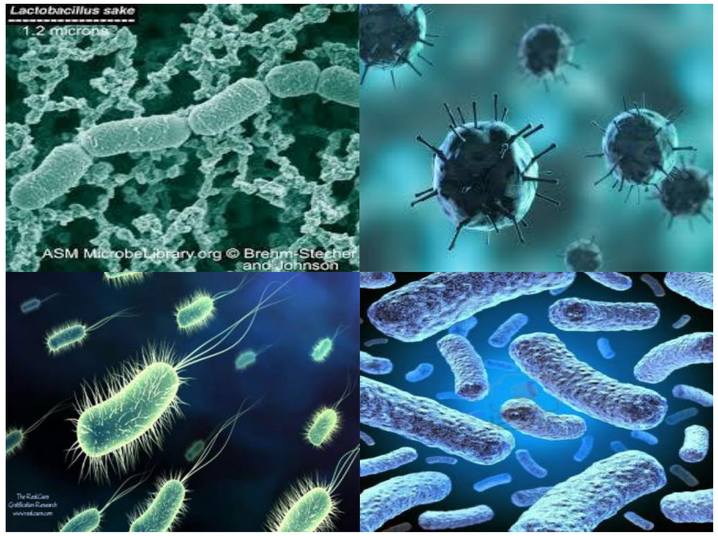
Stainless Steel Surface

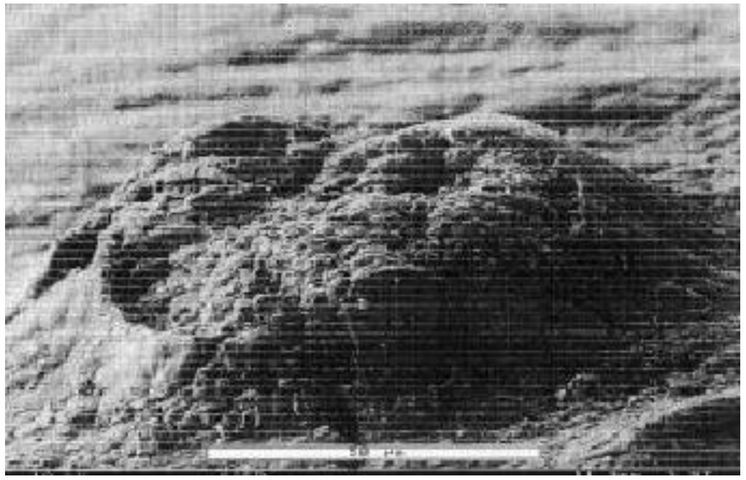


Plastic Curtain Surface #2

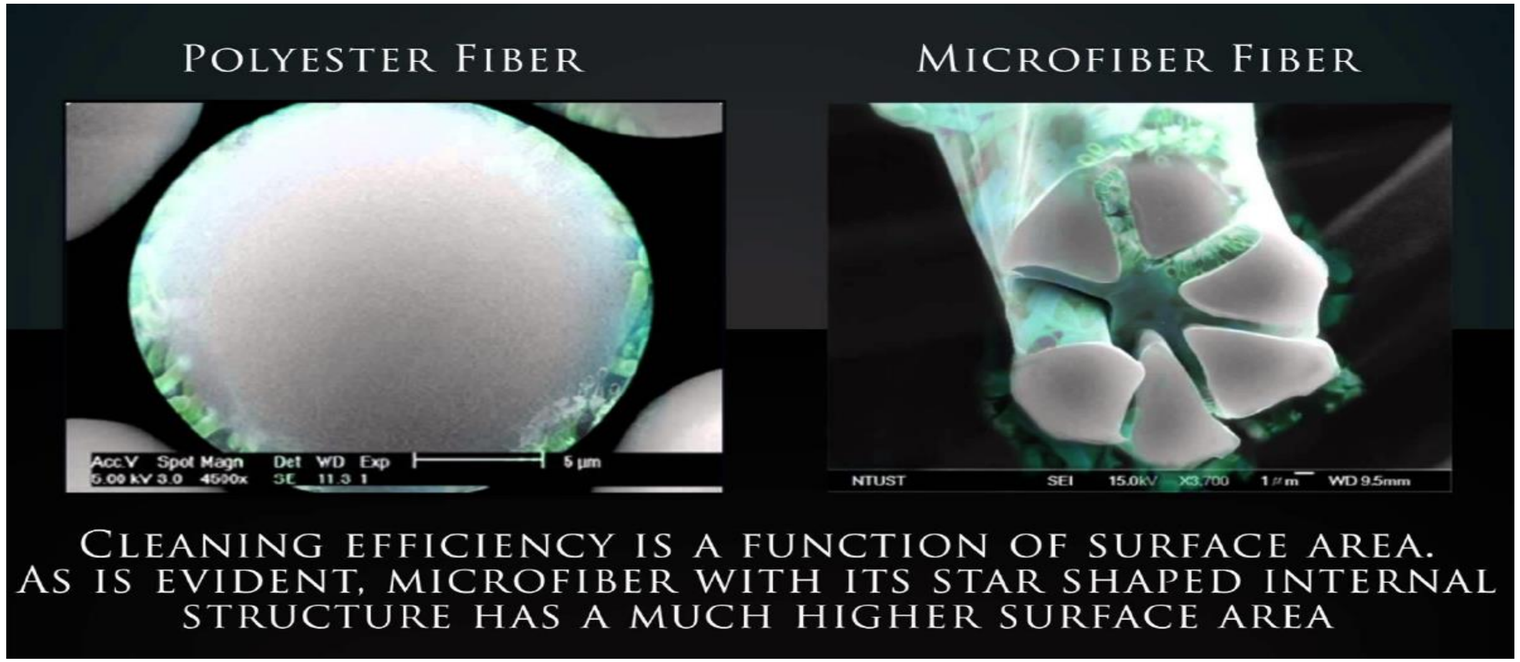


CLEANING PROGRAMS SHOULD BE EFFECTIVE IN THE REMOVAL OF DISINFECTANT RESIDUES.





MATERIALS THAT REMOVE: CLEANING



GMP ANNEX 1 DIFFERENCES (HIGH CRITICALITY)

DRAFT Annex 1 (2019)	Current Version (2008)	Differences And Comments	Critically
Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A **contamination control strategy** should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed. This assessment should lead to corrective and preventative actions being taken as necessary.	Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure.	*New: **A contamination control strategy must be established and documented**. The topics stated below must be discussed in that strategy document.*	**?**
The strategy should **consider all aspects of contamination control and its life cycle with ongoing and periodic review** and update of the strategy as appropriate.		***A contamination control strategy is a "living" document which must be periodically reviewed and updated.***	

GMP ANNEX 1 DIFFERENCES (HIGH CRITICALITY)

DRAFT Annex 1 (2019)	Current Version (2008)	Differences And Comments	Critically
Contamination control and steps taken to minimize the risk of contamination from microbial and particulate sources are a series of successively linked events or measures. These are typically assessed, controlled and monitored individually but these many sources should be considered holistically.		*Holistic approach*	**?**
The development of such strategies requires thorough technical and process knowledge. Potential sources of contamination are attributable to microbiological and cellular debris (**e.g. pyrogens/endotoxins**) as well as particulate matter (glass and other visible and sub-visible particles).		***Description of the contaminants that must be considered.***	

GMP ANNEX 1 DIFFERENCES (HIGH CRITICALITY)

DRAFT Annex 1 (2019)	Current Version (2008)	Differences And Comments	Critically
3.1 The manufacture of sterile medicinal products is a complex activity that requires additional controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's **Pharmaceutical Quality System (PQS)** should encompass and address the specific requirements of sterile product manufacture and **ensure that all activities are effectively controlled** so that all final products **are free from microbial and other contamination.**		*Introduction of the new Pharmaceutical Quality System (PQS) according to ICH Q10 and enumeration of its principal elements. They are summarised in Annex 2 to ICH Q10: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf*	?

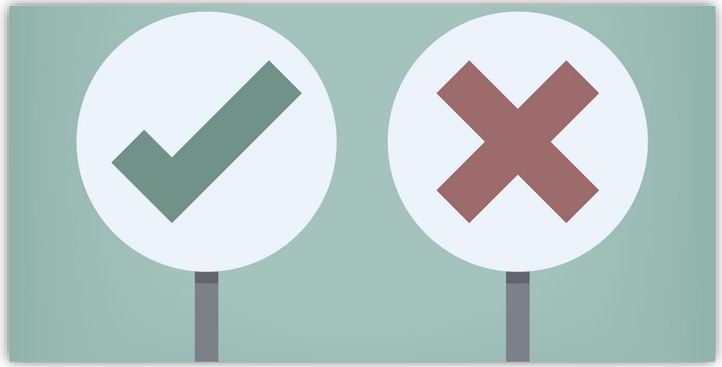
GMP ANNEX 1 DIFFERENCES (HIGH CRITICALITY)

DRAFT Annex 1 (2019)	Current Version (2008)	Differences And Comments	Critically
Grade A/B: **Sterile** headgear should totally enclose hair and facial hair; it should be tucked into the neck of the sterile suit; a **sterile face mask and sterile eye coverings** should be worn to cover all facial skin and prevent the shedding of droplets and particles. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized footwear should be worn (…)**Garments should be packed and folded in such a way as to allow operators to change into the garments** with contact to the outer surfaces of the garment reduced to a minimum.	Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. (…) The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.	*New:* - *Clothing shall always be sterile* - *Clothing shall completely cover the skin* - *Clothing shall be* ***packed an folded in a manner that the outer surfaces are*** *(almost) not touched by the person.*	**?**
4.13 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. It is recommended that facility suits, including **dedicated socks be worn before entry to change rooms for grade C and B.** Where clothing is reused this should be considered as part of the qualification.	44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms.	*New:* ***Wear single use socks before entry to room class C or B.***	

GMP ANNEX 1 DIFFERENCES (HIGH CRITICALITY)

DRAFT Annex 1 (2019)	Current Version (2008)	Differences And Comments	Critically
5.31 The disinfection of clean areas is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme (for disinfection to be effective, cleaning to remove surface contamination must be performed first)., More than one type of disinfecting agent should be employed, **and should include the periodic use of a sporicidal agent.** Disinfectants should be shown to be effective for the duration of their in use shelf-life taking into consideration **appropriate contact time** and the manner in and surfaces on which they are utilized. Monitoring should be undertaken regularly in order to show the effectiveness of the disinfection program and to detect the development of resistant and/or spore forming strains. **Cleaning programs should be effective in the removal of disinfectant residues.**	61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.	*New:* ***Use of sporicidal agents, but already common practice. Cleaning process should be effective !***	**?**

Be Proactive, Compliance with the guidelines will give positive results!



vestilab
clean room control

Preguntas?

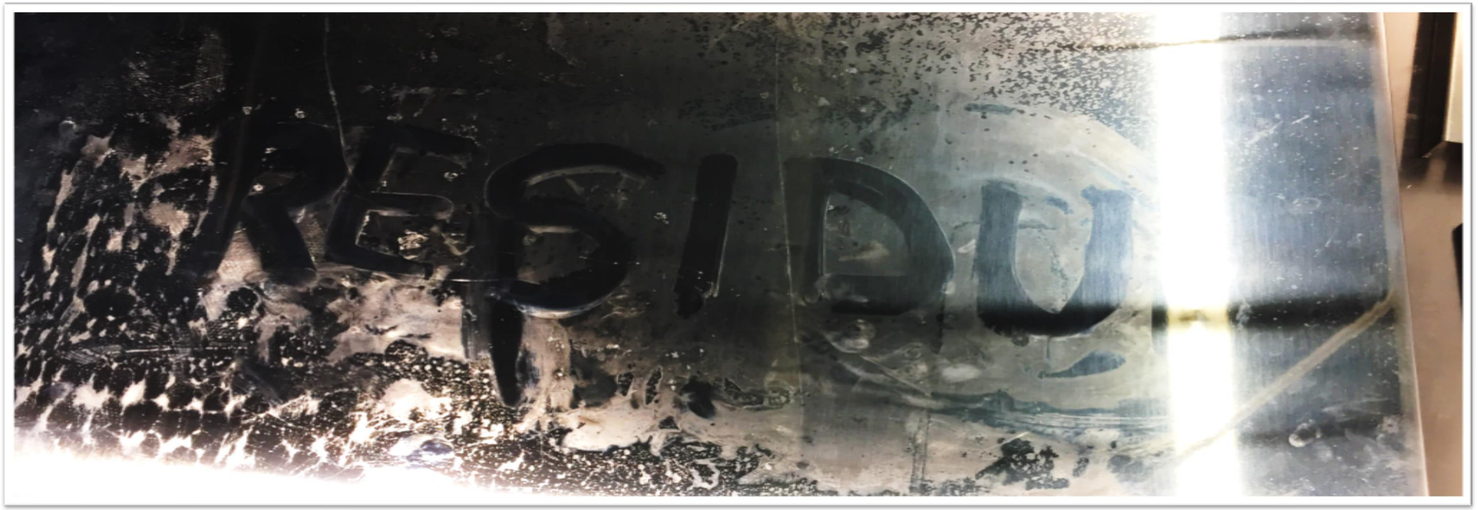
vestilab
clean room control

Obrigado !

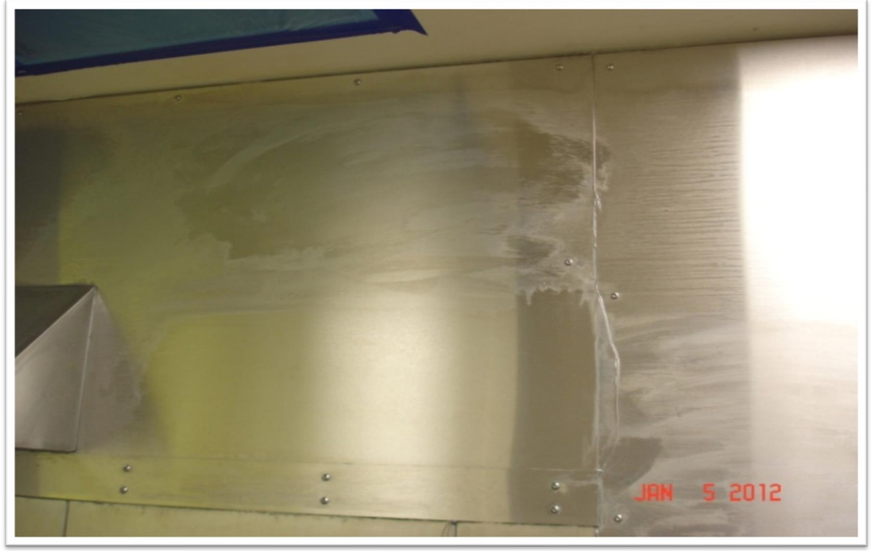
Inyaki Freixa
i.freixa@vestilab.com

vestilab
clean room control

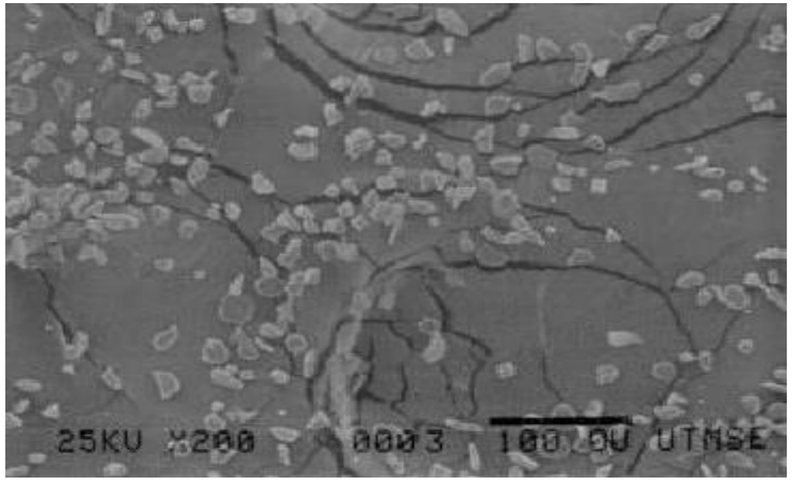
○ DISINFECTANT RESIDUES IN PHARMACEUTICAL



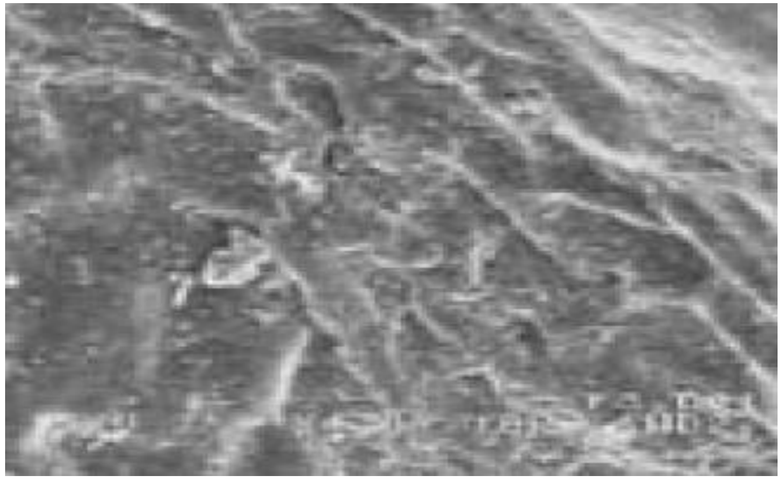
○ DISINFECTANT RESIDUES IN PHARMACEUTICAL



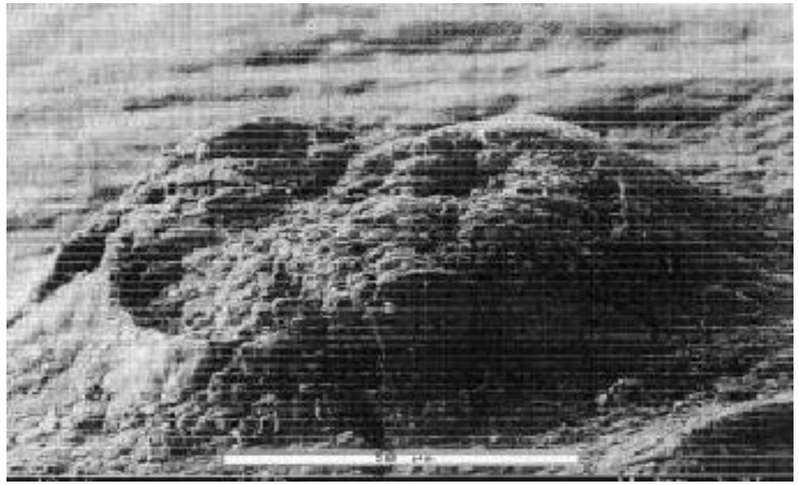
DISINFECTANT RESIDUES IN PHARMACEUTICAL



Sodium hypochlorite



Phenolic



Quaternary Ammonium

www.vestilab.com

ROTACIONES DE DESINFECTANTES SEGÚN ZONAS A TRATAR

SALAS CLASE A Y B (JORNADA LABORAL DE LUNES A VIERNES. SI SE TRABAJA TODA LA SEMANA, ADAPTAR SEGÚN NECESIDADES)

PERIODICIDAD	SUPERFICIES DE BAJO RIESGO TECHOS, PAREDES Y SUELOS	SUPERFICIES DE ALTO RIESGO ZONA CRÍTICA
DIA 1-4	**InSpec QT** Amonio Cuaternario diluido en WFI	**InSpec IPA** en pulverizador Isopropanol 70% diluido en WFI
	O	O
	InSpec AN Diamine diluido en WFI	**InSpec DE** en pulverizador Etanol 70% diluido en WFI
	OR	OR
	DEC-QUAT O HYPOCHLOR	
ENTRE DESINFECTANTE Y ESPORICIDA	*Uso RECOMENDABLE de detergente InSpec **N10***	*Se RECOMIENDA usar exclusivamente detergentes CIP validados en las zonas en contacto con el productos.*
DIA 5	**InSpec OX** (H2o2) 6% and (PAA) 0.4% Diluido en agua purificada	Steri Perox 6% Peróxido de Hidrógeno
	OR	
	InSpec HA Acido Hipocloroso + Detergente InSpec N10	