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Parenteral Drug Association

EU GMP Annex 1

From Guidance to Practice: Bridging Annex1 into daily operations Practical Procedures

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Southern California Chapter
Connecting People, Science, and Regulation

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- CCS
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- Cleaning vs Disinfection vs Residue Removal.
- Mopping Technique Adjustment for Annex 1 compliance
- Biocide Residue Challenges
- Mopping Technique for Effective (and fast) Residue Removal
- Overview of Garment Use impact during life cycle
- CCS Master file example for Spill Recovery in Filling Line: the impact of wipers in particle and fiber risk of contamination
- EN 16617 lessons

1920

International cooperation between EC, EMA, WHO, and PIC/S

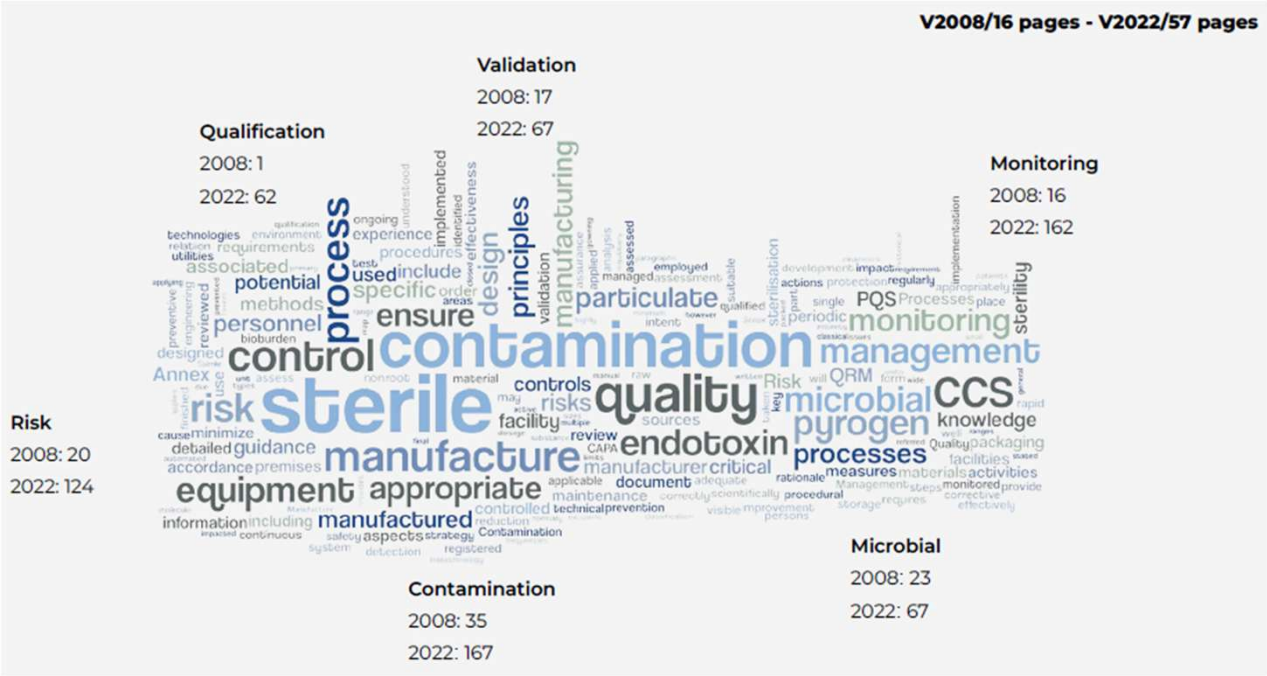
Public consultation:

- December 2017 = 6,300 comments/ 3-month 1st consultation = + 2 year review by the Working Group 2018-19.
- Second Draft +2nd joint consultation 2020 = 2,000 aprx. comments + > 1,5 yr review.

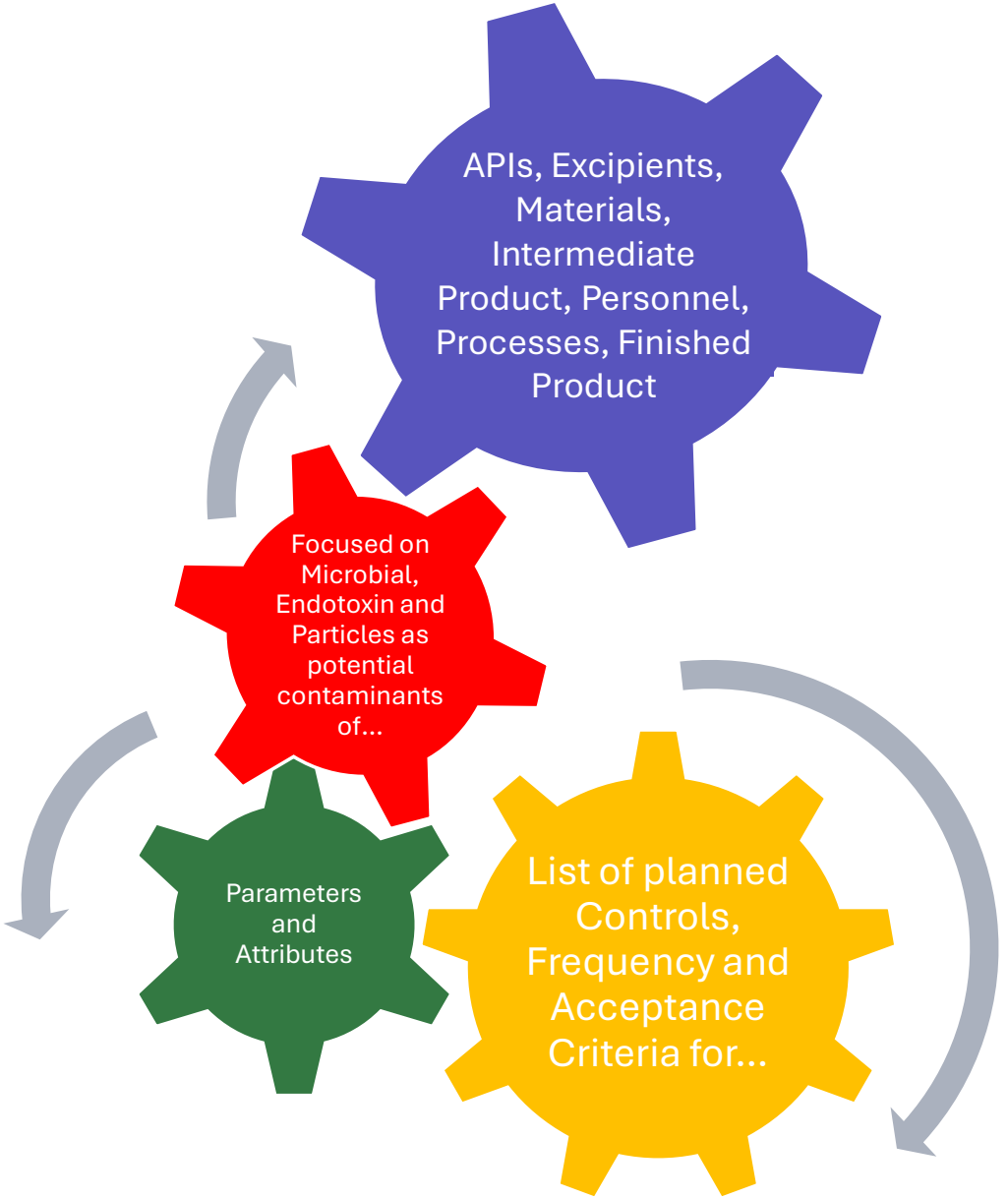
The final version of the revised Annex 1 was published on 25 August 2022, some 7 years after the revision process started.

Effective since 25 August 2023;

And one year later for section 8.123 - lyophilisers that are manually loaded or unloaded with no barrier technology separation - to be sterilised before each load



CCS CONTAMINACIÓN CONTROL STRATEGY



Elements of the CCS have been present and evolved since long before new Annex 1, however consolidating under one single document has provided a powerful tool for communication between:

- Technical Staff and Financial/Upper Management
- Different departments with previous “silo” isolated perspective
- Company auditors and regulator authorities
- CDMOs clients.

CCS MASTERFILE EXAMPLE FOR FILLING PROCESS OF VIALS

1. Process Step	2. Function	3. Source of Contamination	4. Potential Failure	5. Effect	6. Frequency/Occurence	O	7. Severity	S	8. Detectability PoD	D	9. Proximity to Critical Area	RPN	10
Filling process	Intervention for spill and broken vial cleaning	Material	Particle and fiber reaching critical filling area	Potentially contaminated vials with foregin matter	Operation performed several time per batch.		High -Med		Low		Machine non-contact parts but close to direct contact parts		
		Personnel	Microbial content realeased in filling area	Microbial contamination in Class A area	Operation performed several time per batch.		High		Very Low		Machine non-contact parts but close to direct contact parts		

PN	10. Method To control de Hazard	11. Document	12. Corrective Actions	13. Current Status	14. Comments
	Reduce number of wipers per task. Select higher quality materials. Establish testing confirmation frequency	SOP NNXX V-#	Sample surface after intervention with black wipe periodically	Under review	
	Train operators on SOP compliance frequently to ensure minimal use of wipes and unnecessary friction of material.	SOP NNXX V-#	See operators performing intervention. Retrain.	Completed	
	Use 400/600 mm gloves and Sanitize frequently	SOP NNXX V-#		Completed	
	Use high retention fabric in garment arms	URS CRGXX V#		Under review	

Practical Impact of Annex 1 CCS work
Case Isolator Filling Line

1920 working hours

- 12 people
- 2 hours per week
- 2 years (80 weeks)
- 12x2x80 hours of work

Daily practice Contamination Control Challenges under Annex 1

- Wiping
- Mopping
- Gowning and Personnel

PRELIMINARY CLEANING

- Reduces or eliminates residues from the pharmaceutical process, fibers and other “dirt”.
- Requires specific techniques and proper materials to apply mechanical action and release the contaminants from the surface and transfer them to a “carrying liquid”

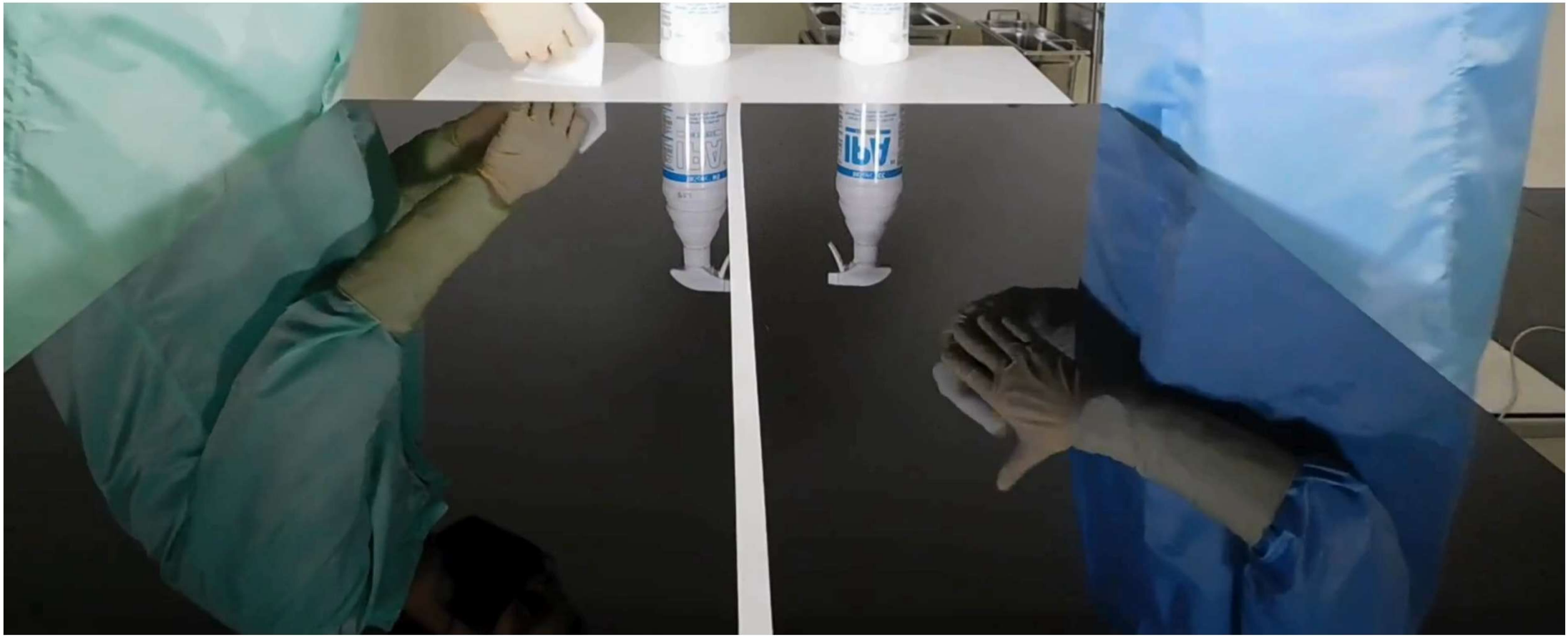
DISINFECTION

- Biocidal action from chemicals.
- Requires a WET CONTACT TIME and is enhanced by Mechanical Action. (EN 16615).
- Leaves residues …some more visible than others! Residues accumulate.
- Technique different to cleaning.

RESIDUE REMOVAL

- Eliminates effectively the residues left by biocides after they dry.
- Requires mechanical action through materials with high dislodging and removal power.
- Visual aspect of surface defines how often needs to be done.
- Accumulated “old residues” usually require “reset” by proper means.
- Critical to prevent corrosion caused by strong sterilant chemicals.

Biocide Wet Contact Time Challenges
Mopping and Wiping



Mopping Technique Adjustments for Annex 1

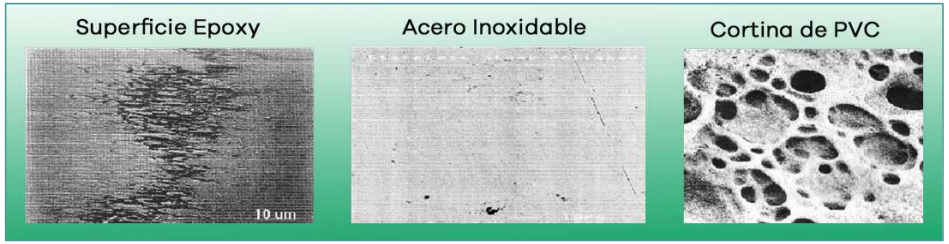
SOP Improvement - Must haves:

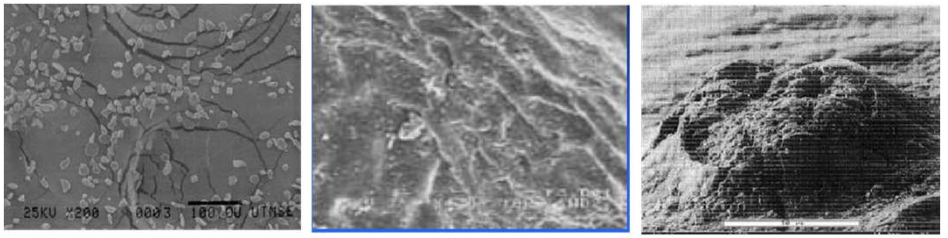
- Wet contact time must be maximized
- Coverage must be even
- Variability of drying time should be the minimum possible.
- Eliminate the need for double application.

Nice to have:

- Liquid waste reduced when doing walls.

Obtaining correct wet contact time will increase visible residue levels not acceptable under Annex 1





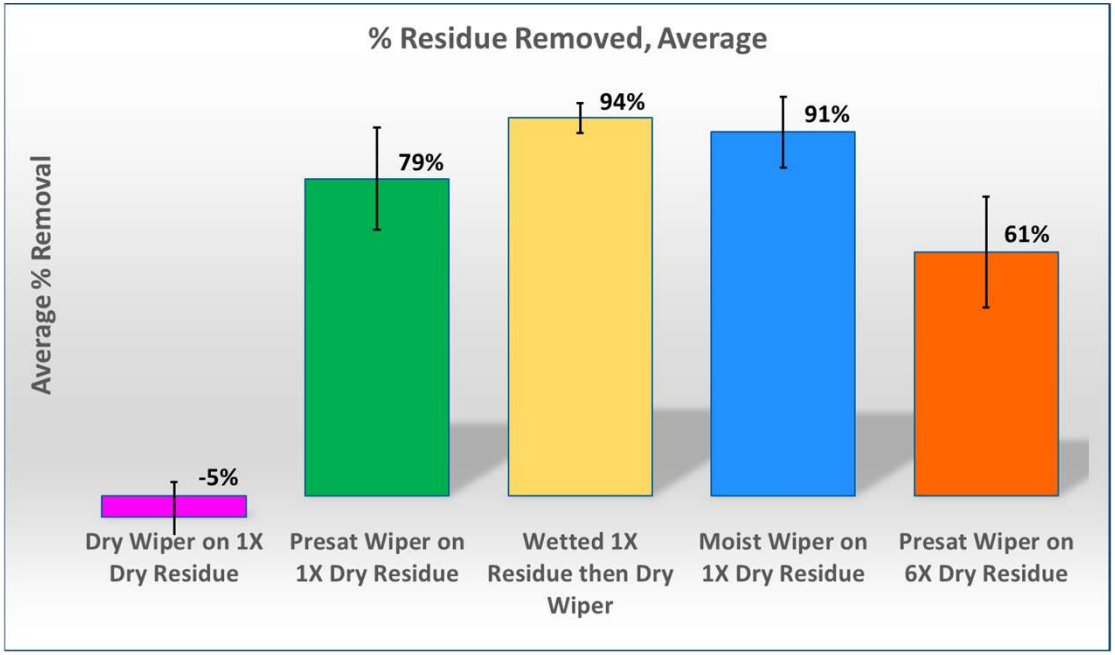
Hipoclorito de sodio

Amonio cuaternario

Source: Foamtec Int and Veltek Associates

Disinfectant Residues and removal

Product	Residue on Evaporation / ppm
IPA	0
Denatured Ethanol	2
6% Hydrogen Peroxide	7
Hypochlorous Acid	1,118
Hypochlorous Acid	1,474
Quat / Biguanide	5,256
Amphoteric / Biguanide	5,948
Quat / Biguanide	6,106
Quat /Chlorine Dioxide	20,595
Amphoteric Surfactant	62,213



Source: Contec Inc

The past and present of expectations

- Disinfected

- Disinfected + residues removed until visually clean

Mopping technique adapted for residue removal or heavy production residue cleaning

Pull & lift

vs

Curling

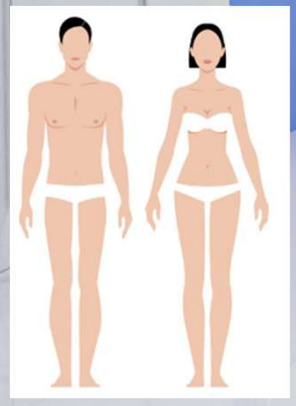
vs

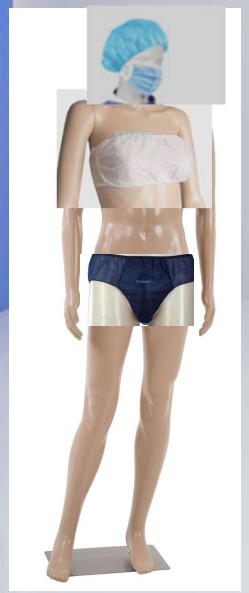
Disinfection

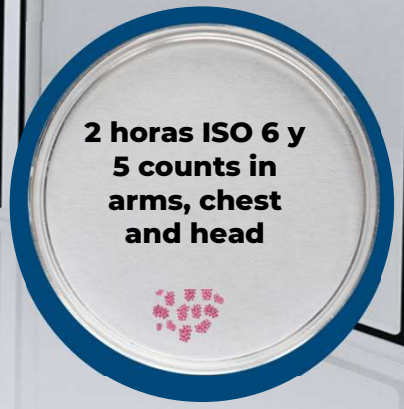
Human Contamination and Garment System as a barrier- Complexities of Life Cycle Approach

- Annex 1 requires qualification of impact of use in the efficacy of garment system:
- In use particle generation changes over lifecycle → Understand Worst Case
- Changes in Gowning Area design to accommodate:
  - Inner Garment
  - Socks
  - Visual inspection pre-use and post-use
- Full gown system qualification
  - Goggles
  - Outer and Inner Garment
  - Gloves

Single Use Sterile Estéril	Poly- Cotton	Two piece polyester	Inner Coverall Pijama Bi-ome

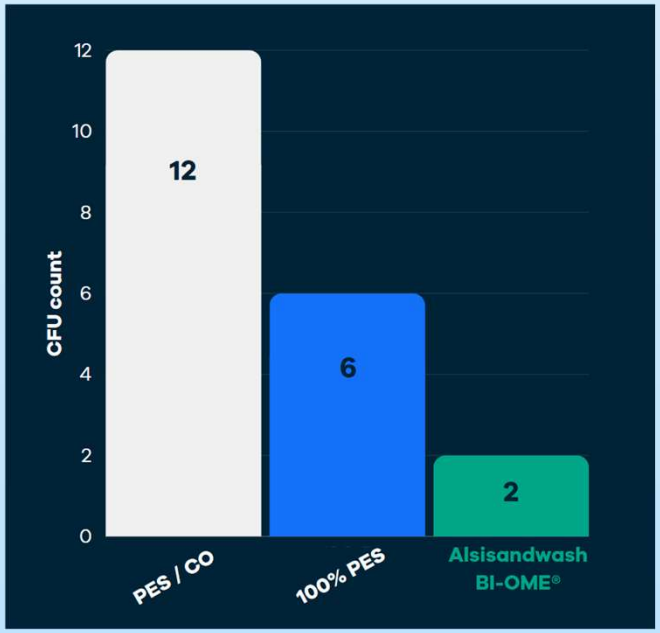




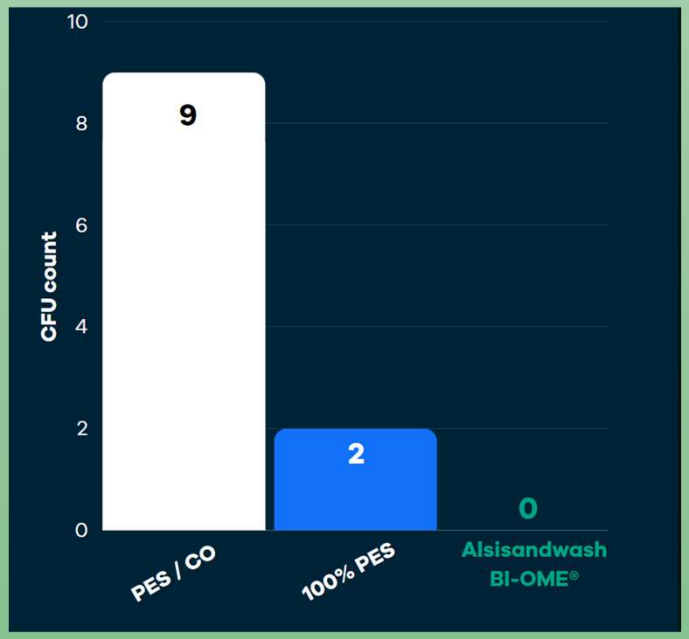


Impact of Inner Garment Choice for Risk Mitigation Under Annex 1 Proactive Approach

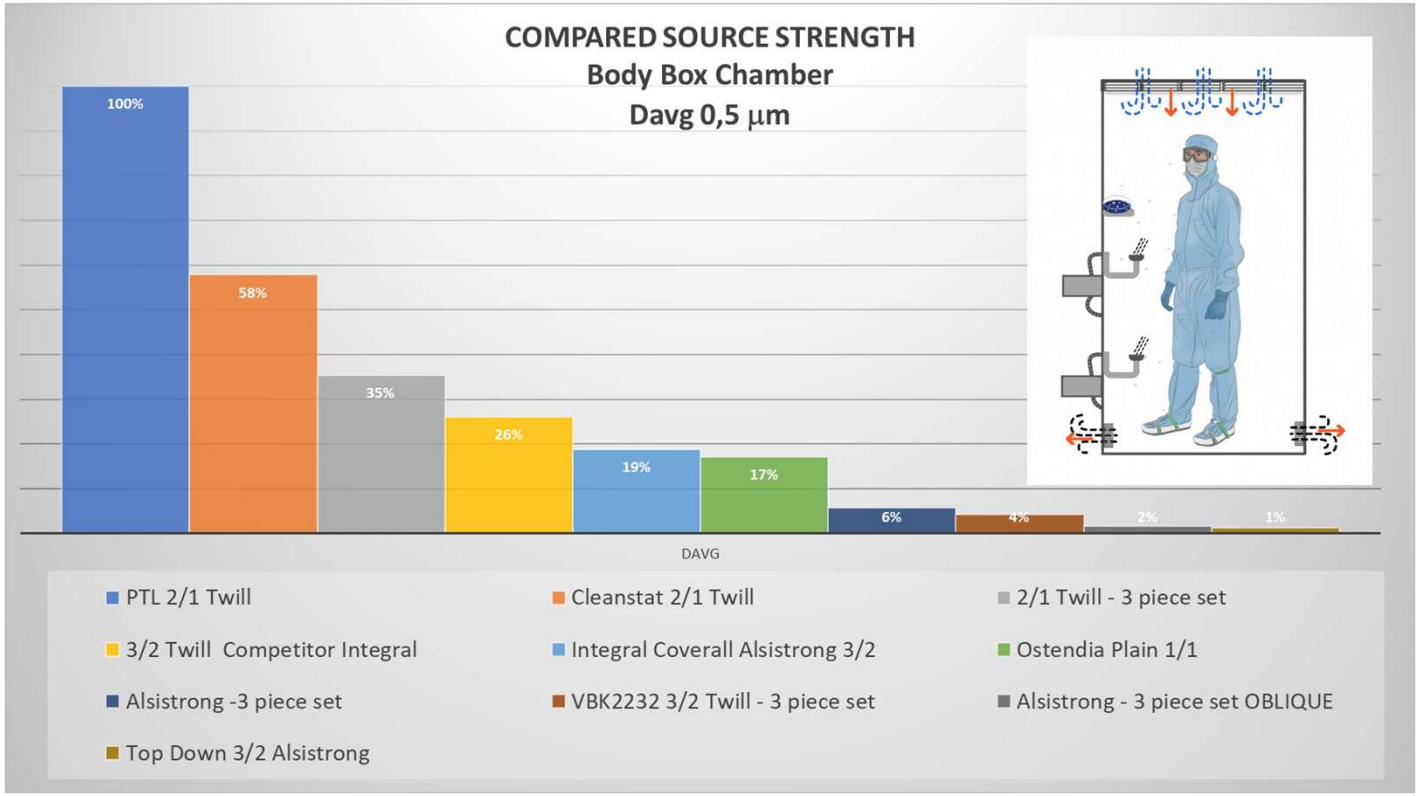
- ISO 6



- ISO 5

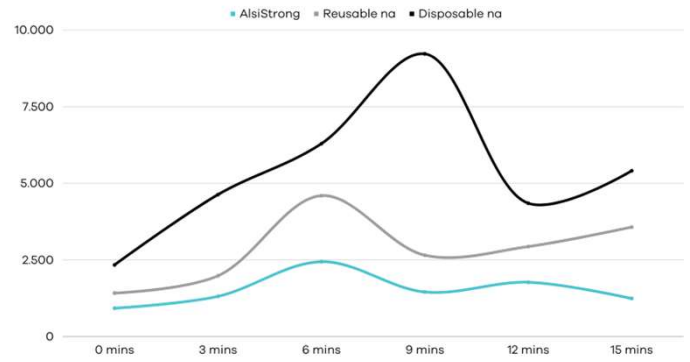


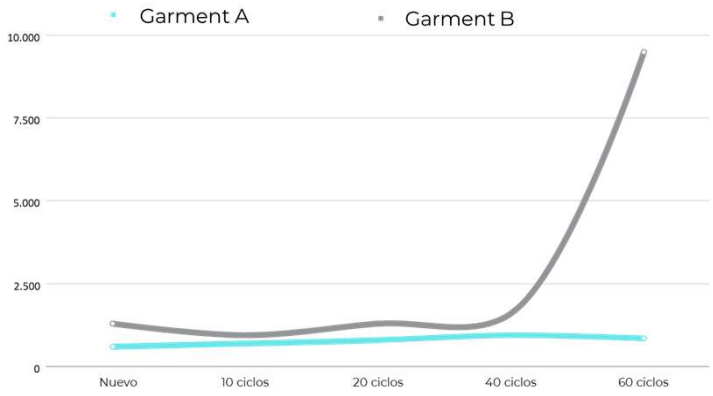
Impact of fabric selection and garment design in particle source strength –Body Box Testing

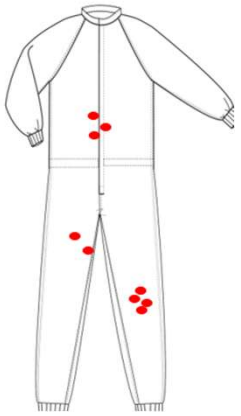


- Impact in risk of operations.
- Impact in particle load in the context of new ISO14644-19

- Risk operations
  - Freeze Dryer load and unload manually
  - Cleaning of Rabs and Isolators prior to disinfection







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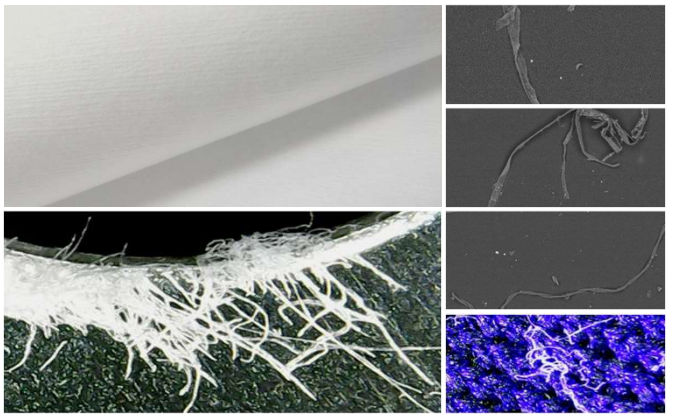
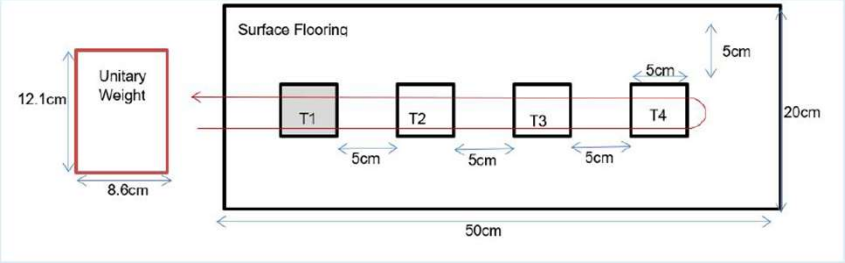


8. Detectability PoD	D	9. Proximity to Critical Area	RPN	10. Method To control de Hazard	11. Document	12. Corrective Actions	13. Current Status	14. Comments
Low		Machine non-contact parts but close to direct contact parts		Reduce number of wipers per task. Select higher quality materials. Establish testing confirmation frequency	SOP NNXX V-#	Sample surface after intervention with black wipe periodically	Under review	
				Train operators on SOP compliance frequently to ensure minimal use of wipes and unnecessary friction of material.	SOP NNXX V-#	See operators performing intervention. Retrain.	Completed	
Very Low		Machine non-contact parts but close to direct contact parts		Use 400/600 mm gloves and Sanitize freque	SOP NNXX V-#		Completed	
				Use high retention fabric in garment arms	URS CRGXX V#		Under review	

Qualifying Disinfectants

- Wider focus to complement surface coupon testing EN13697 with test that simulate practical application.
- EN 16615 (limited reach … but brings some light)
- Combination of contact time requirement + drying time under real conditions lead to require mechanical action to complement the action of certain biocides.



Test Organisms

Identification of the bacterial strain used:

Organism	Source	Number
Bacillus cereus	ATCC	11778

Surfaces Used

The following surfaces were used:

Surface	Source
Stainless Steel 316	Eurofins MGS Laboratories

Wiping

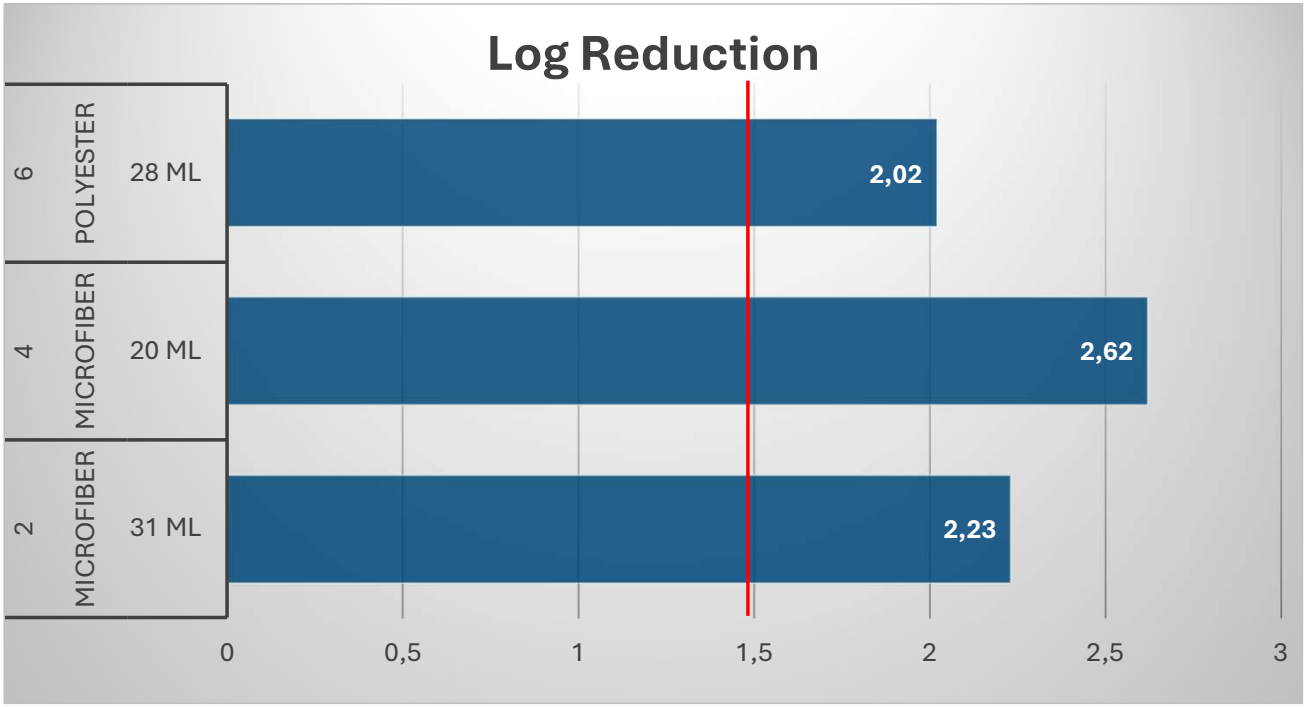
Impact of Mechanical Action in Microbial removal and carry over. Lessons from EN-16615. Impact

Effectiveness of residue removal with different wipe materials and impact in day to day activities

Over simplification vs task effectiveness: when one wipe for all is not the right choice

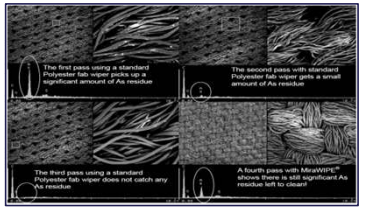
- Risk of particle contamination
  - Number of wipes
  - Material particle and fibres shedding
- Risk of microbial contamination
  - Duration of intervention
  - Repetition
  - Carry over

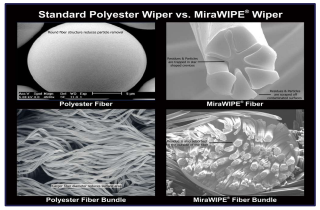
Example for 6% H_2O_2 with 5 minutes contact time (*Realistic* under LAF)

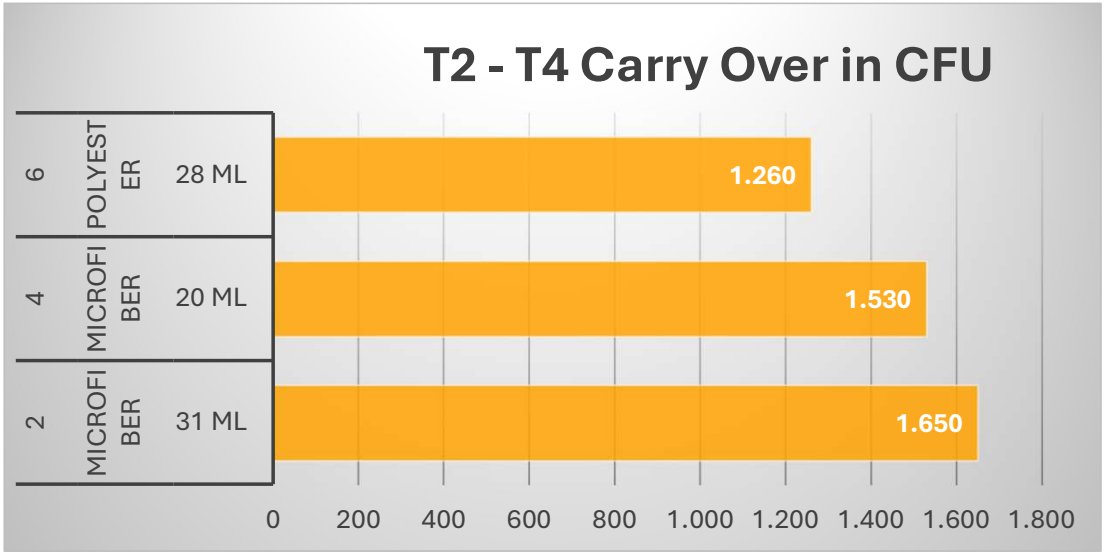


- Achieving maximum kill rate requires both contact time and mechanical action to meet the objectives.
- Advance materials provide extra efficacy in bioburden reduction

Typical EN 13697 Log reduction at that time below 1,5







- Increased risk of carry over of microbes if the biocide chemical cannot kill completely.

Detail analysis of SOPs → Risk Based sound practice in day to day activities:

- From clean to dirty /HACCP
- Unidirectional passes with overlapping.
- Frequent Wipe disposal with minimal contact with hand.
- Sanitize hands thoroughly and use mechanical action in the gloves if possible.

Thank you!

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