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Cleaning & Disinfection Regulations and best practices for sterile and non sterile manufacturing

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Science & Solutions for Life

Regulation Requirements: Cross-contamination Control Management for sterile

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NON EXHAUSTIVE LIST

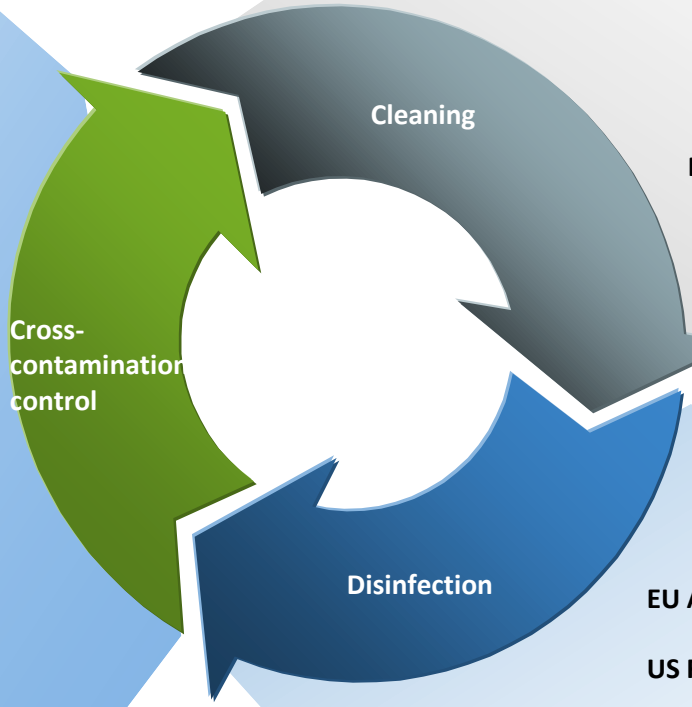
Contamination Sources :

I. Biological

- ✓ Microorganism
- ✓ Endotoxin

II. Chemical

- ✓ Product residue
- ✓ Cleaner residue
- ✓ Other residue



EU GMP:

- Annex 15
- Chapter 3 and 5
- EMA Health based

US GMP

- CFR 211.167
- ISPE Risk MaPP
- PDA TR 29 and 49

PICS/S 006

EU Annex 1

US FDA aseptic guidance and CFR 211.113

PICS/S 009

JP Guidance for sterile manufacturing

Who TRS961 – Annex 6

Regulation Requirements: Cross-contamination Control Management for non sterile

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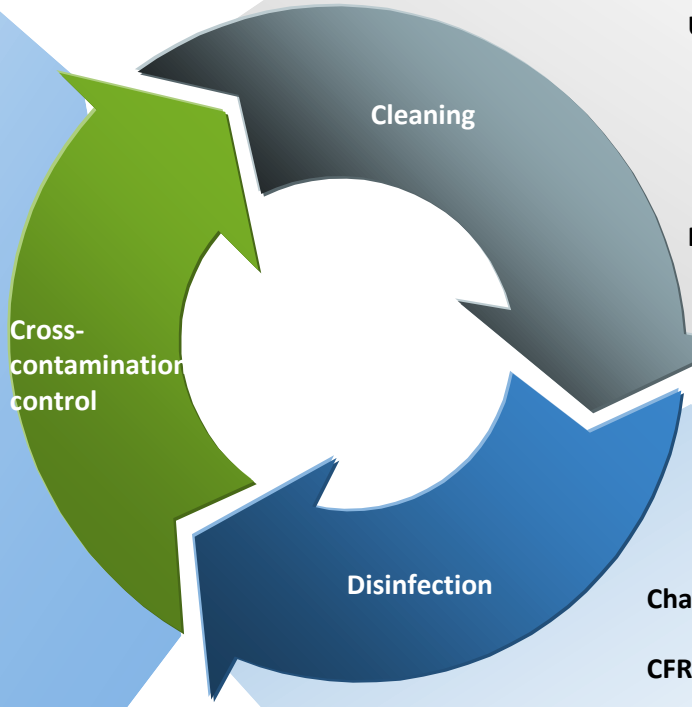

EU GMP:

- Annex 15
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- EMA Health based
- Eur. Ph. (5.1.4)

US GMP

- CFR 211.167
- ISPE Risk MaPP
- PDA TR 29
- USP <1111> & USP <1112>

PICS/S 006

Chapter 3 and 5

CFR 211.113

PICS/S 009

WHO TRS961

Cleaning program strategy for acceptance criteria setting

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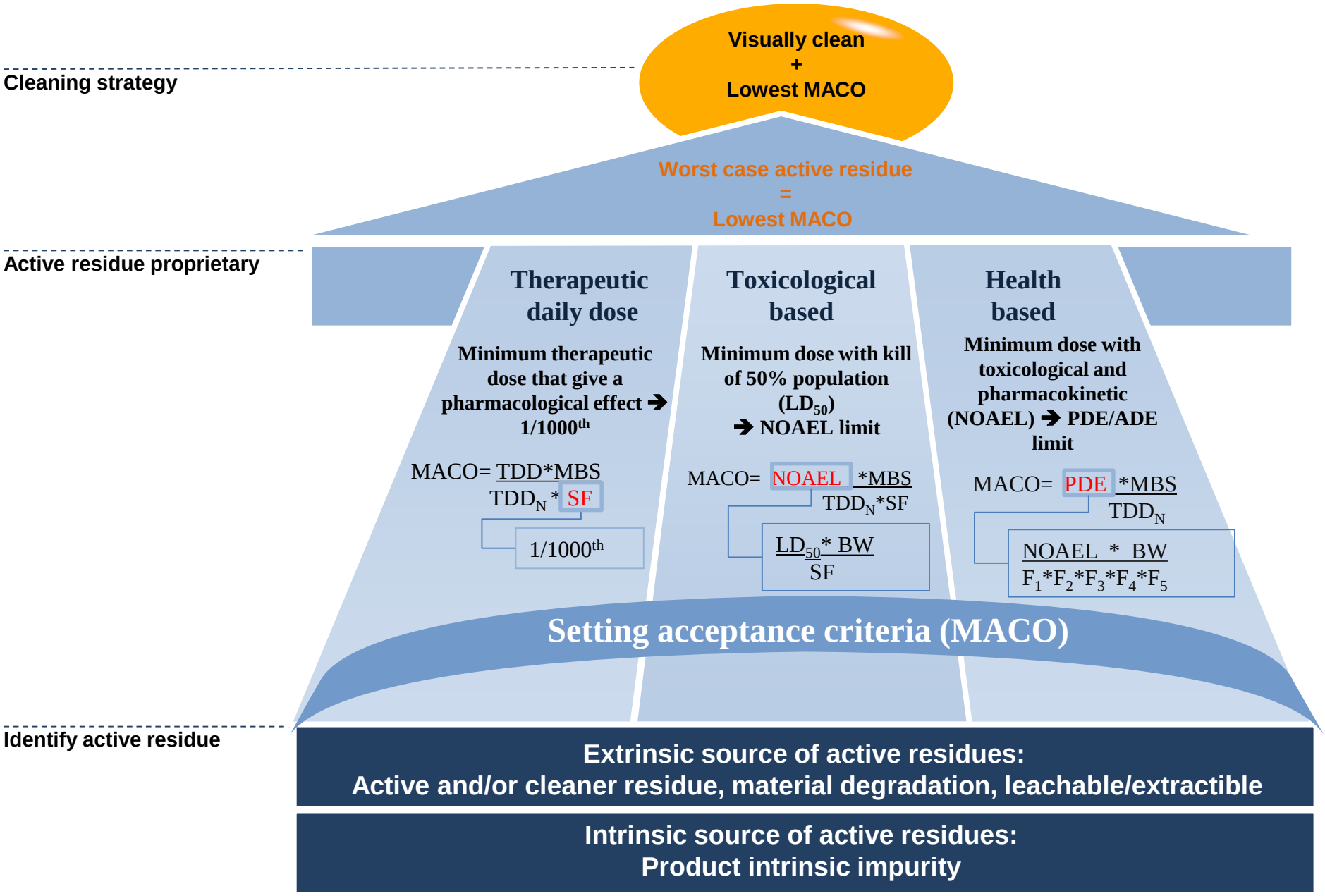

Annex 1 Future – What to Expect?

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SELF INTERPRETATION

Structure of the document :

- **double the number of pages**
- **add chapter about biofilm management, air quality**
- **Scope is only aseptic + no change of the title**
- **Current Technology: RABS, Isolators… LAF is accepted but…**

Emphasis on:

- **Root cause investigation, CAPA effectiveness and product assessment**
- **Personnel training and knowledge**
- **keep the operator away from the product – RABS, Isolators**

Align with other documents:

- **EU GMP and Eur. Ph. Water for Injection productions**
- **ISO 14644 except for 5µm in routine monitoring**

JP, PIC/S, FDA did share their comments to the EMA on the draft Annex 1

Source: EMA and PIC/S concept paper on Annex 1 (2015).

Factors of Microbial Contamination

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Influencing Factors

PRODUCT FORMULATIION

- A_w > 0.6 optimal for microorganism growth
- Viscosity can influence microorganism growth
- Absence of preservative in the product
- Product nature can enhance or inhibit microorganism proliferation

RAW and PACKAGING MATERIAL

- Set microbial limit for raw material, packaging material
- Control the impact of multi- use on the microbial growth

PERSONNEL

- Effective behavior and gowning procedure
- Effective cleaning and sanitization procedure

CLEAN ROOM and UTILITIES

- Adequate process/equipment/product flows
- Utilities systems under control and correctly maintained
- Effective cleaning and disinfection program
- Adequate housekeeping

EQUIPMENT

- Adequate equipment design and maintenance program
- Effective process equipment cleaning and sanitization program

CLEANING and DISINFECTION

- Adequate control of the CPP and CQA
- Ineffective cleaner or disinfectant against microbial contaminant

BEST WAY TO AVOID MICROORGANISM CONTAMINATION IS TO CONTROL THESE FACTORS

Parameters Affecting Cleaning and Disinfection Performance

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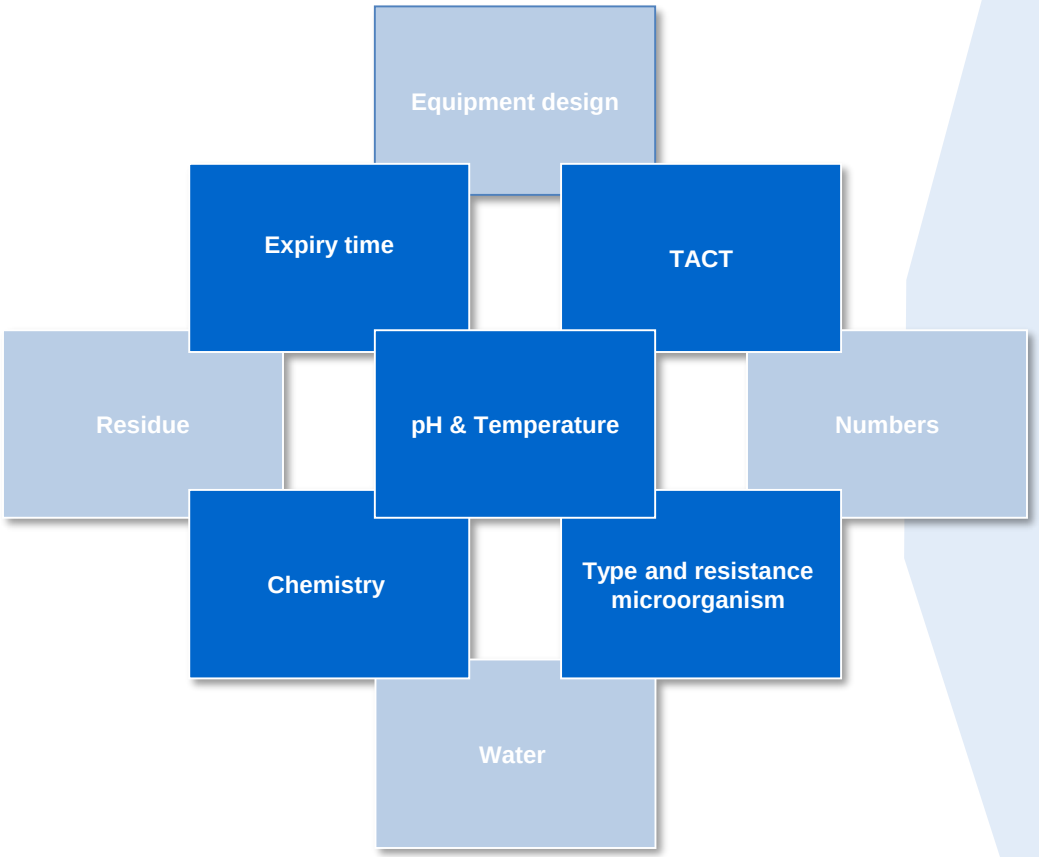

Equipment design	Design is one of the key aspect for effective cleaning and disinfection. 100% recovery should always be reached.
TACT	Time, action, concentration and temperature are considered critical process parameter for effective cleaning
Numbers	Disinfectant is more effective against low number of microorganism than high number
Type and resistance	Sporicidal agent kills spore and vegetative microorganism. However, non oxidizing disinfectant kill vegetative microorganisms and could kill some spore microorganisms
Water	Hard water could reduce efficacy of many disinfectants
Chemistry	The choice of the chemistry should depend on the residue nature and aspect
Residue	Residue should not interfere with the disinfectant efficacy. Rinse strategy should be put in place periodically.
pH & temperature	pH could influence the ionic biding of disinfectant, while temperature could affect the log kill over time (Q10).
Expiry time	The quality and flow of new ideas and ability to adapt and shape the organisation as needed

Efficacy of the disinfectant is demonstrated through performance testing

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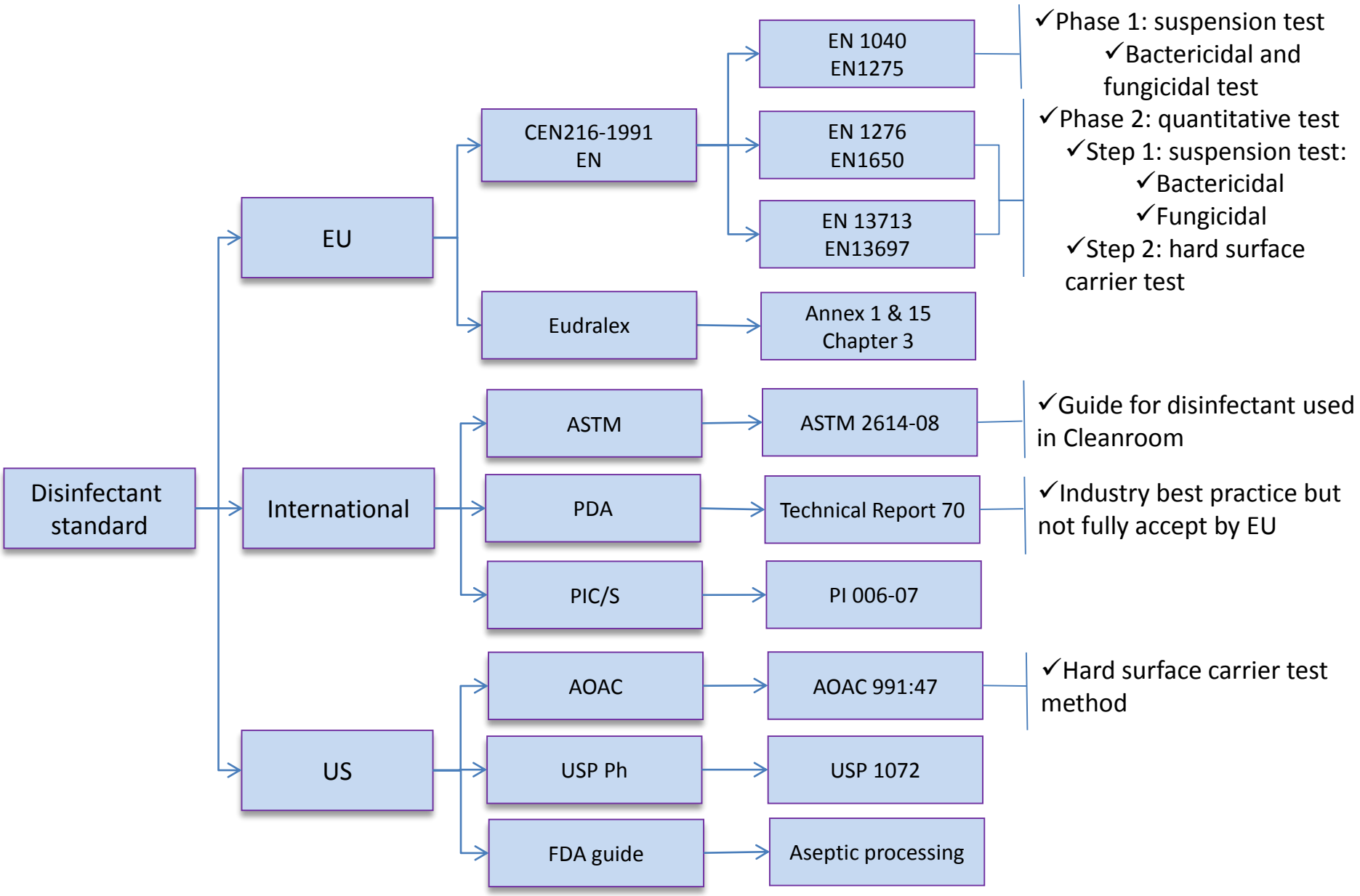
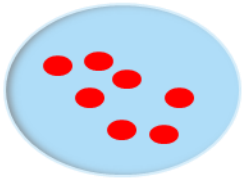
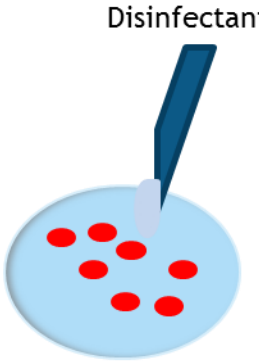
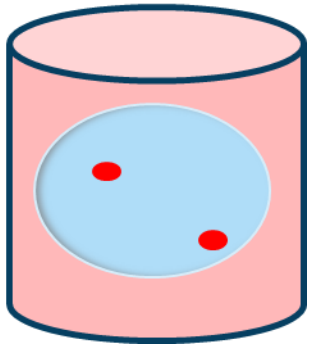
Regulation



Disinfectant testing







Step 1:
Test carrier

- ✓ 1- 3 controls:
  1. One positive control with no disinfectant
  2. One to confirm neutralization does not affect the bacteria
  3. Recovery validation control
- ✓ 1- 3 tests

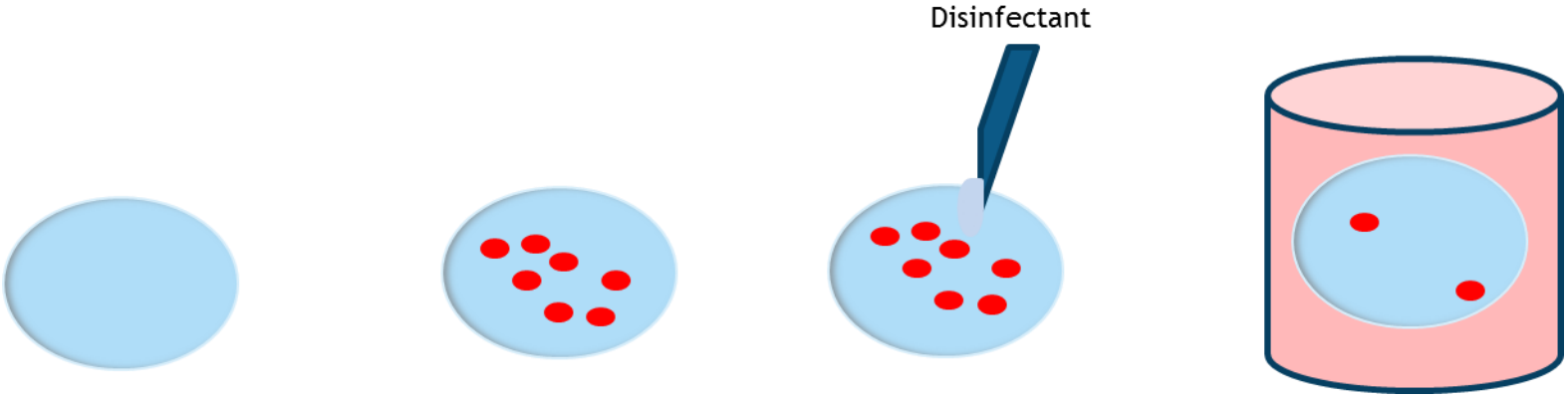
Step 2:
Contamination of the test carrier

Step 3:
Disinfectant applied in the concentration at which it is used in practice and left at appropriate time

Step 4 – 5 - 6:
Beaker of neutralizing solution before being rinsed.
Micro-organism present in the rinsing solution are investigated, followed by enumeration.

Log reduction= #bacteria control - #bacteria treated

Reference strains



Reference strains:

- ATCC 15442 : Pseudomonas aeruginosa
- ATCC 6538 : Staphylococcus aureus
- ATCC 10541 : Enterococcus hirae
- ATCC 10536 : Escherichia coli
- ATCC 10231 : Candida albicans
- ATCC 16404 : Aspergillus brasiliensis

Regulatory agencies expect isolate from actual environment.

Approach for Cleaning and Disinfection Process and non-Process Equipment

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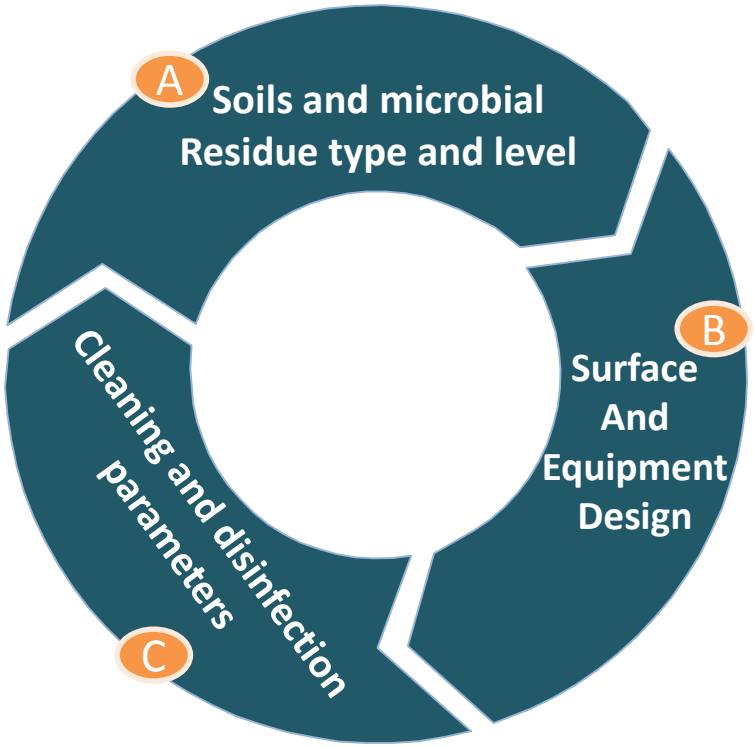
INDUSTRY PRACTICE

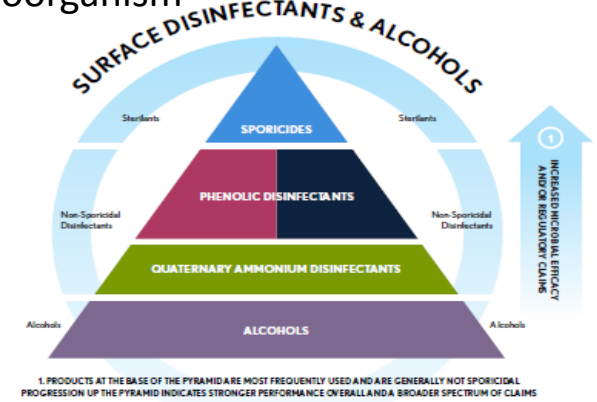


A Microbial residue: Is the cleaner agent used efficient

	Microorganism	Examples
More Resistant	Prions	Scrapie, Creutzfeld-Jacob disease, Chronic wasting disease
	Bacterial Spores	*Bacillus, Geobacillus, Clostridium*
	Protozoal Oocysts	*Cryptosporidium*
	Helminth Eggs	*Ascaris, Enterobius*
	Mycobacteria	*Mycobacterium tuberculosis, M. terrae, M. chelonae*
	Small, Non-Enveloped Viruses	Poliovirus, Parvoviruses, Papilloma viruses
	Protozoal Cysts	*Giardia, Acanthamoeba*
	Fungal Spores	*Aspergillus, Penicillium*
	Gram negative bacteria	*Pseudomonas, Providencia, Escherichia*
	Vegetative Fungi and Algae	*Aspergillus, Trichophyton, Candida, Chlamydomonas*
	Vegetative Helminths and Protozoa	*Ascaris, Cryptosporidium, Giardia*
	Large, non-enveloped viruses	Adenoviruses, Rotaviruses
	Gram positive bacteria	*Staphylococcus, Streptococcus, Enterococcus*
Less Resistant	Enveloped viruses	HIV, Hepatitis B virus, Herpes Simplex virus

B Material substrate, design and soiling condition

C Cleaning and Disinfection or Sanitization program against microorganism



Source: Image from McDonnell, "Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance" 2007, ASM Press

Thank You

For your listening

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