Lessons Learned from Industry on Contamination Control

Risk assessment approaches used in industry and possible planetary protection applications to crewed missions to Mars

Industrial Contamination Controls

Industrial Definitions

- Contamination: presence of material (e.g., chemical, biochemical, or microbiological) not intended to be part of a product or process.
- Contamination [or microbiological] control strategy: integrated set of controls, planned actions, and conditions that are designed to limit product contamination to defined criteria

Industries that rely on contamination control

Microbiological control

- Reduce or eliminate sources of organisms to protect patient or consumer safety
- Examples
  - Medical device
  - Pharmaceuticals
  - Food and water
  - Cosmetics
  - Agriculture

Control of contaminates

- Reduce or eliminate sources of impurities, particulates, residues etc. to protect product performance and safety
- Example industries include
  - Semiconductor
  - Lithium-Ion battery
  - Additive manufacturing
  - Optical and photonics

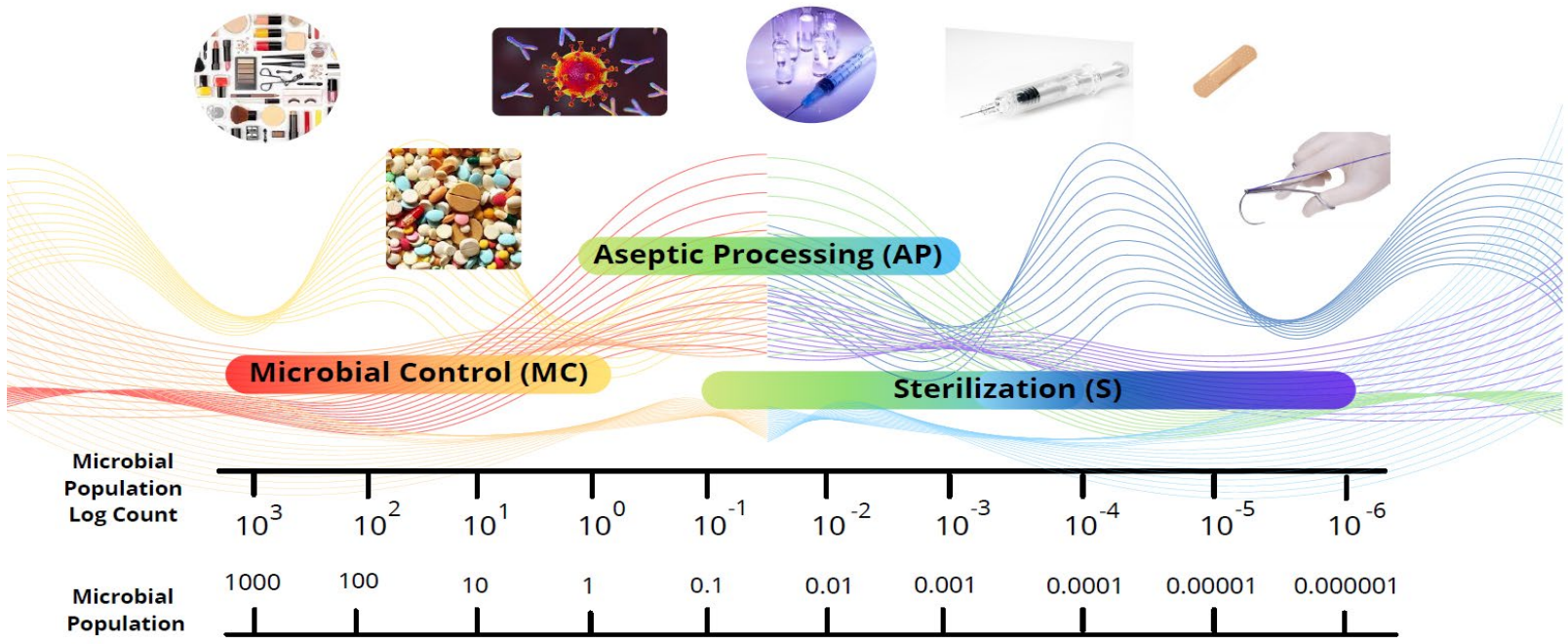
Contamination Control Focus for Products

- Risks include
  - Consumer (e.g., patient) harm
  - Product damage/spoilage
  - Other user (e.g., nurse) harm
- Risk-benefit examples
  - Equipment use
  - Surgical implantation
  - Vein-to-vein technology

Source of Contamination

Microbial Quality Assurance Options

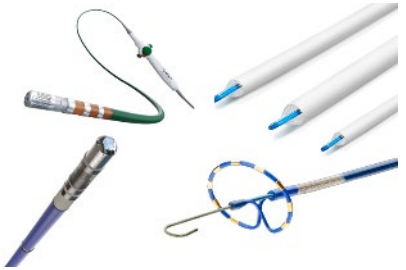
- Preservation
  - Remove water
  - Chemicals
- Microbial controls (exclusion)
- Cleaning
- Disinfection
- Aseptic Processing
- Sterile filtration
- Terminal sterilization

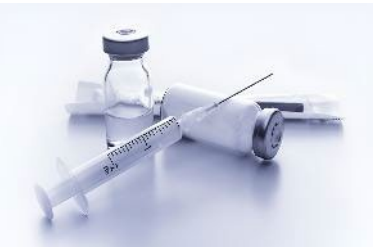


What is the appropriate level?

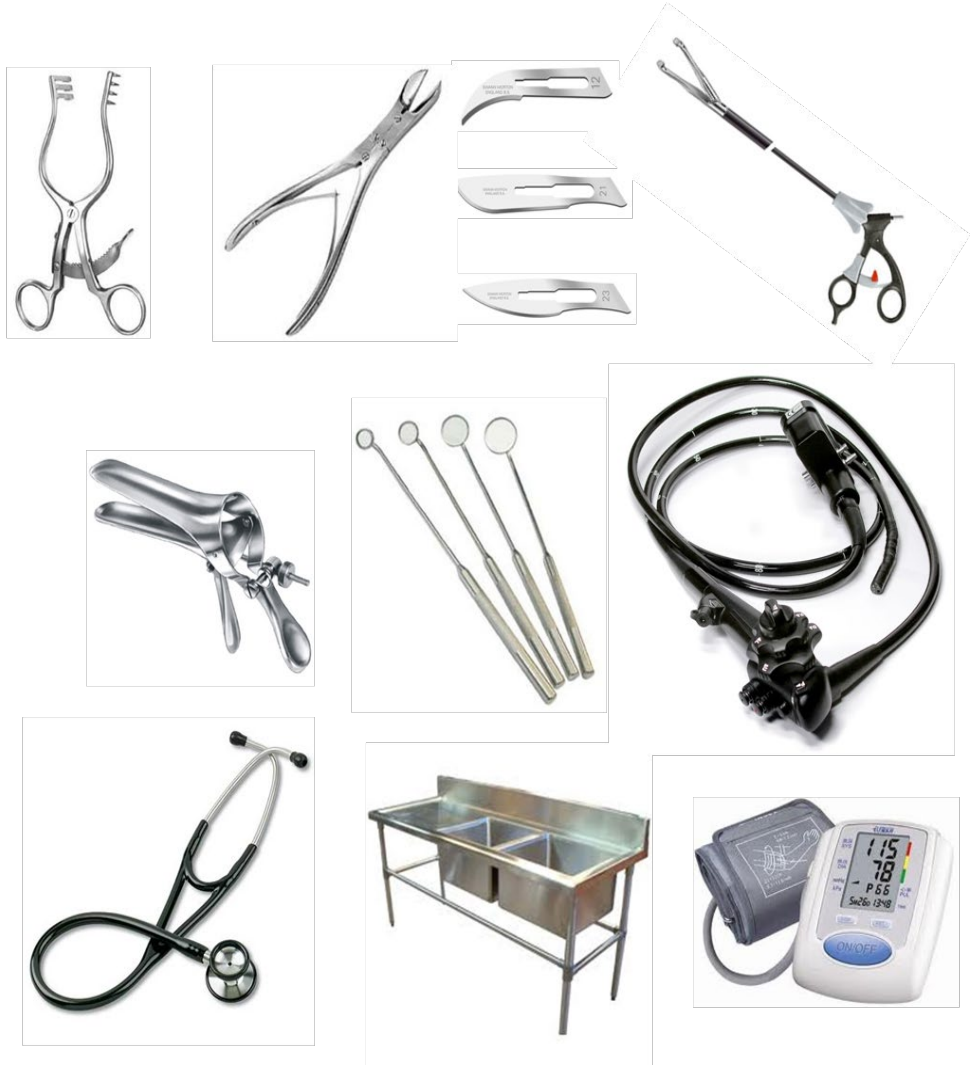
What is the right standard of care?

1. Primum non nocere
2. Balance of product safety, effectiveness and what is practical

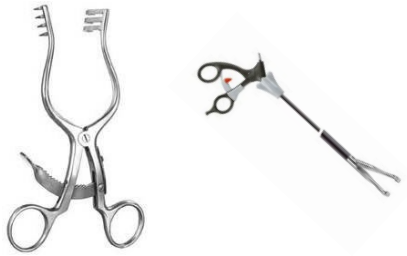


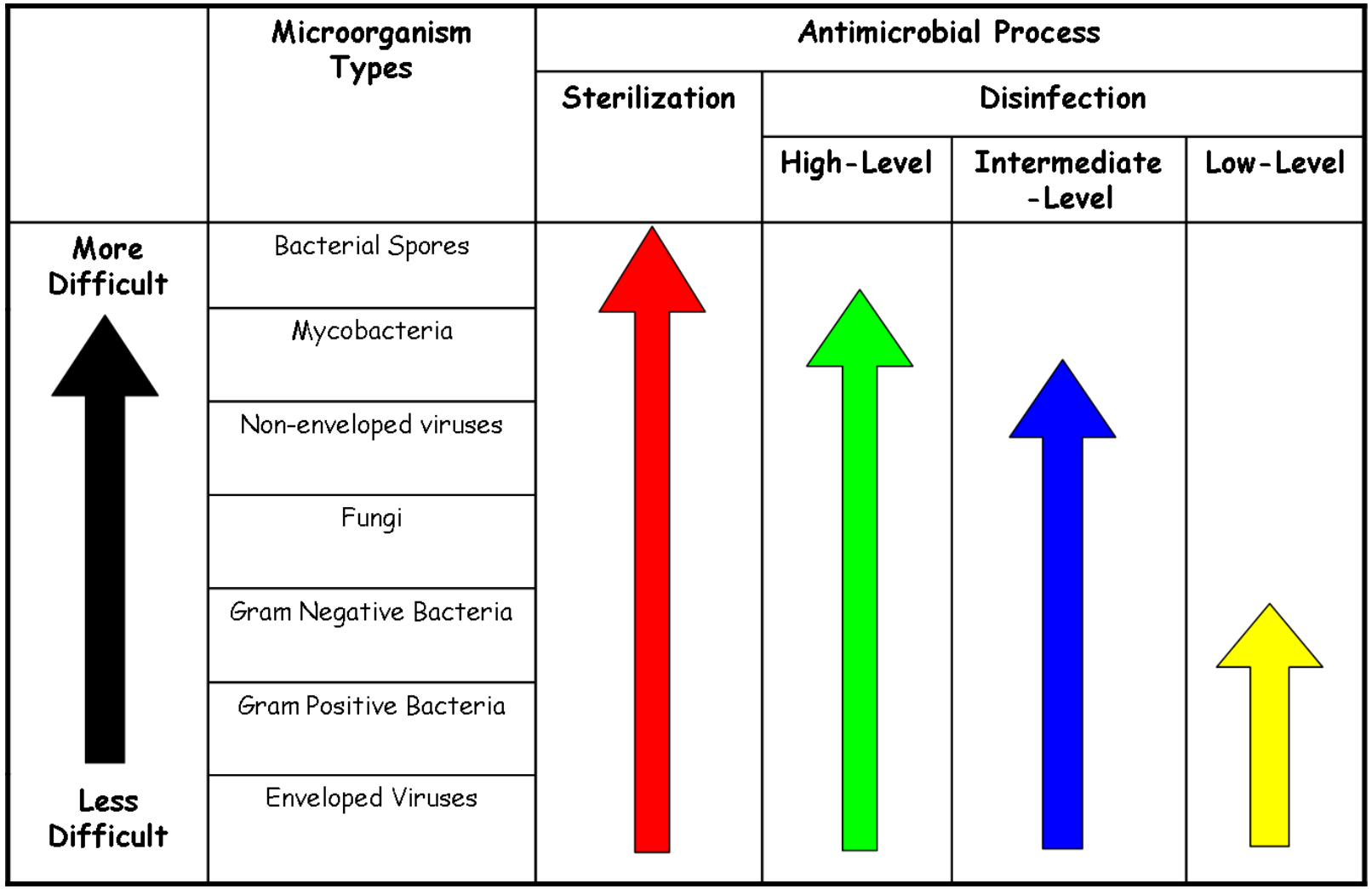


Example: Medical Devices and Risk



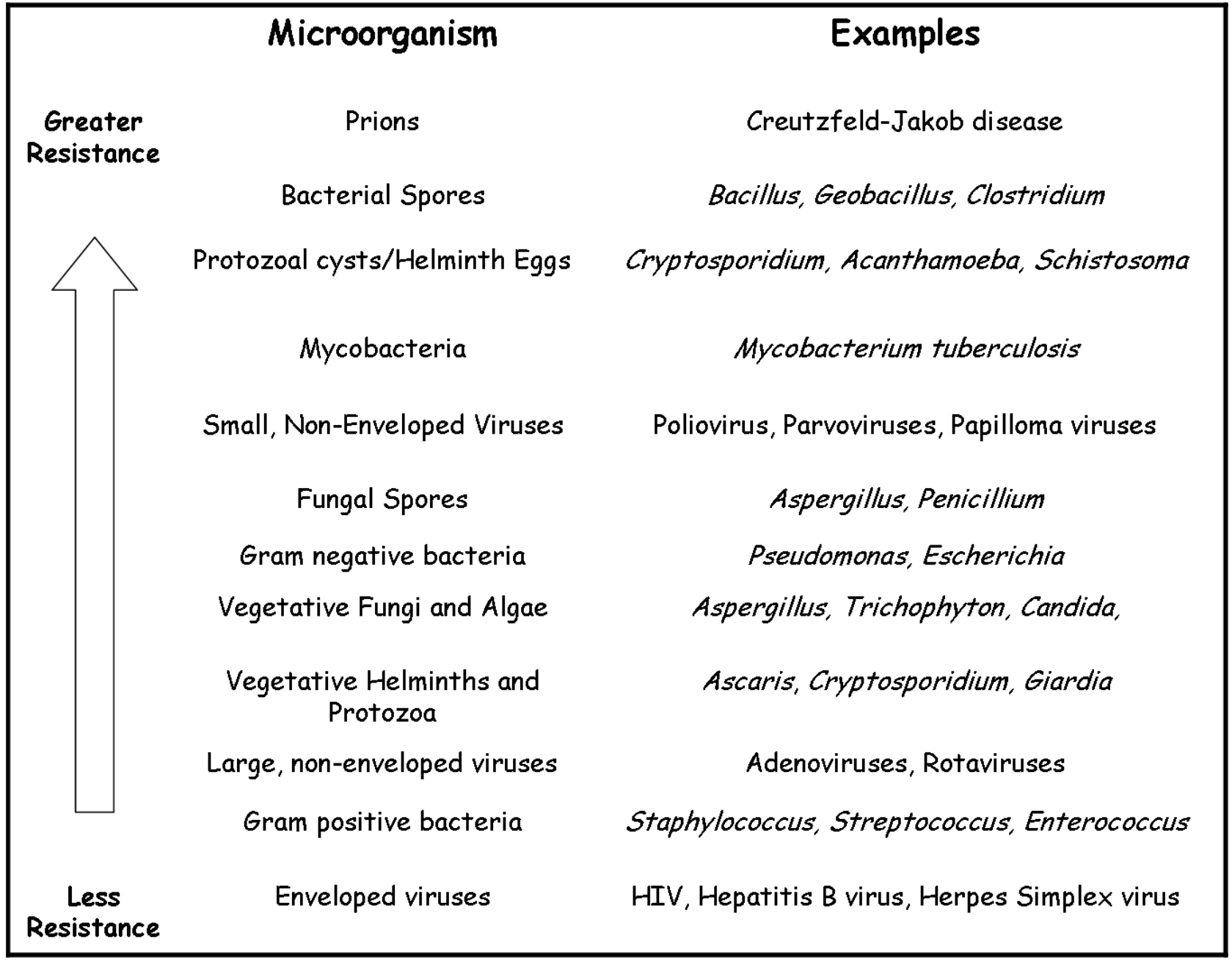
The Spaulding Classification

Patient Contact	Examples	Device Classification	Minimum Inactivation Level
Intact skin		Non-Critical	Cleaning and/or Low/Intermediate Level Disinfection
Mucous membranes or non-intact skin		Semi-Critical	Cleaning and Sterilization or High Level Disinfection
Sterile areas of the body, including blood contact		Critical	Cleaning and Sterilization

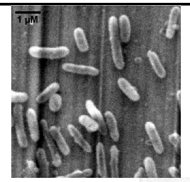
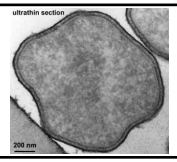
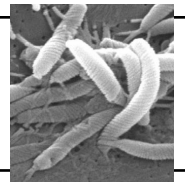
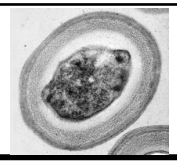

Microorganism Types
Antimicrobial Process
Sterilization
Disinfection
High-Level
Intermediate -Level
Low-Level
More Difficult
Bacterial Spores
Mycobacteria
Non-enveloped viruses
Fungi
Gram Negative Bacteria
Gram Positive Bacteria
Enveloped Viruses
Less Difficult

Challenges to the tradition

- When things have gone wrong: emphasis on cleanliness requirements
- Environmental considerations
- Device design or mis-use
- Microbiological challenges

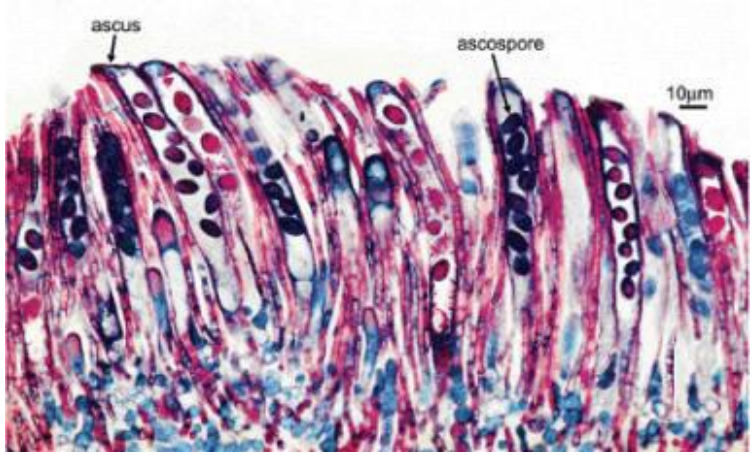

Microorganism
Examples
Greater Resistance
Prions
Creutzfeld-Jakob disease
Bacterial Spores
Bacillus, Geobacillus, Clostridium
Protozoal cysts/Helminth Eggs
Cryptosporidium, Acanthamoeba, Schistosoma
Mycobacteria
Mycobacterium tuberculosis
Small, Non-Enveloped Viruses
Poliovirus, Parvoviruses, Papilloma viruses
Fungal Spores
Aspergillus, Penicillium
Gram negative bacteria
Pseudomonas, Escherichia
Vegetative Fungi and Algae
Aspergillus, Trichophyton, Candida,
Vegetative Helminths and Protozoa
Ascaris, Cryptosporidium, Giardia
Large, non-enveloped viruses
Adenoviruses, Rotaviruses
Gram positive bacteria
Staphylococcus, Streptococcus, Enterococcus
Less Resistance
Enveloped viruses
HIV, Hepatitis B virus, Herpes Simplex virus

Extreme Resistance

Microorganism	Resistance
Thiobacillus 	Arsenic/Copper Resistance
Deinococcus 	Radiation
Pyrolobus 	Temperature (>85^{o}C)
Helicobacter 	Acidic pH (1-2)
Geobacillus 	All Biocides

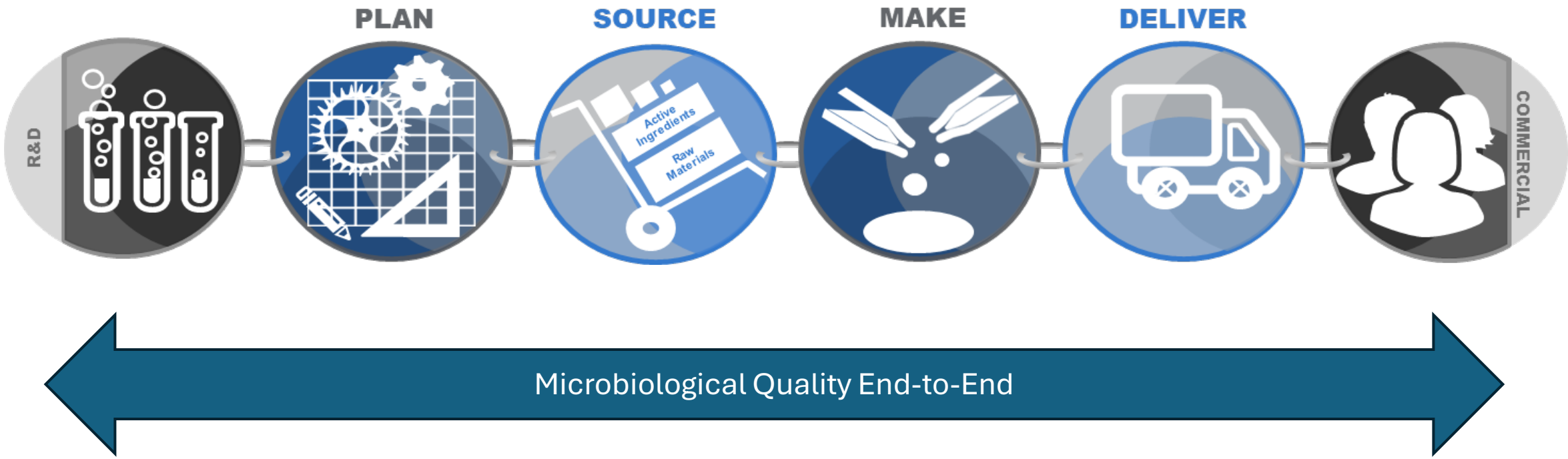
Common ‘Extremophiles’ In Manufacturing or Clinical Environments

- Biofilm-related (gram positive and negative bacteria)
  - Pseudomonads, ‘objectionable microorganisms’
  - *Bacillus cereus*
- Radiation, desiccation, *Deinococcus, Koruria, Roseomonas*
- Fungi
  - *Pyronema domesticum*
  - Proliferation: where there is moisture
- *Mycobacterium* sp.
  - Aldehydes
- Spore-forming bacteria and fungi (e.g., construction)
- Where there is pressure there is opportunity
  - Chemical use, UV light, temperature
- What we do not see
  - What we do not test for (classical growth media and temperature conditions)



Risk Assessment Philosophy

End-To-End Philosophy



What is *Proactive* Risk Management?

A forward-looking approach to identifying, assessing, and mitigating risks before they manifest into issues.

This process involves anticipating risks and implementing strategies to reduce their likelihood or impact.

Main Goal:

Anticipate and prevent potential unknown risks before they occur.

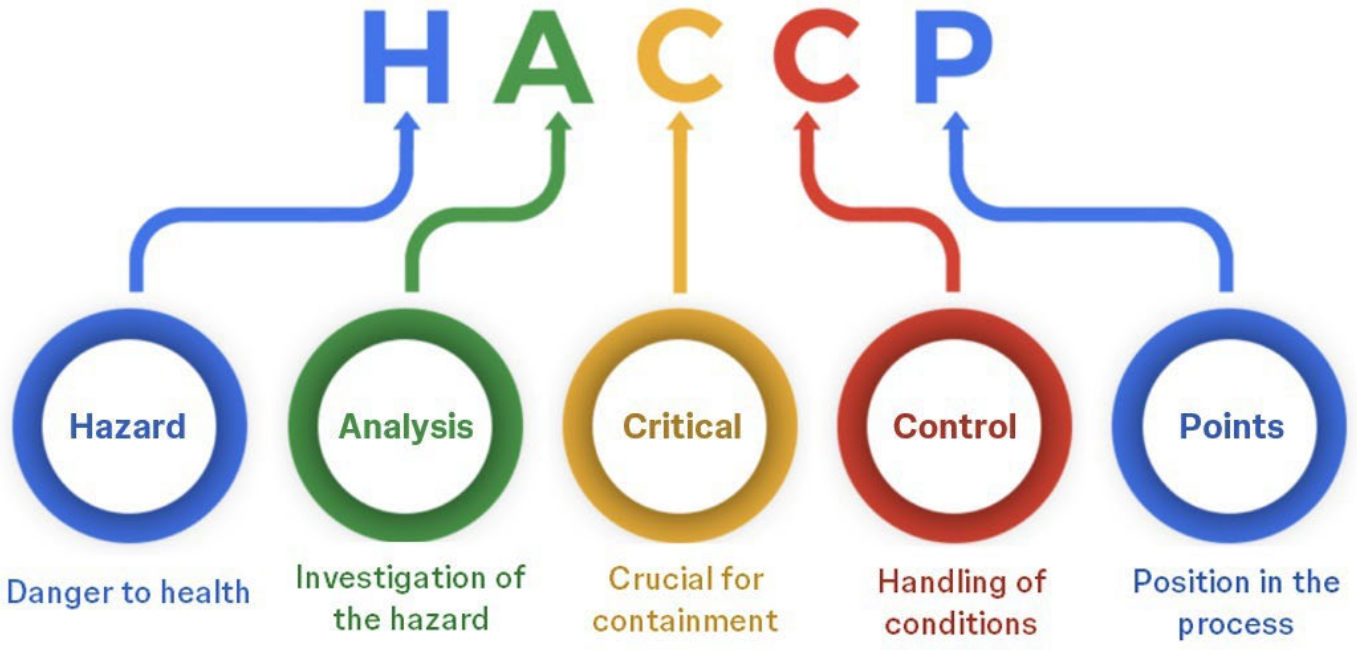
Regulatory Emphasis on Risk Management and Contamination Controls

Manufacturing Process Design

- Step 1: define your needs, and desired outcomes
  - Includes regulatory requirements
- Step 2: define your process and risk assessment
- Step 3: implement your process
- Step 4: maintain your process and process improvement

Proactive Risk Management Approach

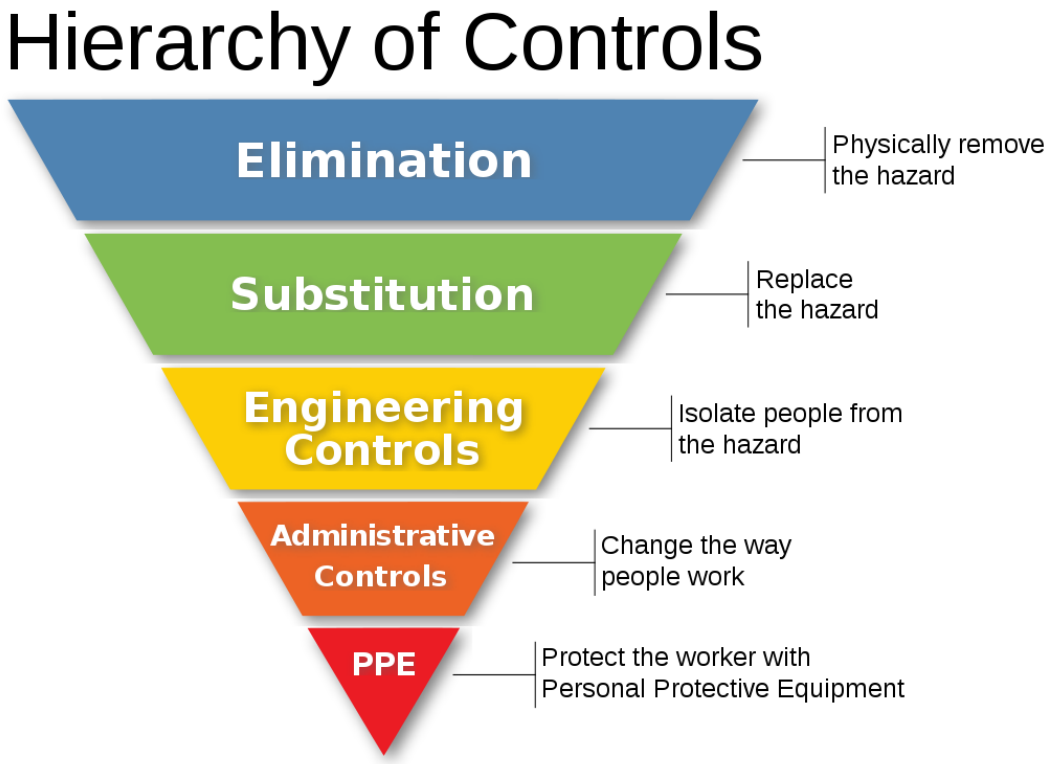
- Map your processes
  - Value Stream Mapping
- Identify hazards, prioritize risks
- Identify critical control points
  - Evaluate controls & tools
- Design, Implement & monitor controls
- Integrate risk thinking into daily decisions… Be proactive



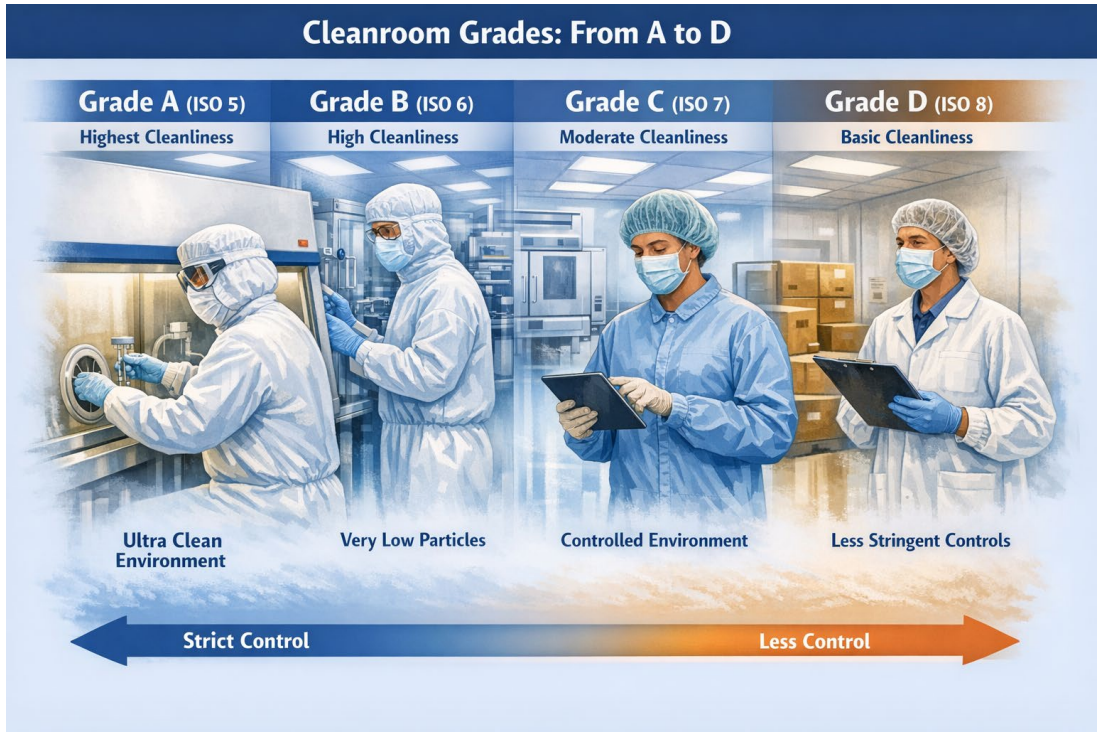

CONTAMINATION CONTROL STRATEGY
The Three Pillars of Contamination Control
FACILITIES
PERSONNEL
PROGRAMS
Controlled Environment
Trained & Compliant Staff
Effective Procedures

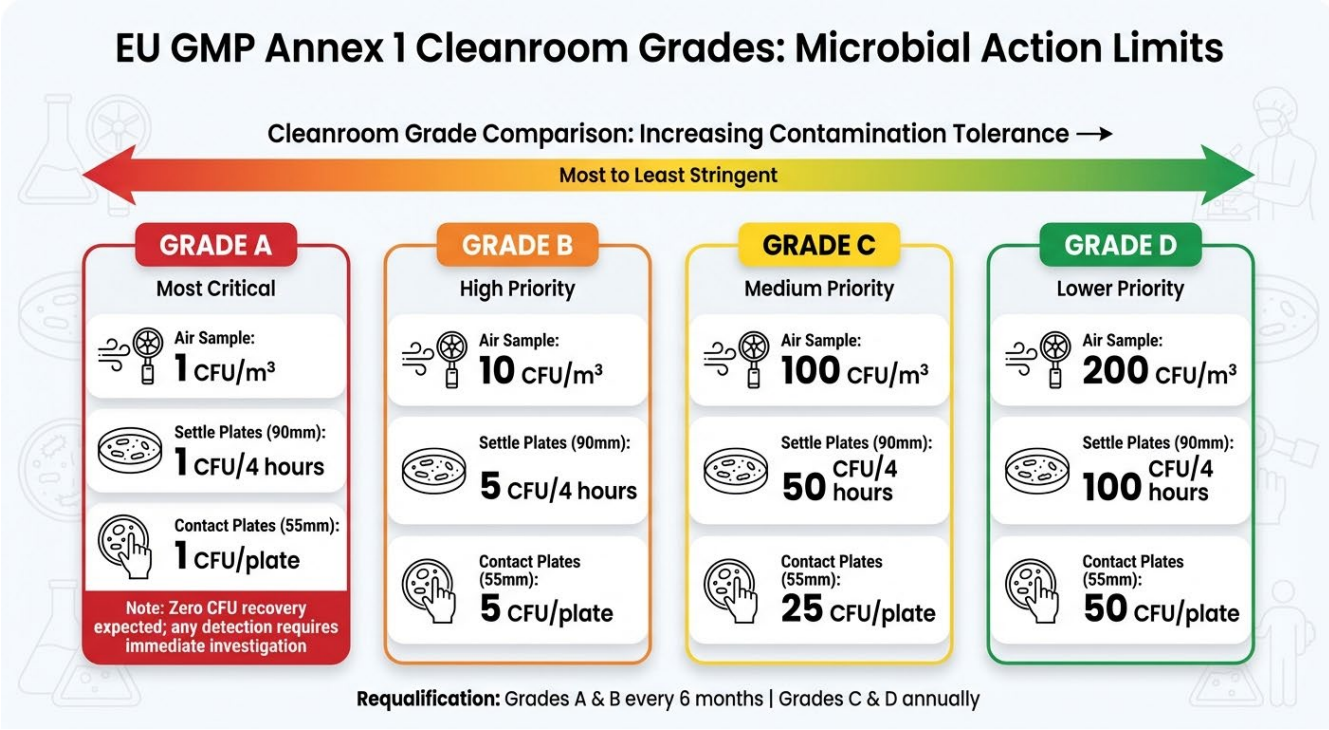
Hierarchy of Controls

- Concept originated in 1950 by the National Safety Council.
- The philosophy of this was simple, “controlling exposures to occupational hazards is the fundamental method of protecting workers.”
- This model was created to show that that design, elimination and engineering controls should be used and/or exhausted first, as they are the most effective when available.



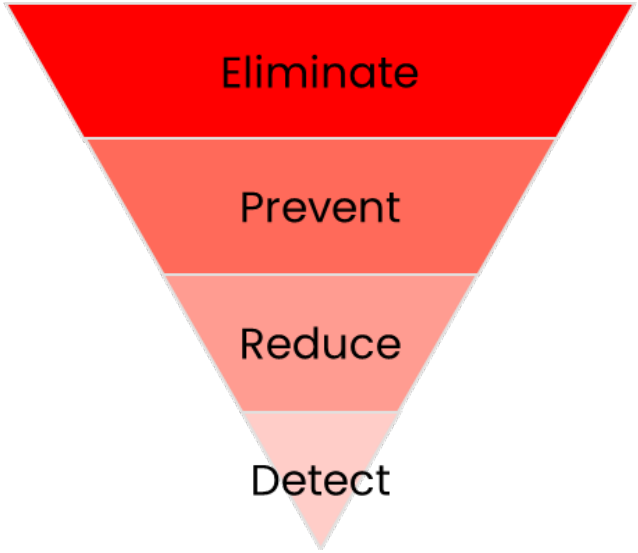
Cleanroom Classifications



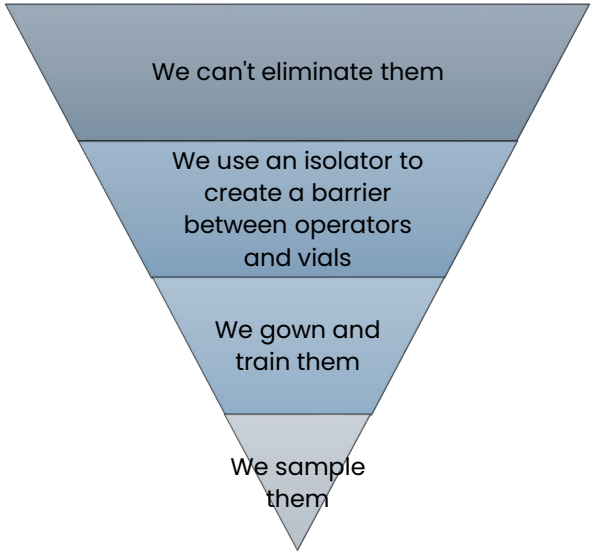


The Problems with People in Controlled Environments

Hierarchy of Controls



People



.....and we do not let them live there!

Proactive….Learning From Experience

- Outbreaks
- Literature
- Integration of guidance, standards and regulations

Innovation

- Proactive risk management
  - Contamination controls plans and reactive monitoring
  - Microbiological knowledge (limits of life/persistence, infection risk, risk-benefit)
- Rapid microbiological detection
- Isolator and clean zone design (e.g., robotics, glove-less isolators)
- Adoption of ‘new’ sterilization modalities or approaches (e.g., bioburden controls with terminal sterilization, combination approaches)

Sterilization

Sterility Assurance

- Sterile is defined as being free from viable microorganisms
- Sterility assurance level (SAL) is the probability of a single viable microorganism occurring on an item after sterilization, expressed as the negative exponent to the base 10

SAL for most medical devices is 10^{-6} or a 1 in one million chance of a single viable microorganism remaining on a device after sterilization*

*This does not take into consider the potential for that microorganism to cause an infection

Alternative SALs (10^{-5}, 10^{-4}, 10^{-3}) may be considered based on a risk assessment when 10^{-6} is not feasible

Definitions from ISO 11139:2018

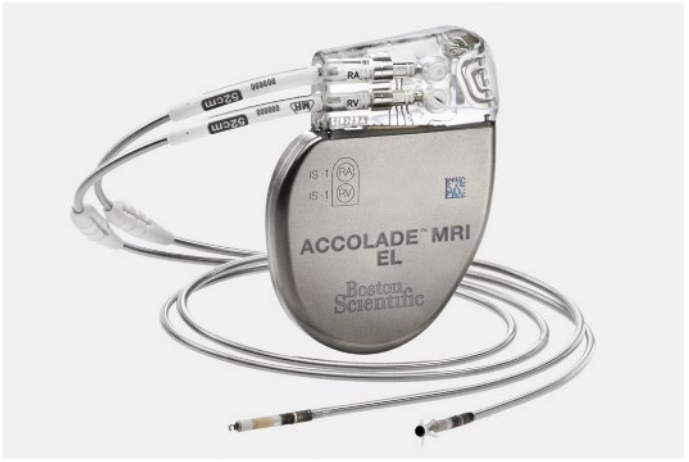
Terminal Sterilization: Risk profile

Input	Considerations
Intended use	What part of the body will it contact (Spaulding classification)
Product design and materials	How will the device itself present challenges to sterilization, e.g. long lumens, tight interferences, material compatibility, consistency
Manufacturing environment	Degree of human interaction, environmental monitoring, contamination controls
Bioburden numbers and types	What risks are associated with the bioburden in terms of both infection risk and resistance to the sterilization process
Validation method	Overkill processes vs bioburden-based validation methods
Sterilization method	Under or over delivery of process outputs and impacts to lethality and product performance
Residual risks	Any temporary (chemical residuals or degradation products) or permanent (material properties) changes post sterilization
Packaging	Stresses to the sterile barrier system pre, during and post sterilization including transportation up to point of use

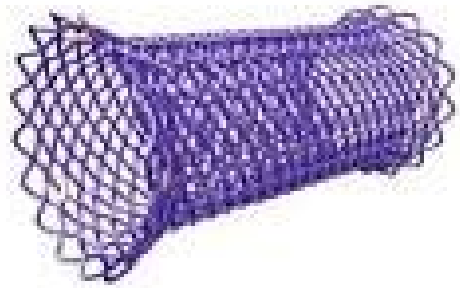
Terminal Sterilization: Risk profile examples

Input
Intended use
Product design and materials
Manufacturing environment
Bioburden numbers and types
Validation method
Sterilization method
Residual risks
Packaging

Surgical Gown –
limited patient contact

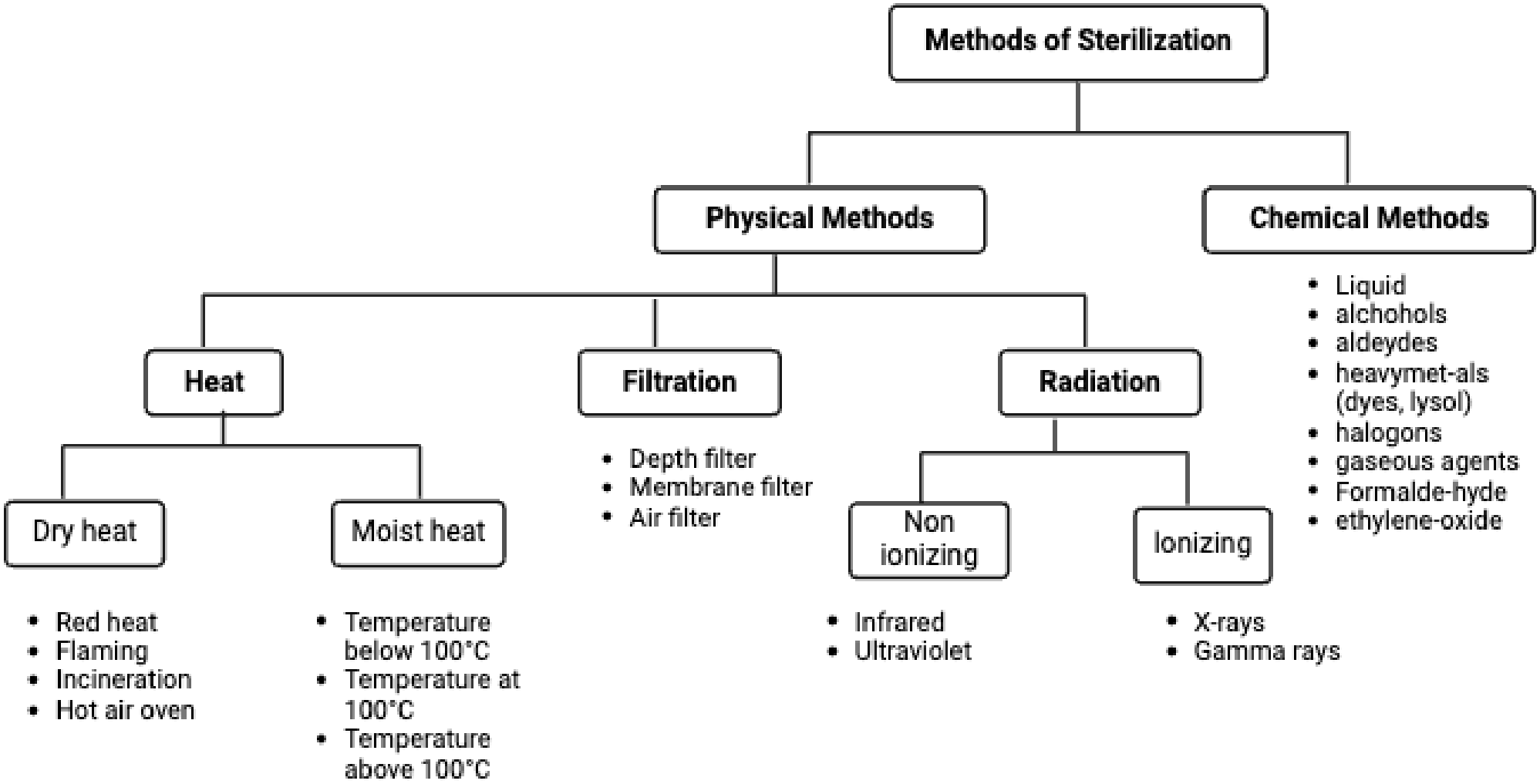


Implantable device –
robust construction
and overkill validation



Biodegradable stent –
Sterilization process impacts
material properties

Sterilization - Physical and Chemical methods



https://biologynotesonline.com/

Reframing the Conversation

Reframing the conversation

Forward planetary protection

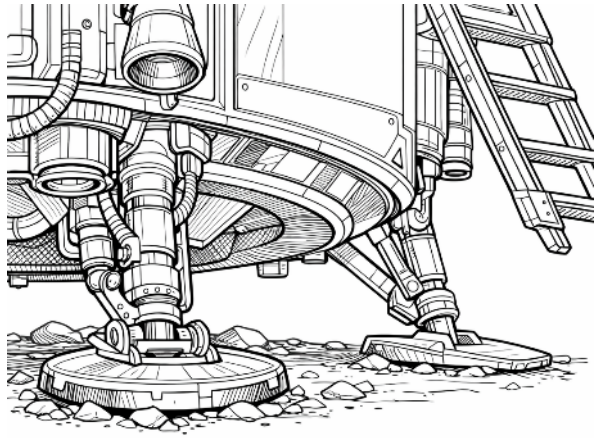
- Understand the risk of terrestrial organism growth in target environment considering what you are introducing (understanding microbiological quality), what processes you have used to remove or inactivate, and what mechanisms exist locally to additionally reduce (e.g. vacuum, temperature, UV, etc)

Backwards planetary protection

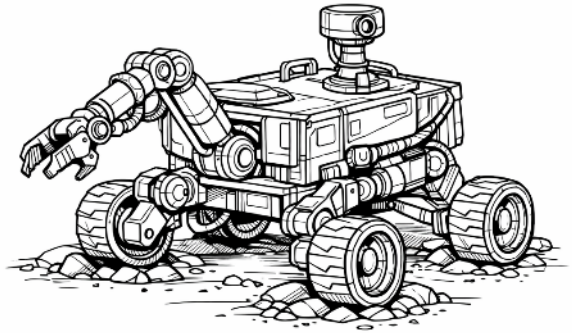
- Not necessarily possible to understand the risk to humans/biosphere
- “Spaulding classification” is high unless demonstrated otherwise
- Applicability of Sterility assurance level of 10-6 may not apply

Planetary protection: Risk profile examples

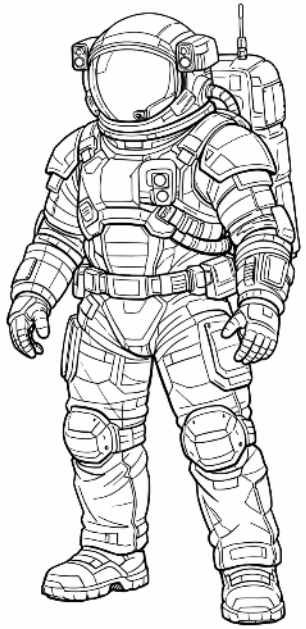
Input
Intended use Use environment
Product design and materials
Manufacturing environment Process environment
Bioburden numbers and types Microbiological challenges and detection
Validation method
Sterilization method In-situ decontamination method
Residual risks FPP and BPP
Packaging Barrier systems



Outside of spacecraft – FPP considerations



Robotic sample retrieval – FPP critical for protected regions, BPP for crew



Planetary EVA suit – FPP and BPP potential

Mars Missions

- Fact: We are going to Mars
- Assume that contamination will happen
- What is the practical risk, based on our current scientific knowledge?
- How can we reduce this risk and maintain the initial scientific integrity of the environment?
- Think short term and long term