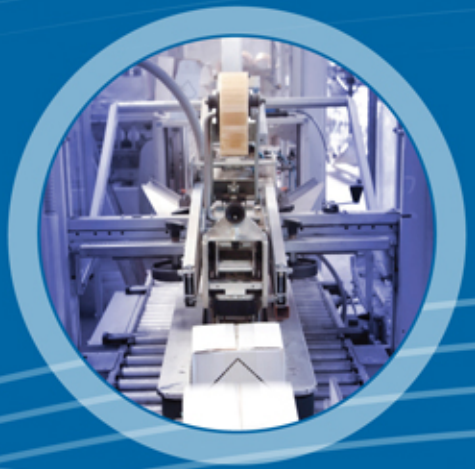
Connecting People, Science and Regulation

Reliability of H_2O_2



Simone Bläsi

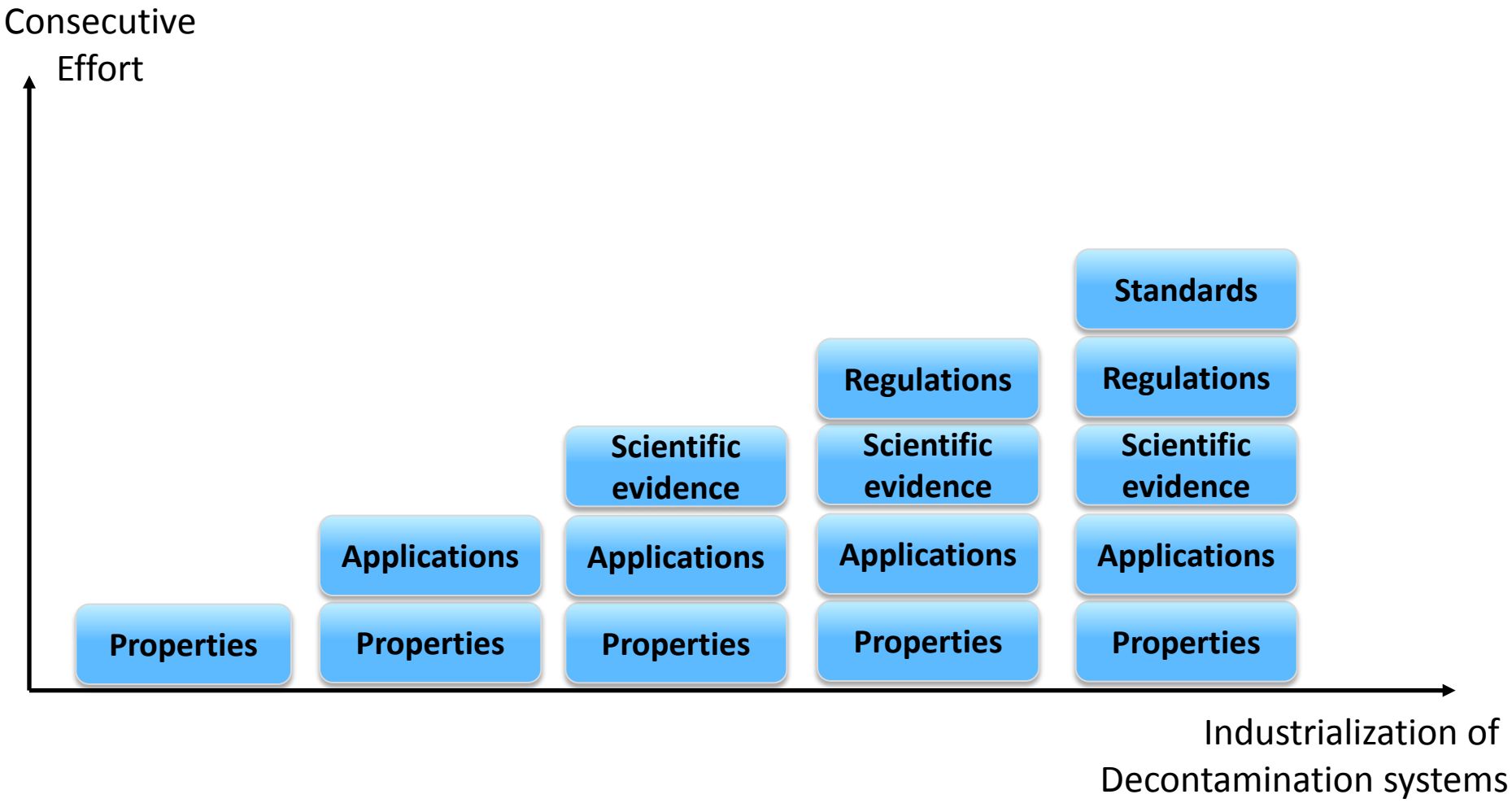
How it all began…

… the field of clean room equipment and construction of **isolators** for the pharmaceutical chemical industry …

Depending on customer request, you are responsible for the **qualification** and optimization of **H_2O_2 decontamination systems**, their documentation and the training of our customers.

Furthermore …

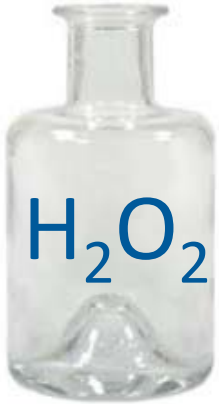
Development of Reliability



Development of Reliability

H_2O_2 in general

Available concentrations:



- 50%
- 35%
- < 8%

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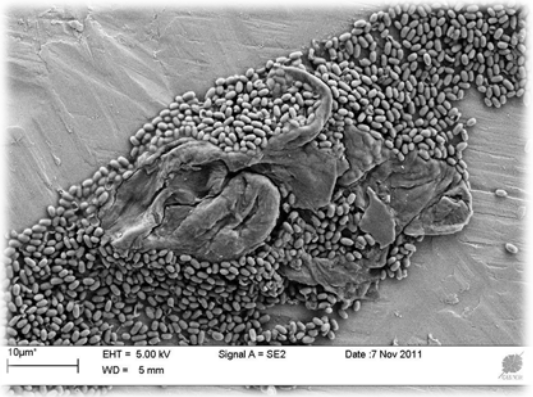
Effect:

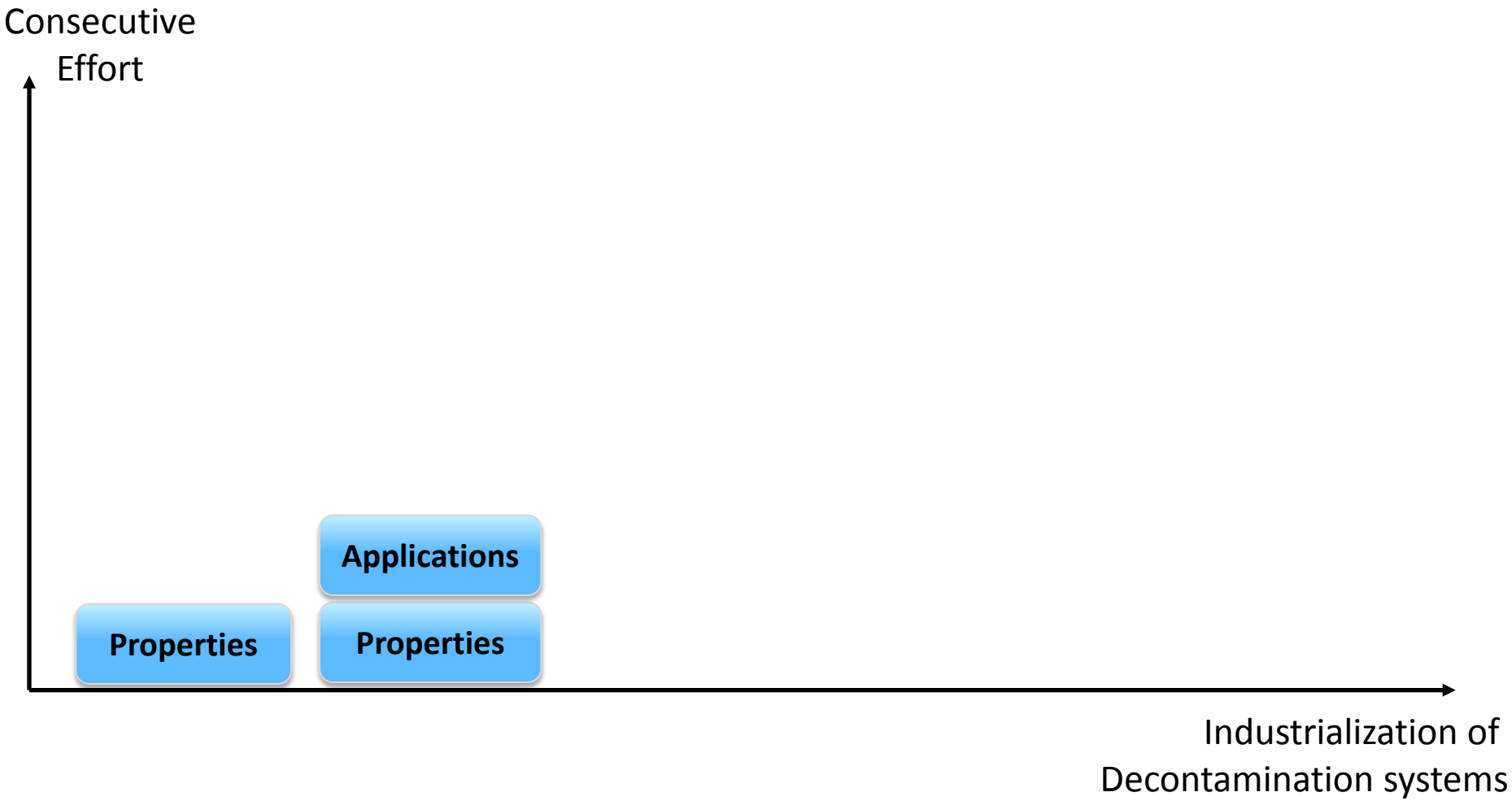
- Microbiocidal
- Sporocidal
- Fungicdal
- Virocidal



Chemical properties:

- Water-miscible
- Non penetrating
- Boiling point: 108˚C, 35%
- Strong oxidizing agent
- End products: O_2 + H_2O
- Non-hazardous
- Low toxicity
- Non-corrosive
- Non-persistent
- TLV: 1 ppm

Development of Reliability



Applications

General use:

- Wound desinfektion
- Food industry
- Pharmaceutical industry

Spray & Wipe

Nebulization

Vaporization

Isolator technology

Room disinfection

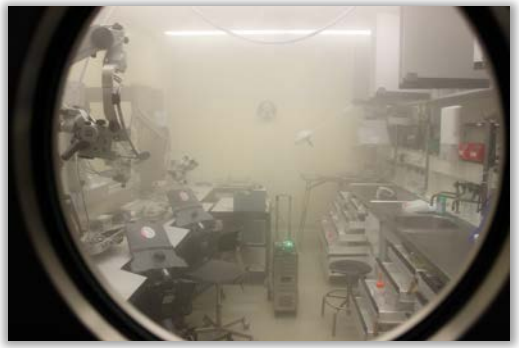
Surface decontamination

Applications

Nebulization

- Production Areas
- Aseptic rooms
- Open/Closed RABS
- Material Air Locks
- Incubators
- Microbiological Labs
- Clean bench
- Hospitals
- Sickrooms

Production Area



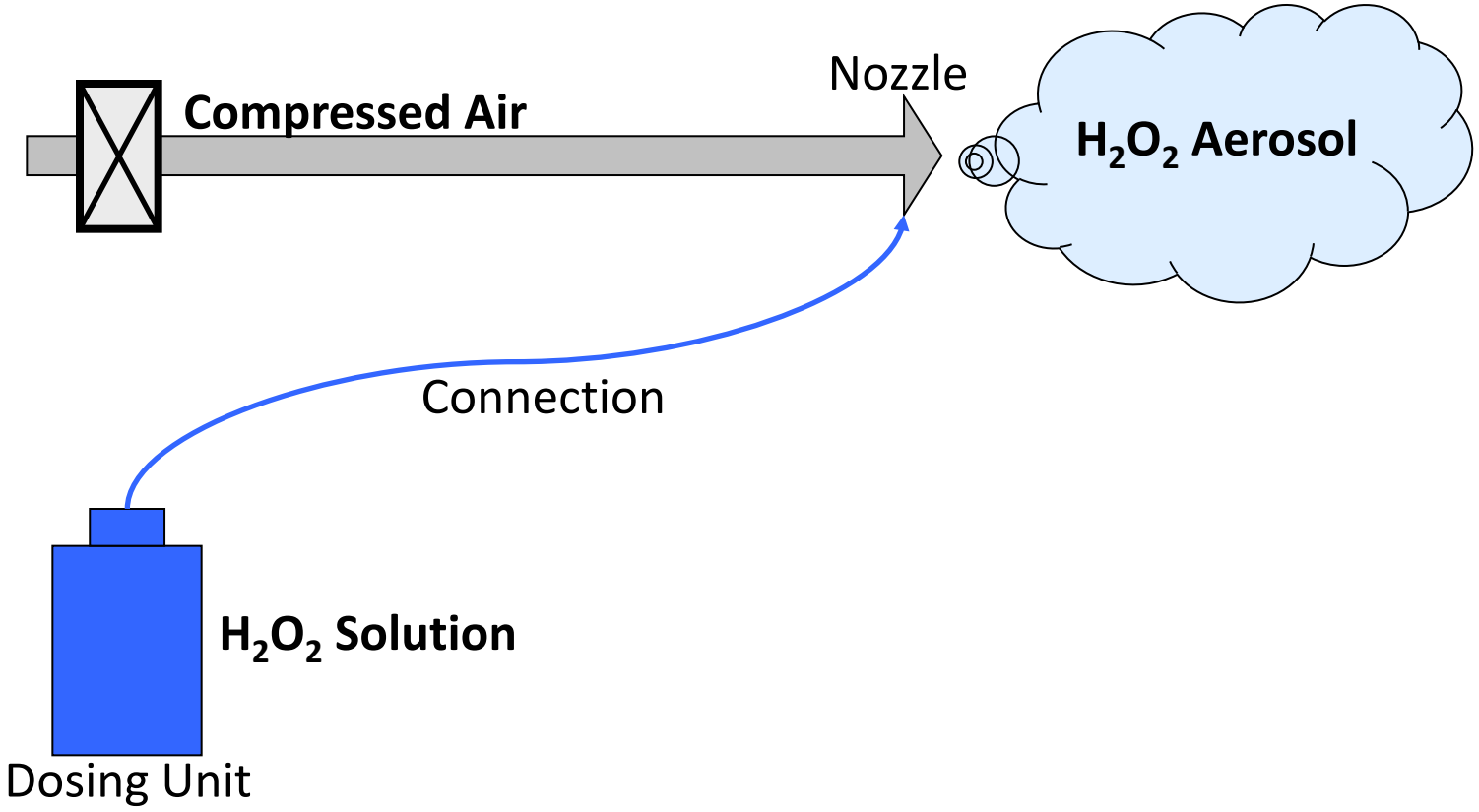
Microbiological Lab

RABS

Clean Bench

Material Air Lock

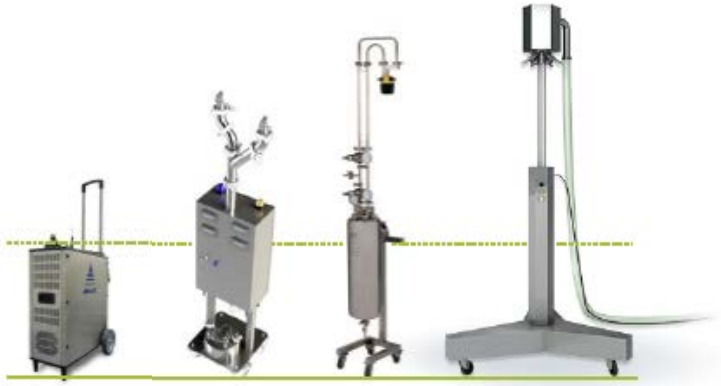
Applications



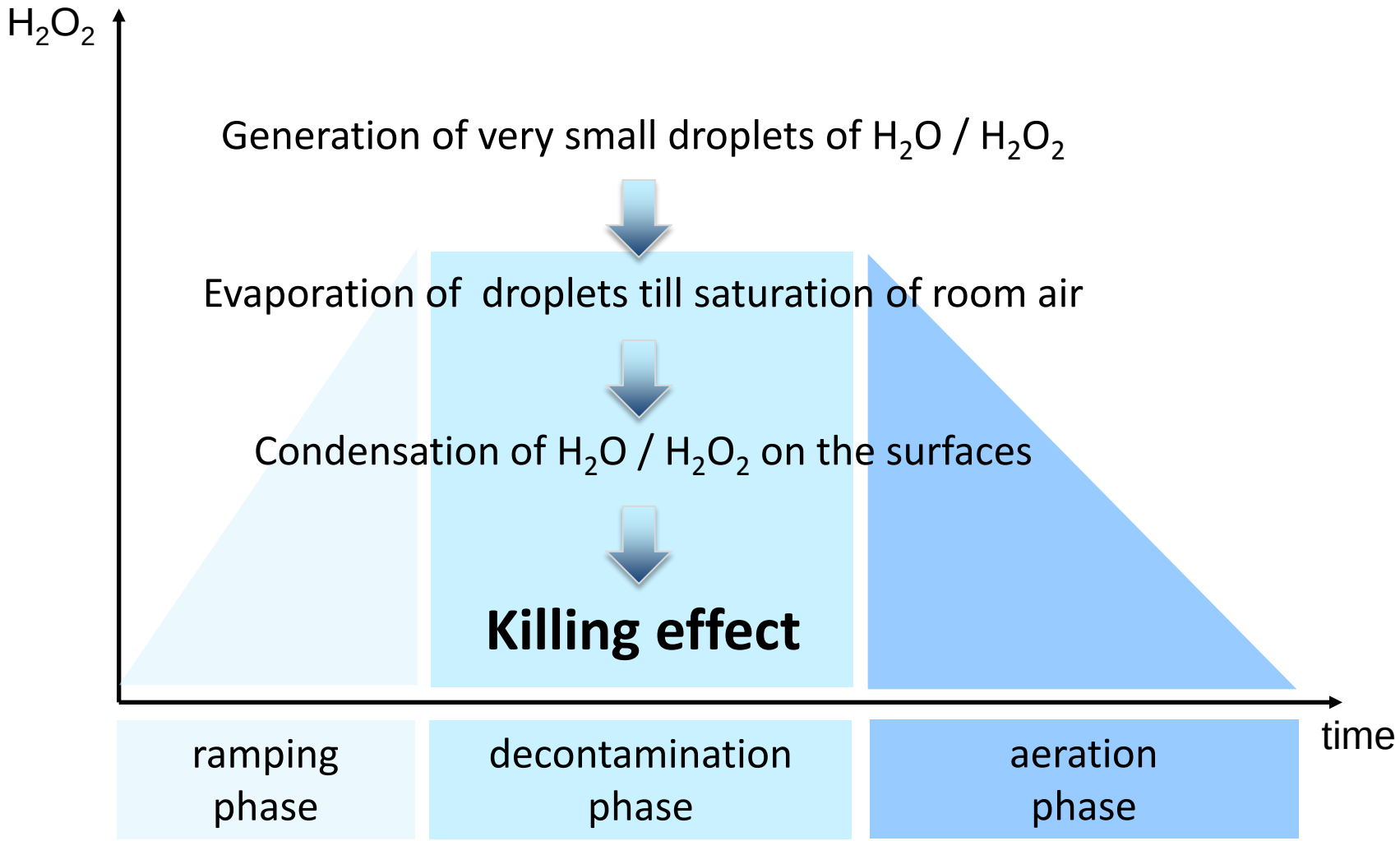
Applications

Properties of Nebulization (12% - 50% H_2O_2)

- Nebulized by nozzles, compressed air
- Efficient distribution of biocide, good access of difficult to reach areas
- Scalable for small and large rooms, no external fans necessary
- Minimal requirements for environmental conditions; no preconditioning
- Fast and robust process
- Cycle duration approx. 10 min - 3 h
- Excellent material compatibility
- Process validation by BIs and CIs
- Reproducible 4- to 6-log sporicidal reduction (Total Kill)



Applications

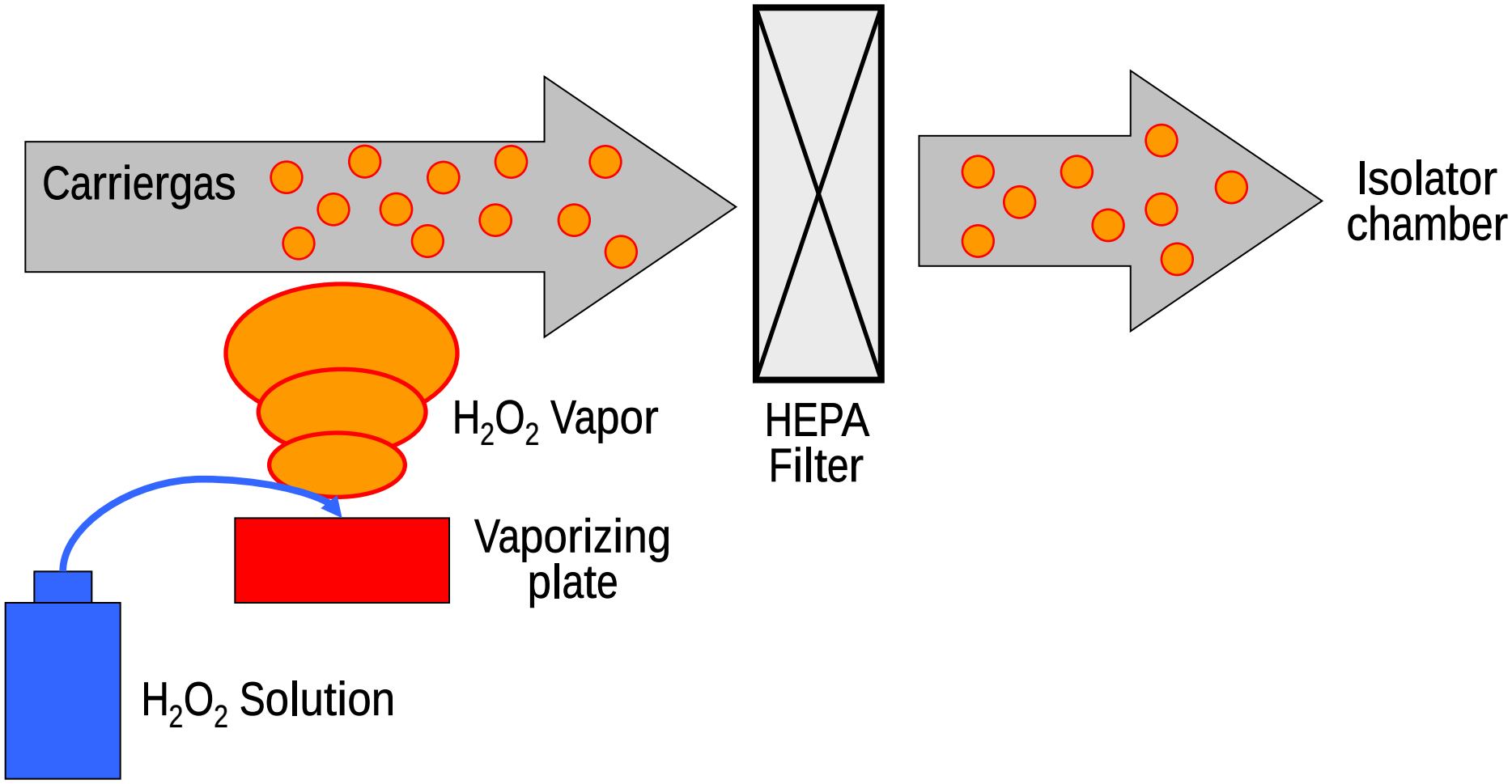


Applications

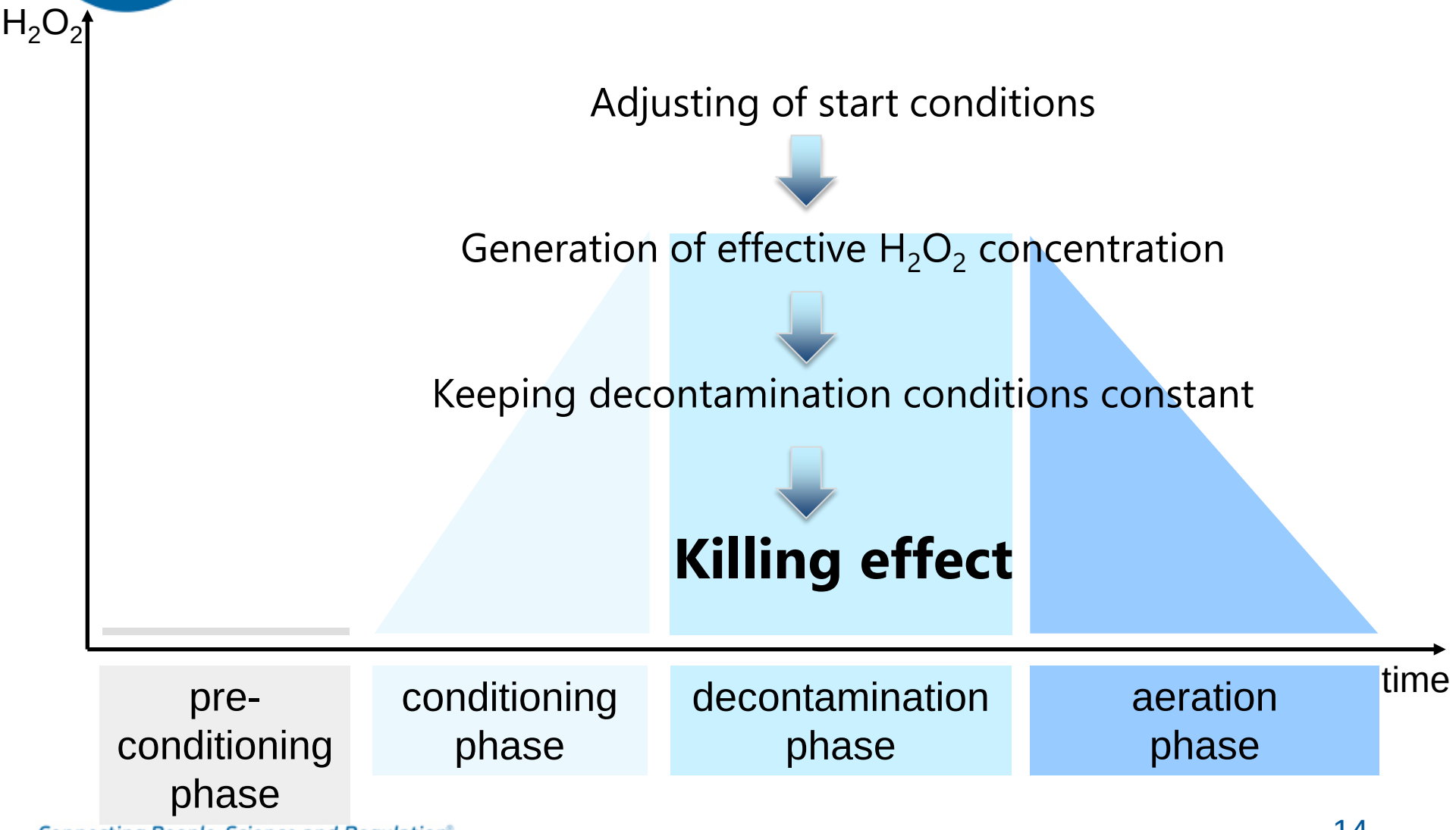
Vaporization

- Sterility testing
- Processing or production of aseptic and toxic compounds
- Room decontamination

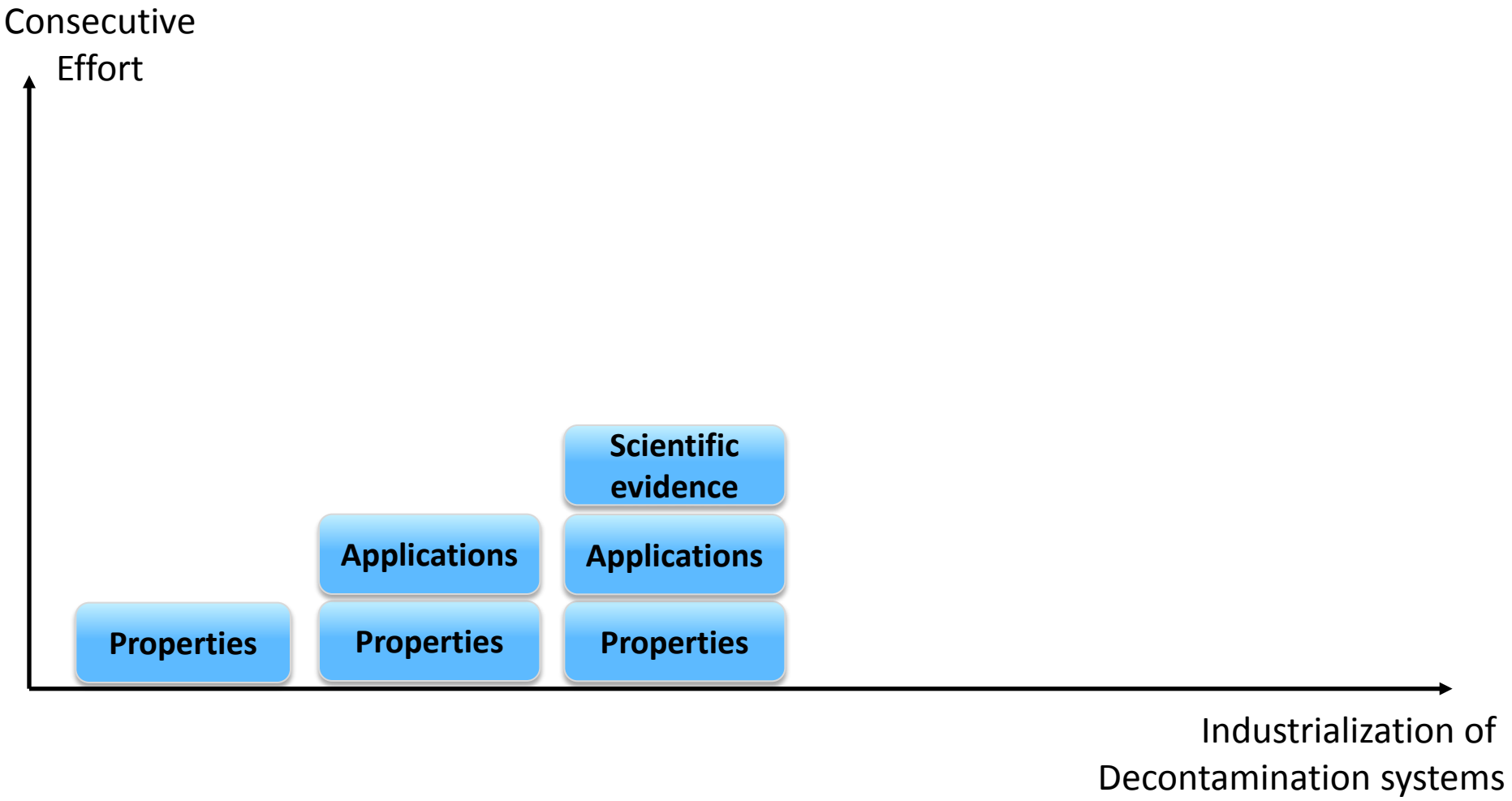
Applications



Applications



Development of Reliability

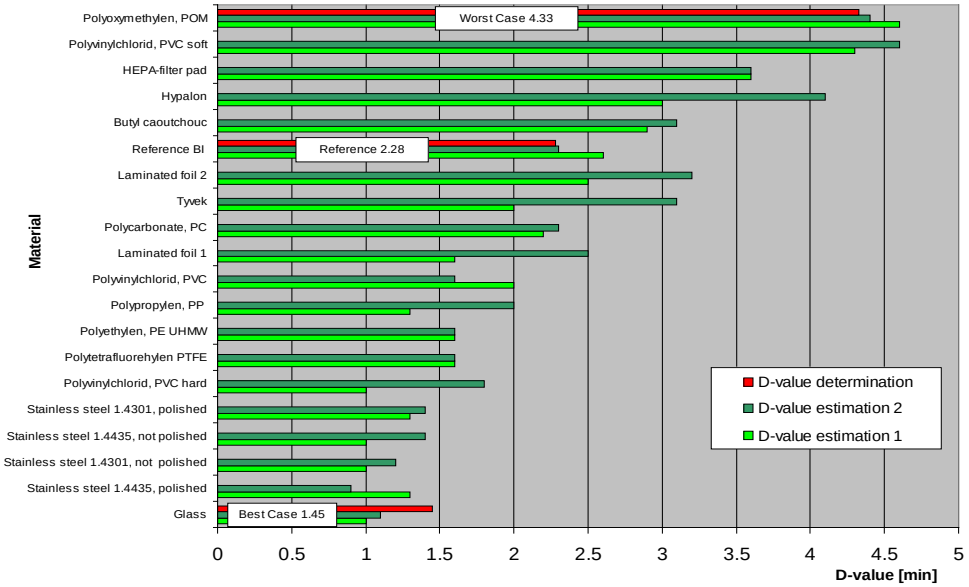


Scientific evidence

- **Research Articles**

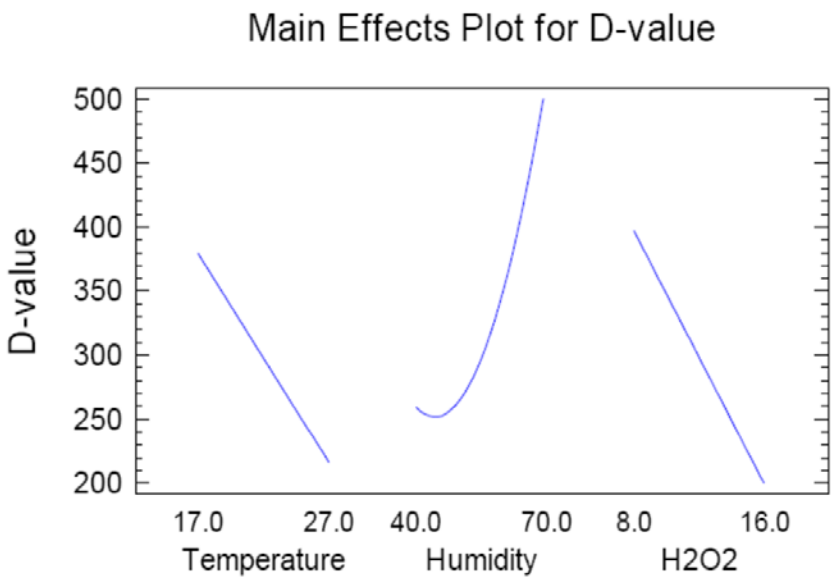
Effect of Carrier Materials on the Resistance of Spores of Bacillus Stearothermophilus to gaseous Hydrogen Peroxide

Volker Sigwarth, Skan AG
Alexandra Stärk, Novartis Pharma AG
PDA Jounal, Vol. 57, January / February 2003



Scientific evidence

Parameter impact on room decontamination:



A: Temp. higher temperature

B: Humidity lower humidity

C: H_2O_2 higher concentration

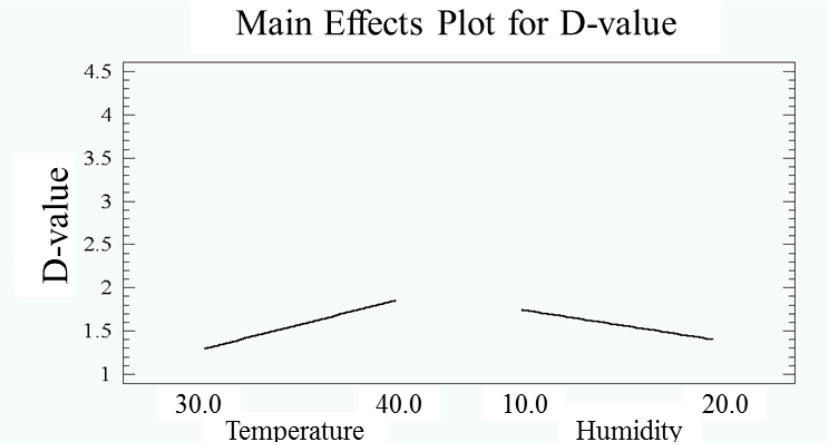
The more H_2O_2 is assimilated by the air, the better the decontamination effect.

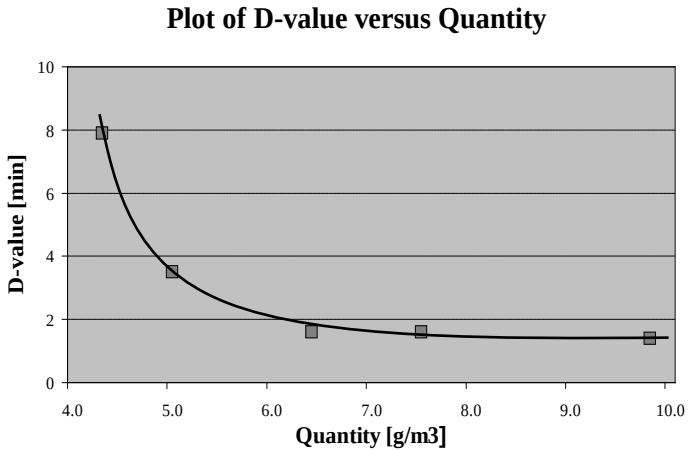
A potent and safe H_2O_2 Fumigation Approach

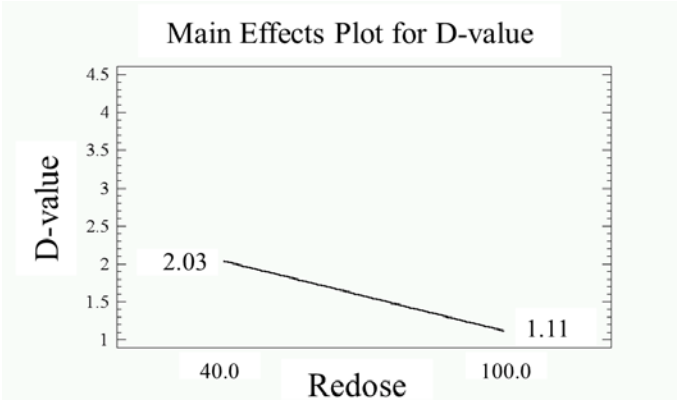
Volker Sigwarth, SKAN AG
Patrick Vanhecke, GSK
Claude Moirandat, C. Moirandat Dienstleistungen
PDA Jounal, Vol. 66, July/ August 2012

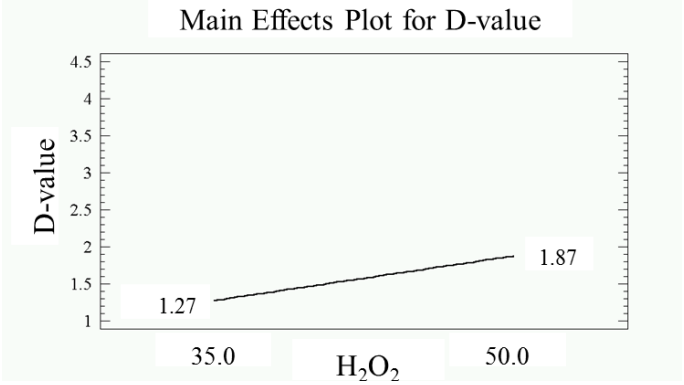
Scientific evidence

Parameter impact on isolator application:









Scientific evidence

A: Quantity	steady state
B: Redose	stability
C: Temp.	lower temperature
D: Humidity	higher humidity
E: H_2O_2	lower concentration

} higher **saturation** of gaseous phase

Decontamination effect depends on **saturation of gaseous phase**

"Physical Pressure" from gaseous phase to surface

No useful correlation between H_2O_2 concentration (ppm) and microbial reduction
High impact of temperature and humidity

Cycle Development

Scientific evidence

- **Research Articles**

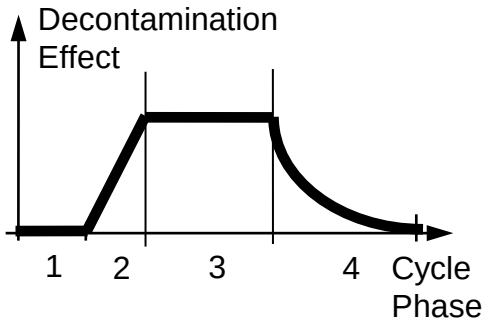
Development and Quantification of H_2O_2 Decontamination Cycles

Volker Sigwarth, Skan AG

Claude Moirandat, C. Moirandat Dienstleistungen
PDA Journal, Vol. 54, July / August 2000

Hydrogen Peroxide in Pharma Isolators, Investigation about Behaviour, Measurement and Effects

Alexander Sterchi
Dissertation, ETH, Swiss Federal Institute of Technology Zurich, 2001

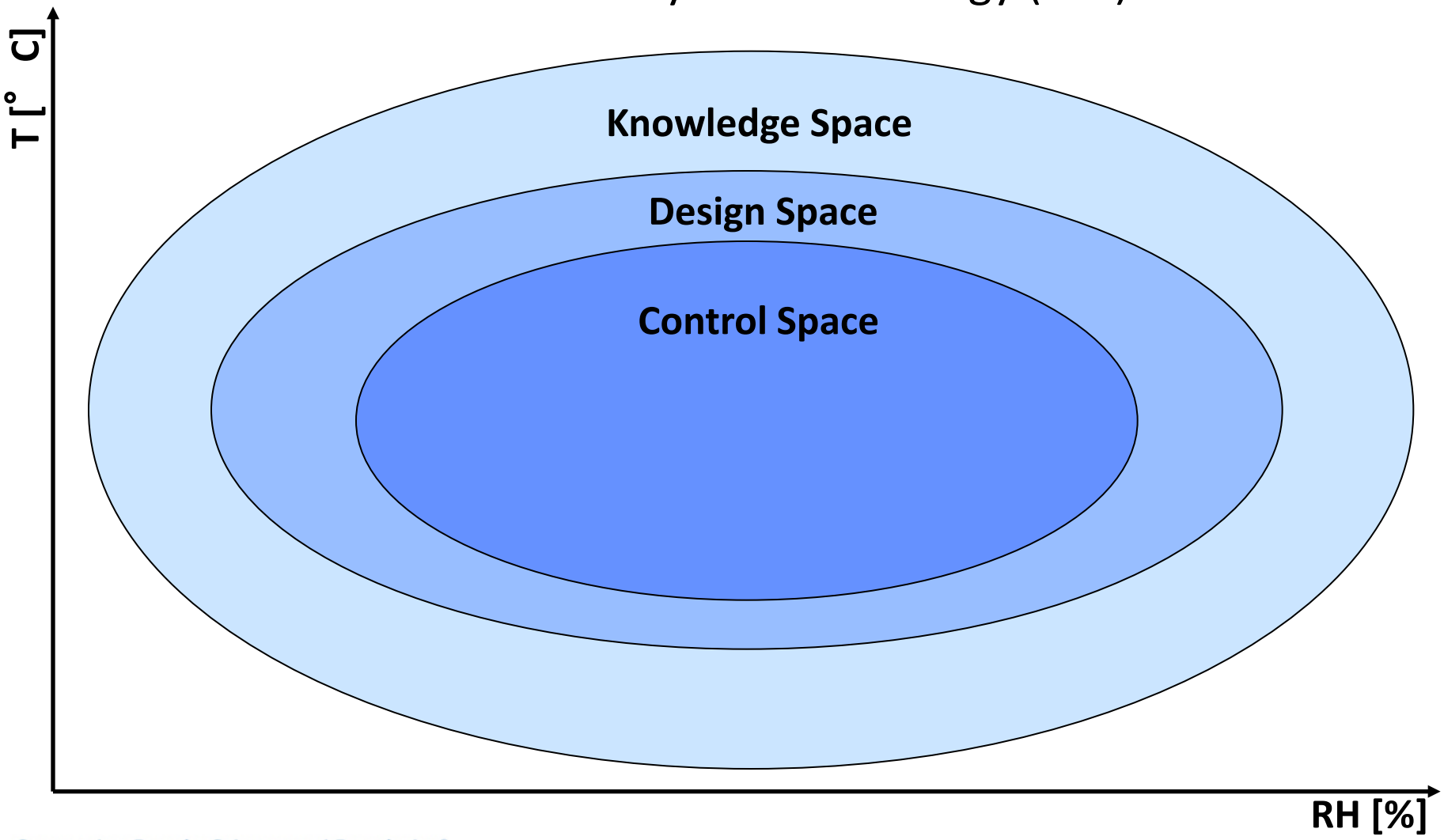


Process Development of alternative Sterilization Methods

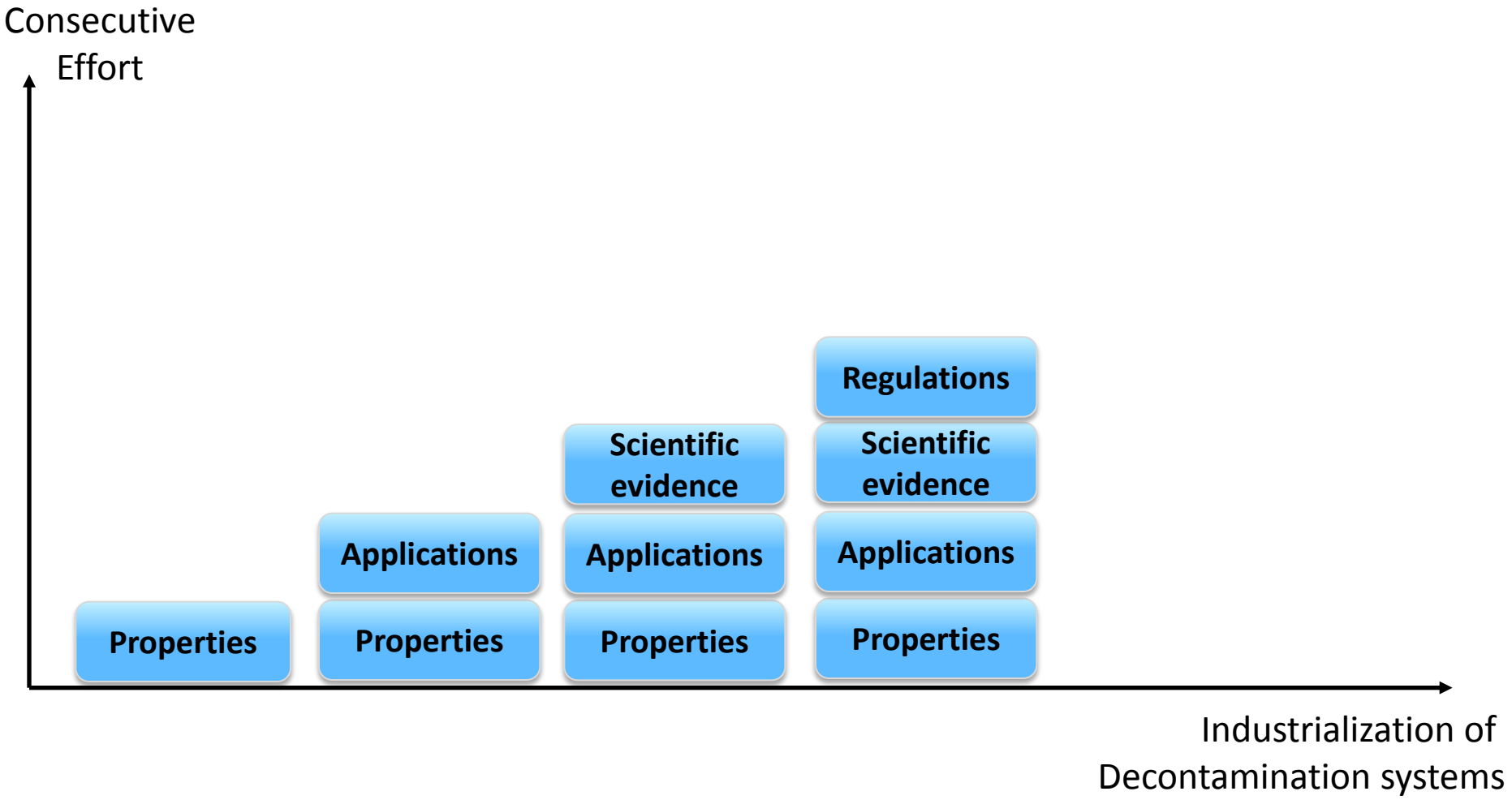
Volker Sigwarth, Skan AG
Chapter of the book: Microbial Contamination Control in Parenteral Manufacturing, 2003

Scientific evidence

Process Analytical Technology (PAT)



Development of Reliability

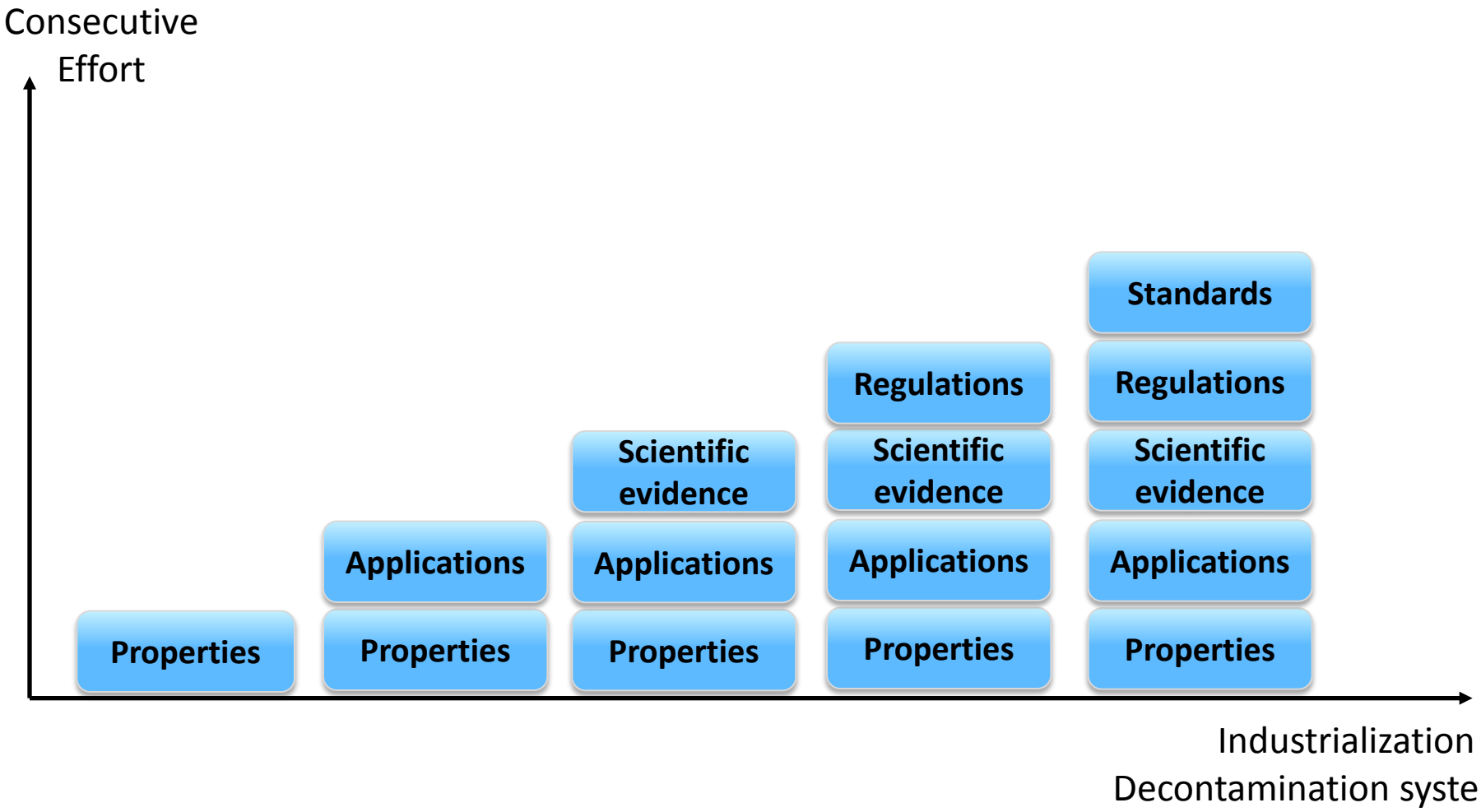


Regulations

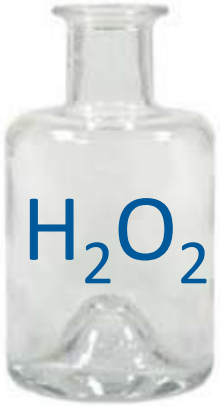
cGxP request

- **FDA** Guideline for Industry –
  Sterile Drug Products Produced by Aseptic Processing
- **PIC/S** Recommendation on Isolators used for
  Aseptic Processing and Sterility Testing
- **USP <1208>** Sterility Testing – Validation of Isolator Systems
- **USP <1035>** Biological Indicators for Sterilization
- **USP <55>** Biological Indicators – Resistance Performance Tests
- **PDA** Decontamination Methods
  Development and Quantification of H_2O_2 Decontamination Cycles
  Design and Validation of Isolator Systems for Manufacturing and Testing Health Care Products
- **ISO 13408-6** Aseptic processing of health care products

Development of Reliability



Standards

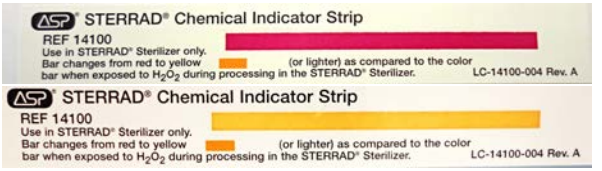


H_2O_2

- Worldwide available
- Several concentrations: 50%, 35%, 8% ...
- Several suppliers: Solvay, Merck, Bioquell, Steris …
- Several applications

Chemical Indicators (CIs)

- Reflect H_2O_2 distribution
- Qualitative proof

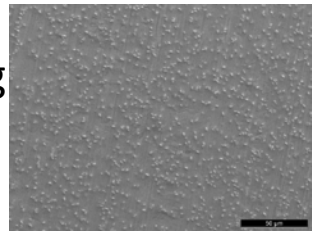


Standards

Biological Indicators (BIs)

Test Organism

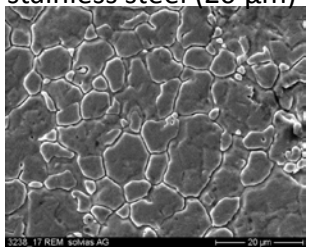
- Definition: System consisting of test organism, carrier and primary packaging
- Defined test organism with high resistance to sterilization process
- Defined population depending on process requirements



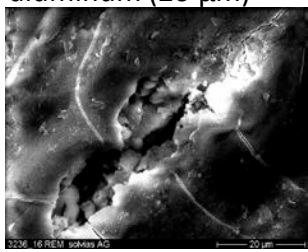
Carrier

- Reflecting environment
  Isolator materials (stainless steel, glass, equipment parts)
  Product materials (Tyvek or polystyrene from syringe tubs;
  polyethylene film from stopper bags)

stainless steel (20 µm)



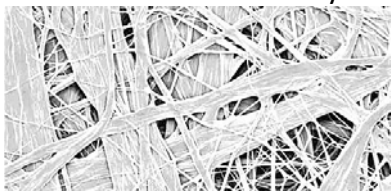
aluminum (20 µm)



Primary Packaging

- Tyvek
  Material compatibility acc. to ISO 11138
  Gas passively crosses the package
  Barrier to H_2O_2 depending on conditions, e.g. airspeed, humidity

Tyvek



Standards

Suppliers Steris, Bioquell, Optima, Bosch, Getinge, TechSpray, DIOP …

Where no competition can be found, no market exists.

Competition

- reflects the industrial standardization
- gives customer possibility to choose

H_2O_2 Sensors

Process control

- Low and high concentrations: Dräger

Room

- TLV: Dräger

Product protection

- Very low concentrations: Picarro

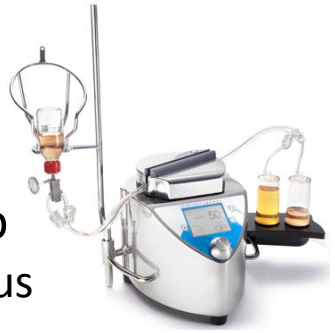
Standards

Consumables

- Steritest units
  Merck Millipore, Satorius

- Contact plates
  Merck Millipore

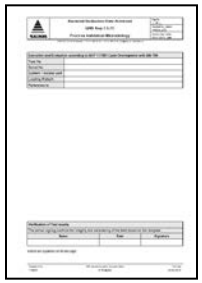
Equipment



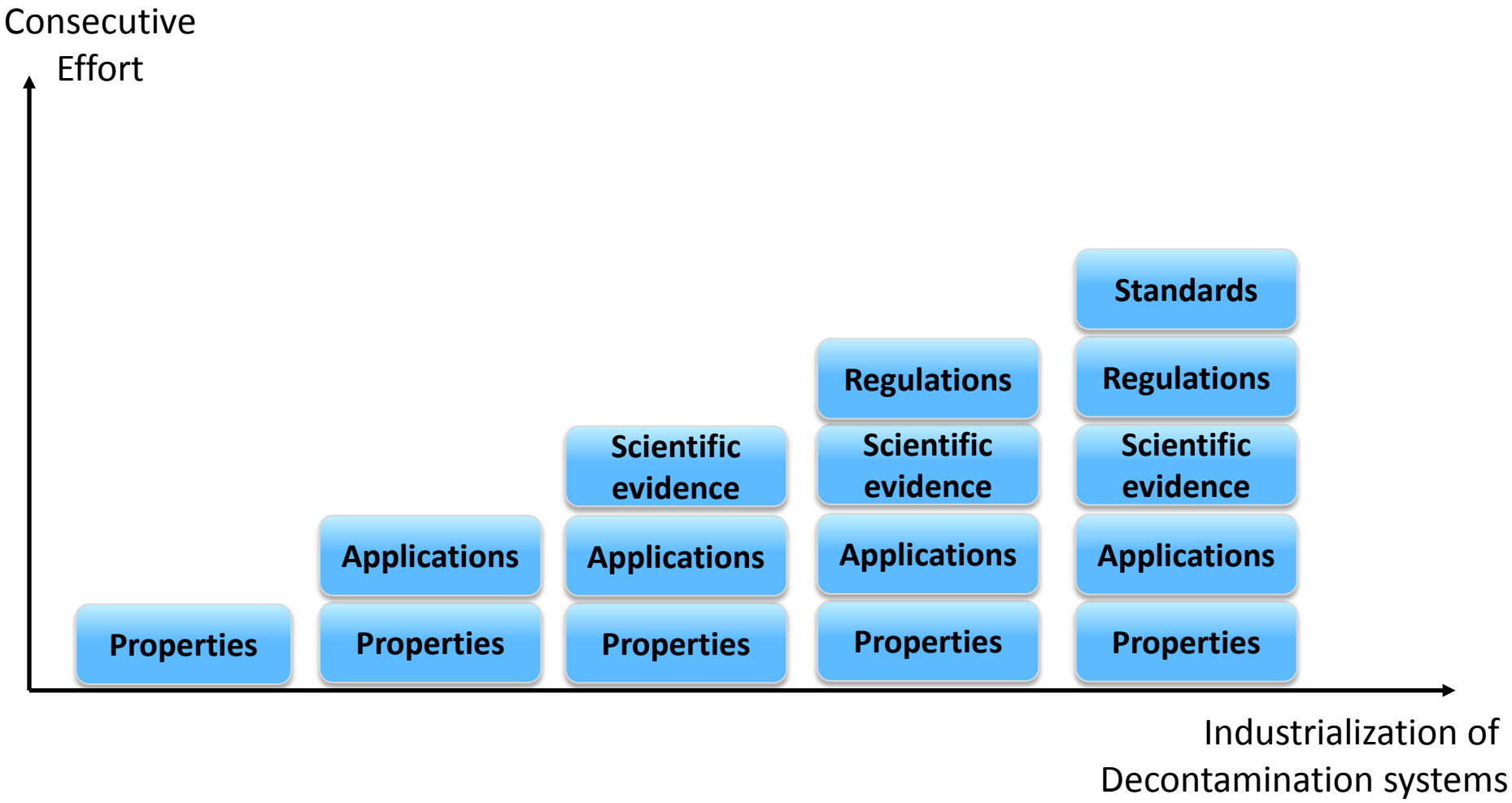
- Sterility testing pump
  Merck Millipore, Satorius
- Ports
  Getinge

Qualification

- Standard documentation
  Cycle Development
  Qualification
  Requalification



Development of Reliability



For further information: Simone.Blaesi@skan.ch

Standards

Biological Indicators (BIs)

Definition:

- System consisting of test organism, carrier and primary packaging
- Defined test organism with high resistance to sterilization process
  - Endospore forming species, e.g. *Geobacillus* (resistant bacterial endospore)
  - Correlation between kill kinetics and change in process factors, e.g. exposure time, concentration of sterilant
  - Stability of microorganism over time
  - H_2O_2: *Geobacillus stearothermophilus*
    - Growth conditions 55-60°C → low risk of cross contamination
    - Strains used: ATCC12980/**DSM22**, ATCC7953/**DSM5934**
    - Higher differences in resistance between production lots than between strains

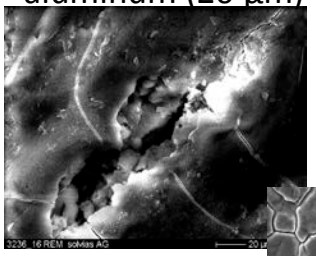
Standards

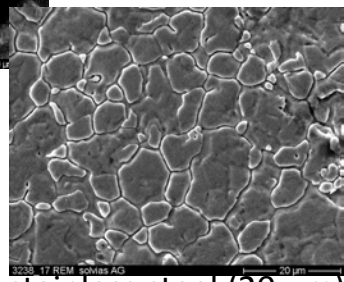
Biological Indicators (BIs)

Carrier

- Reflecting environment
  Isolator materials (stainless steel, glass, equipment parts)
  Product materials (Tyvek or polystyrene from syringe tubs; polyethylene film from stopper bags)
- Commercially available BI:
  construction materials depending on manufacturer
- Design/Shape
  ribbon, disc, table, spoon

aluminum (20 µm)





stainless steel (20 µm)

Characteristics of stainless steel carriers

- Standard material: grade 304 or 316L stainless steel
- Representative of many isolator components and surfaces
- Does not absorb or react with sterilant
- Non-reactive in growth media (not inhibitory)

Standards

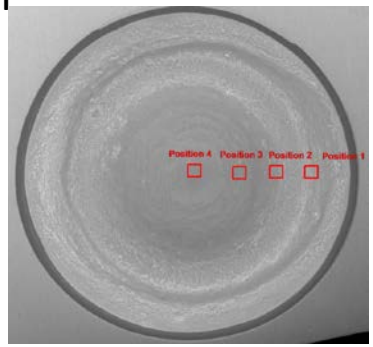
Biological Indicators (BIs)

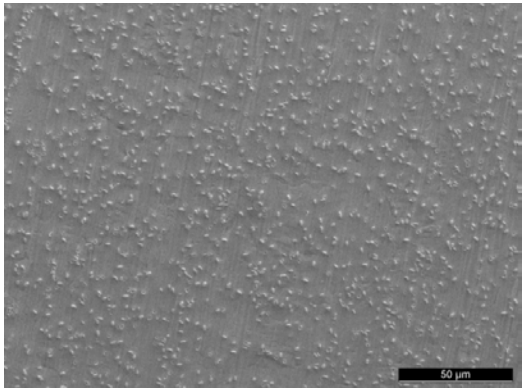
Test Organism

- Definition:
  System consisting of test organism, carrier and primary packaging

  Defined test organism with high resistance to sterilization process
- Defined population
  - Depending on process requirements
  - H_2O_2 isolator decontamination cycle: ≥ 1.0 x 10^6 spores/carrier
  - H_2O_2 room decontamination: ≥ 1.0 x 10^4 spores/carrier

- Process characteristics H_2O_2 decontamination
  - Surface decontamination
  - Spores in homogeneous, thin monolayer





Regulations

ISO 13408-6: 2005, 7.4.3.1 Biodecontamination

The biodecontamination agent selected shall be compatible with the materials of the isolator, the cleaning agent, the process application. The volume and configuration of the load, and the biodecontamination of the internal isolator equipment.

USP 35_NF 30, May 2012, <1035> Selection for Specific Sterilization Process

Hydrogen peroxide is used as a surface decontaminating agent in the treatment of sterility testing, biological and chemical containment, manufacturing isolators and clean rooms.

USP 35_NF 30, May 2012, <1035> Performance evaluation, Instrumentation

Reproducibility of hydrogen peroxide concentration (delivered within a finite time and maintained within a specific concentration range) should be controlled.

Regulations

FDA 2004, Appendix 1, Aseptic Processing Isolators, Decontamination Efficiency

Process development and validation studies should include a thorough determination of the cycle capability.

USP 35_NF 30, May 2012, <1208> Validation of the Isolator System, Decontamination Cycle Development (CD)

CD to establish the parameters necessary for process control during routine decontamination cycles.

FDA 2004, Appendix 1, Aseptic Processing Isolators, Filling Line Sterilization

Where decontamination methods are used a minimum of a six-log reduction should be demonstrated using suitable biological indicators.

Regulations

PDA Vol 54, Development and Quantification of H_2O_2 Decontamination Cycles, 2000

Better bacterial reduction rates are obtained at lower temperatures than at higher initial temperatures.

It is essential to prove the stability of the bacterial reduction rate over time in order to design a decontamination cycle.

USP 35_NF 30, May 2012, <1208> Validation of the Isolator System, Operational Qualification (OQ)

When elevated relative humidity is required, the ability to control it must be verified during OQ.

FDA 2004, Appendix 1, Aseptic Processing Isolators, Decontamination Efficiency

Chemical Indicators as a qualitative tool to show that the H_2O_2 reached a given location.

PIC/S DEFINITIONS / GLOSSARY

5.3. Sporicidal process.

A ***gaseous, vapour or liquid treatment*** applied to surfaces, using an agent that is recognised as capable of killing bacterial and fungal spores.

The process is normally validated using ***biological indicators*** containing bacterial spores.

PIC/S DEFINITIONS / GLOSSARY

5.3. Sporicidal process.

The number of spore log reductions ***is not specified*** in this definition,
but a ***target of six log reductions is often applied***.

The process is applied to internal surfaces of the isolator and external surfaces of materials inside the isolator, when conventional sterilization methods are not required.

PIC/S DEFINITIONS / GLOSSARY

5.3. Sporicidal process.

The application of a sporicidal process to isolators is ***not considered to be a sterilization process*** in the same way as, for example, a sealed container subjected to a validated dry heat, moist heat or irradiation process.

FDA Aseptic Guidance

D. Decontamination

1. Surface Exposure
Decontamination procedures should ensure full exposure of all isolator surfaces to the chemical agent. ***The capability of a decontaminant to penetrate obstructed or covered surfaces is limited***. For example, to facilitate contact with the decontaminant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle. It is also important to clean the interior of the isolator per appropriate procedures to allow for a robust decontamination process.

FDA Aseptic Guidance

D. Decontamination

2. Efficiency
The decontamination method should render the inner surfaces of the isolator free of viable microorganisms. ***Multiple available vaporized agents are suitable for achieving decontamination***. Process development and validation studies should include a thorough determination of cycle capability.

FDA Aseptic Guidance

D. Decontamination

Cycles should be developed with an appropriate margin of extra kill to provide confidence in the robustness of the decontamination processes

Normally ***a four- to six- log reduction*** can be justified depending on the application

PIC/S

7.4.13

The design, development and validation of the gassing process should encompass all ***relevant aspects from methods of gas distribution to quantification of target lethality, selection, calibration and culture of the biological indicator and definition of the final protocols.*** The stage of degassing is critical in all applications and the absence of residual lethality due to inadequate degassing should be demonstrated for isolators used for sterility testing. Reference to Appendix 1 is recommended.

- DEFINITIONS / GLOSSARY (PI 014-3 25 September 2007)
- 5.3. Sporicidal process.
- A gaseous, vapour or liquid treatment applied to surfaces, using an agent that is recognised as capable of killing bacterial and fungal spores. The process is normally validated using biological indicators containing bacterial spores. The number of spore log reductions is not specified in this definition, but a target of six log reductions is often applied. The process is applied to internal surfaces of the isolator and external surfaces of materials inside the isolator, when conventional sterilization methods are not required. The application of a sporicidal process to isolators is not considered to be a sterilization process in the same way as, for example, a sealed container subjected to a validated dry heat, moist heat or irradiation process.

- DETAILED POINTS TO BE CONSIDERED FOR THE IMPLEMENTATION OF
- THE PRINCIPLES TO ISOLATORS SUBJECTED TO A SPORICIDAL
- PROCESS. THESE POINTS ARE EXPANDED UPON IN APPENDIX

- 1. 7.4.6
- The delivery of gas from the generator into the isolator should assure that only
- the gas generated is supplied. All inlet and outlet filters associated with the
- isolator should be exposed to gas or sterilized. Any air supplied by the
- generator e.g. during a purge stage, should be filtered though microbiologically
- retentive filters that have been sterilized or subjected to a sporicidal process.

- 7.4.1 The agent selected for gas generation should be sporicidal.

- 7.4.13 The design, development and validation of the gassing process should
- encompass all relevant aspects from methods of gas distribution to
- quantification of target lethality, selection, calibration and culture of the
- biological indicator and definition of the final protocols. The stage of degassing
- is critical in all applications and the absence of residual lethality due to
- inadequate degassing should be demonstrated for isolators used for sterility
- testing. Reference to Appendix 1 is recommended.

- 7.5.1
- All gases, fluids and air supplied to the isolator or that may gain access, should
- be filtered using microbiologically retentive filters or sterilized prior to entry.

- 9.4.1
- The agent selected for gas generation should be sporicidal. The agent
- used for gas generation or other means of application should be capable of
- rapidly killing bacterial endospores, fungal spores and vegetative
- microorganisms. Activity against virus, such as is claimed for peracetic acid,
- may be necessary in some applications or a general advantage. Peracetic
- acid, hydrogen peroxide and formaldehyde are used. The use of other
- chemicals such as chlorine dioxide is being developed.

- 9.4.5 The release of the gassing process with regard to the gas generator
- should verify that all critical parameters met the specifications defined
- during validation.

- 9.4.12 The range of parameters and events that should be monitored to
- assure the delivery of the validated process should be defined.

- 9.4.13 The design, development and validation of the sporicidal process
- should encompass all relevant aspects from methods of gas
- distribution to quantification of target lethality, selection, calibration
- and culture of the biological indicator and definition of the final
- protocols.