Decontamination with H2O2 for aseptic Isolators

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2 Key Factors for Aseptic Processing

Cleaning/Disinfection

- Requirements get higher in aseptic processing
- Validation of Cleaning and Disinfection

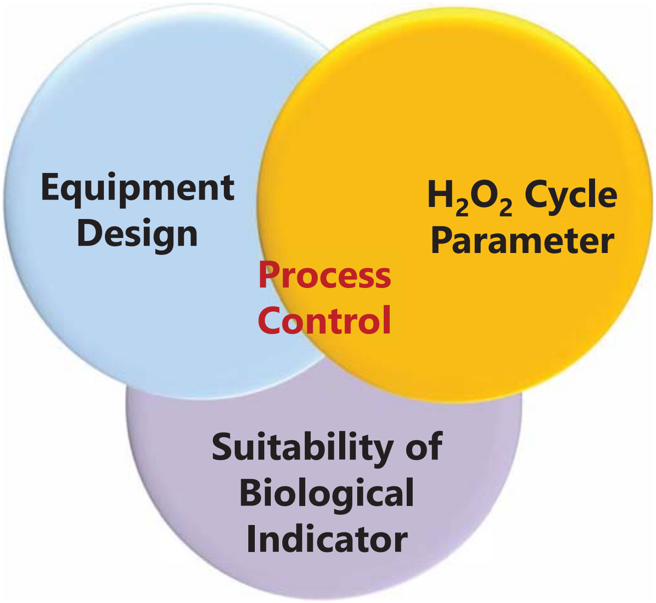
H2O2 Decontamination

- Process well established
- Isolator Technology
- Vaporized Hydrogen Peroxid vH2O2

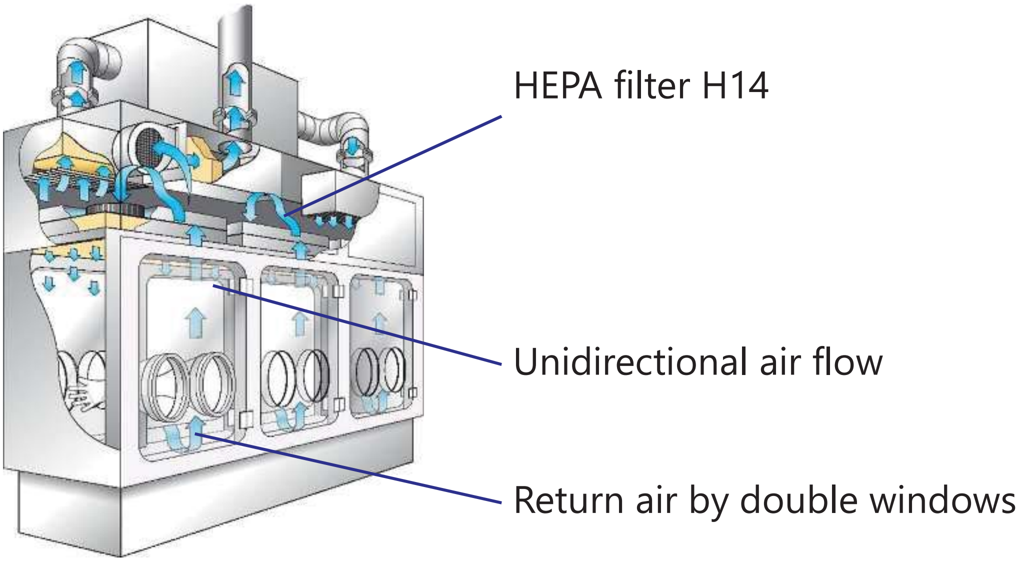
3 Key Factors for Aseptic Toxic Processing

Cleaning/Cross Contamination	H2O2 Decontamination	Operator Protection
▪ Requirements get higher in aseptic processing ▪ Validation of Cleaning and Disinfection ▪ New to the BioTech industry	▪ Process well established ▪ Isolator Technology ▪ Vaporized Hydrogen Peroxid vH2O2	▪ Requirements for high potent substances ▪ Less Experience with aseptic Isolators

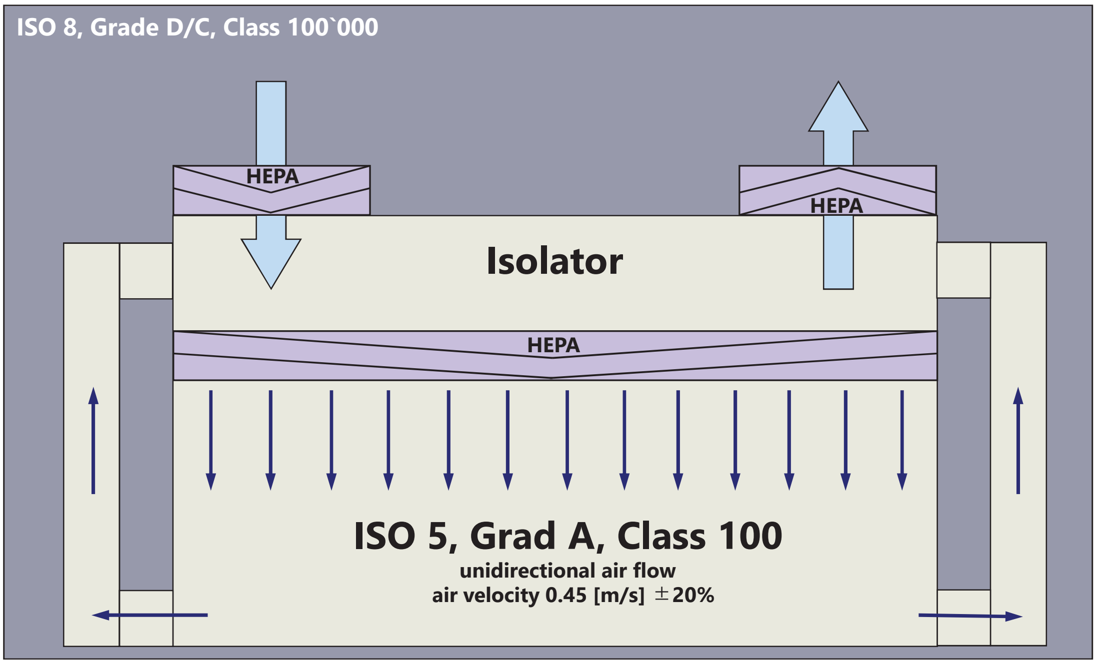
Isolator Process Control



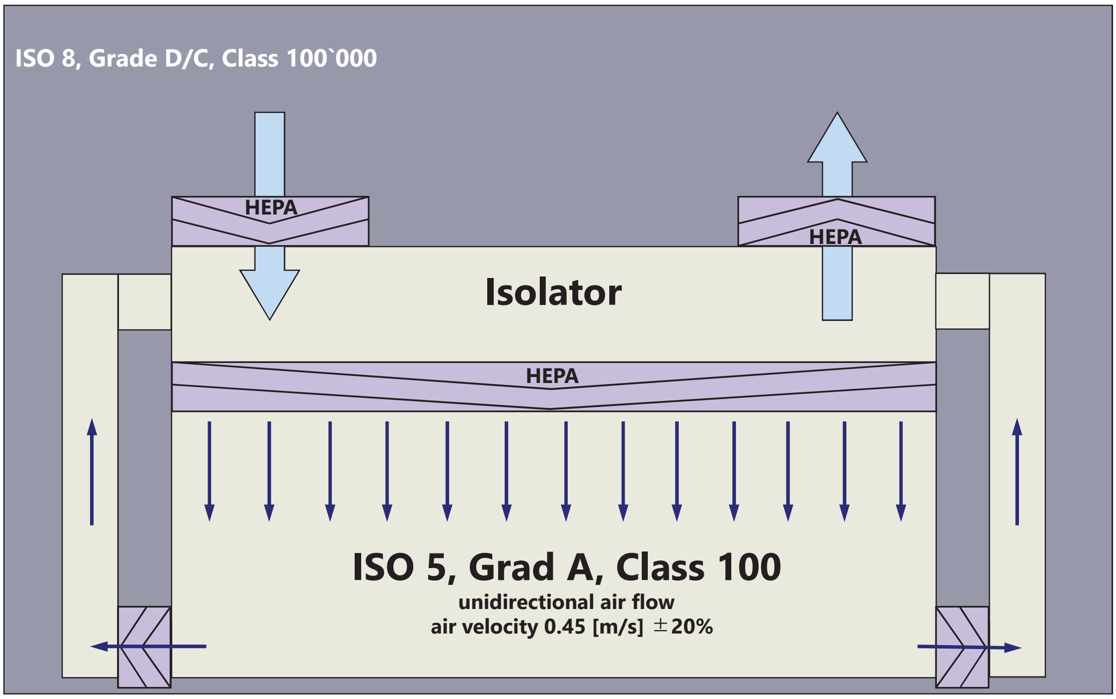
Isolator Air Handling Know-How



Filter System

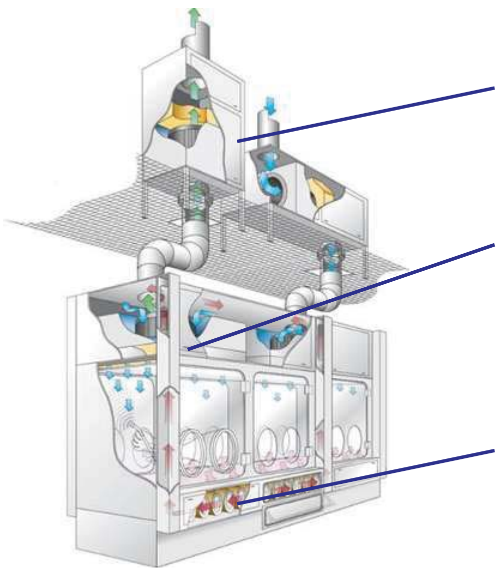


Air Recirculation (for Aseptic-Toxic System)



Air Recirculation (for Aseptic-Toxic System)

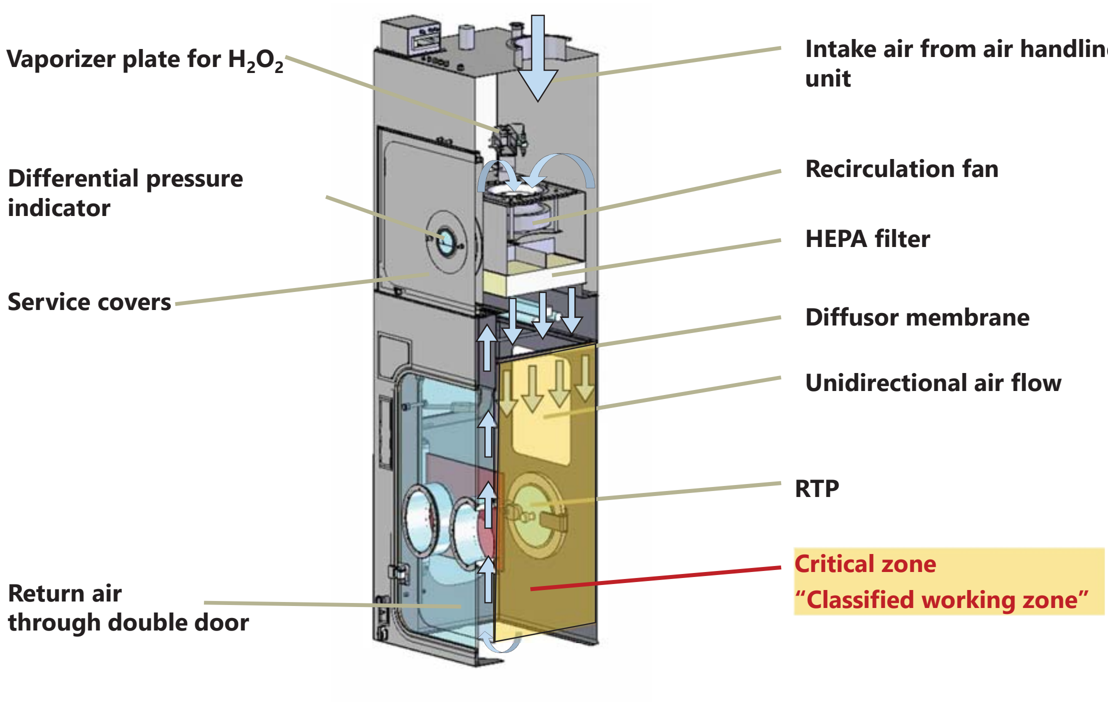
Cartridge HEPA filter system FIPA-FL



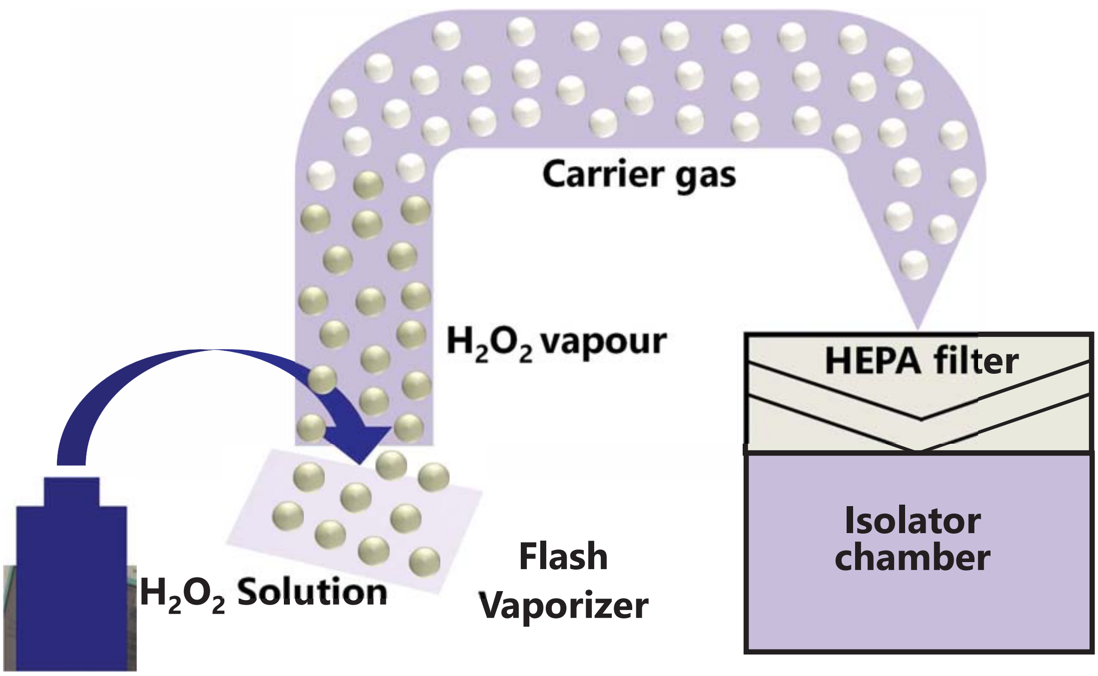
no extra space in technical area needed

return air ducts protected with cartridge filters don't require wash down

Critical Zone



H2O2 Decontamination Principle

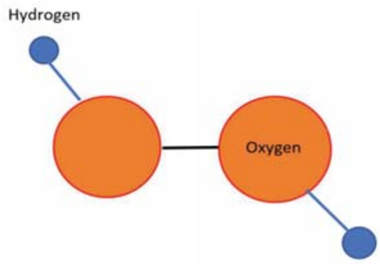


BH2

Why Flash Vaporizing?

Physical Properties of H_2O_2

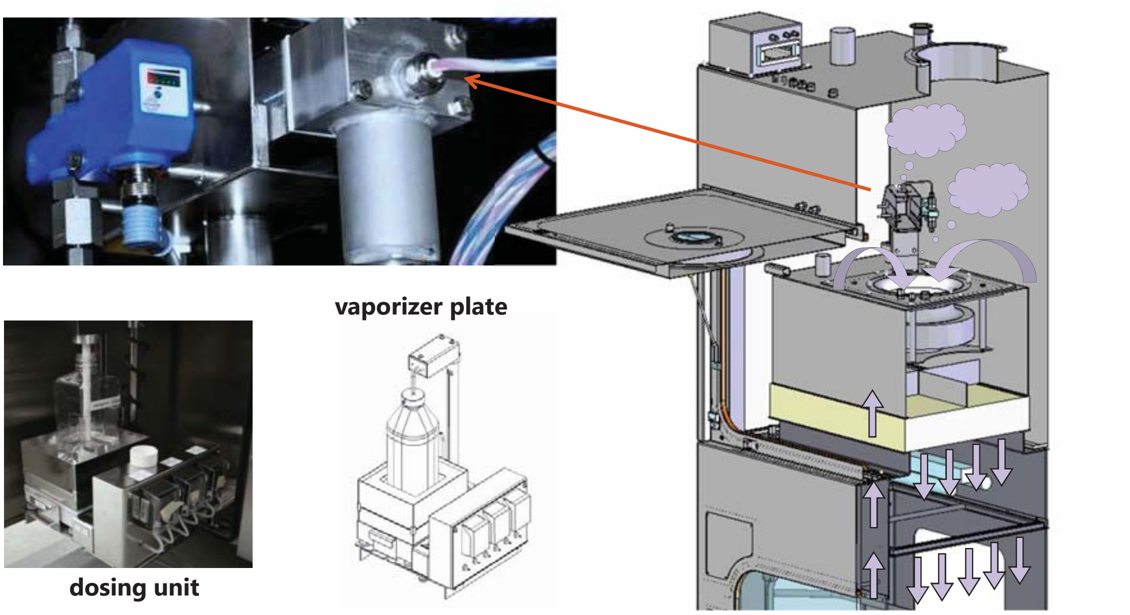
Property	Hydrogenperoxide	Water
Molecular Weight	34,016	18,016
Boiling Point	150,2	100,00
Evaporation Energy	51,66	44,04
Thermic Capacity of the Steam	42,82	33,62



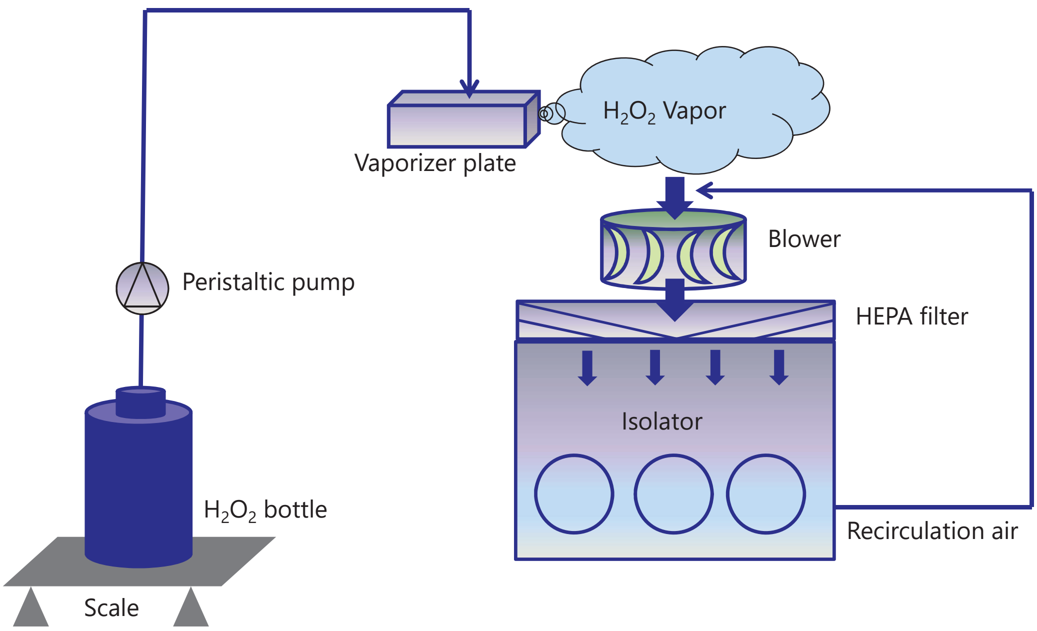
Folie 11

BH2 The important difference of water and hydrogen peroxide for the evaporation technology is the difference in the boiling point due to the hydrogen bonds which are stronger in hydrogen peroxide. As we always use a mixture of hydrogen peroxide and water we need a flash evaporation to avoid the splitting of the mixture in water and hydrogen peroxide during evaporation.
The other important difference is the much lower vapor pressure of the hydrogen peroxide than water vapor. Therefore, hydrogen peroxide vapor will readily condense on the isolator and load surfaces reaching a high concentration. This condensate forms a thin film on the surfaces and is responsible for the rapid bactericidal and sporicidal effect. [2]
Bässler Hans-Jürgen; 21.08.2018

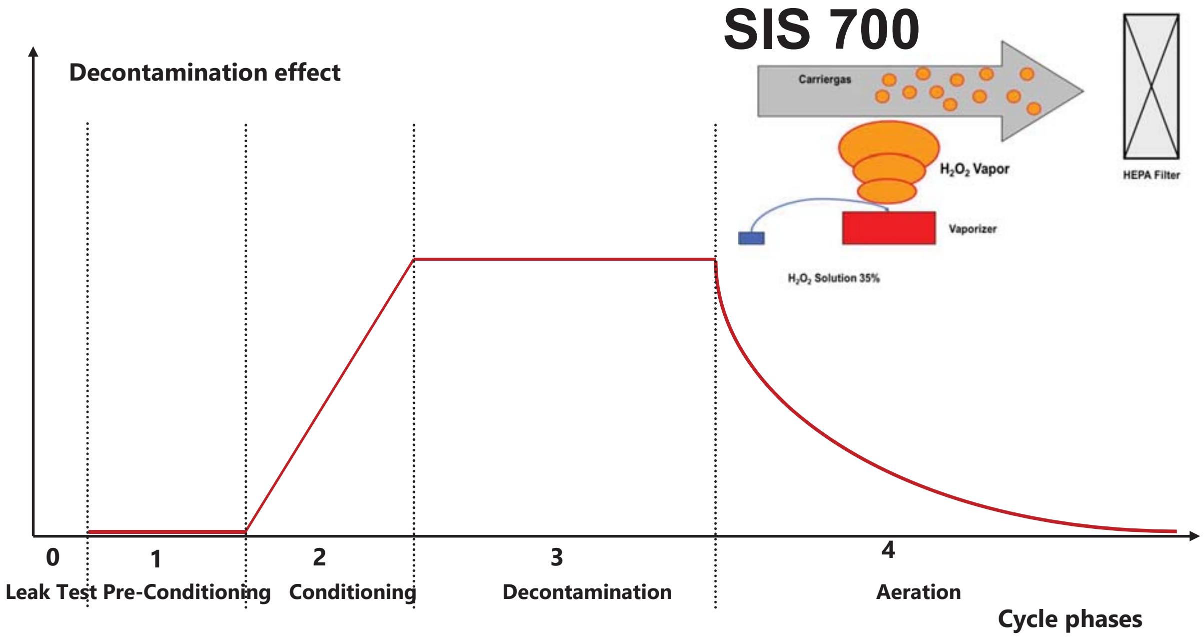
H2O2 Decontamination System



H2O2 Evaporation Principle



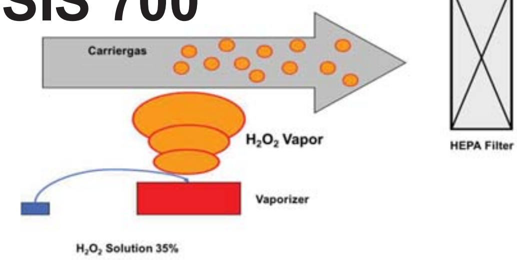
Phases of Decontamination Cycle



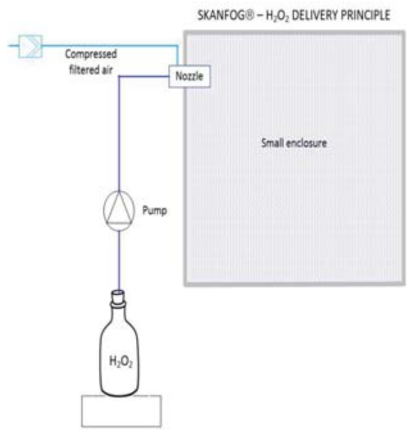
H2O2 Decontamination System

Two Technologies of Decontamination with H_2O_2

SIS 700



SKANFOG®

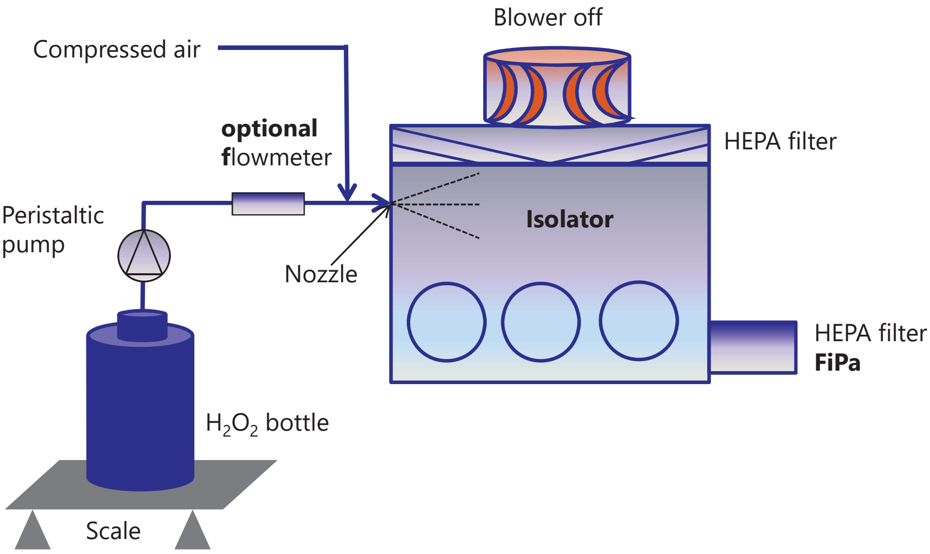


H2O2 Decontamination System

Fastest H_2O_2 cycles with state-of-the-art SKANFOG® decontamination technology

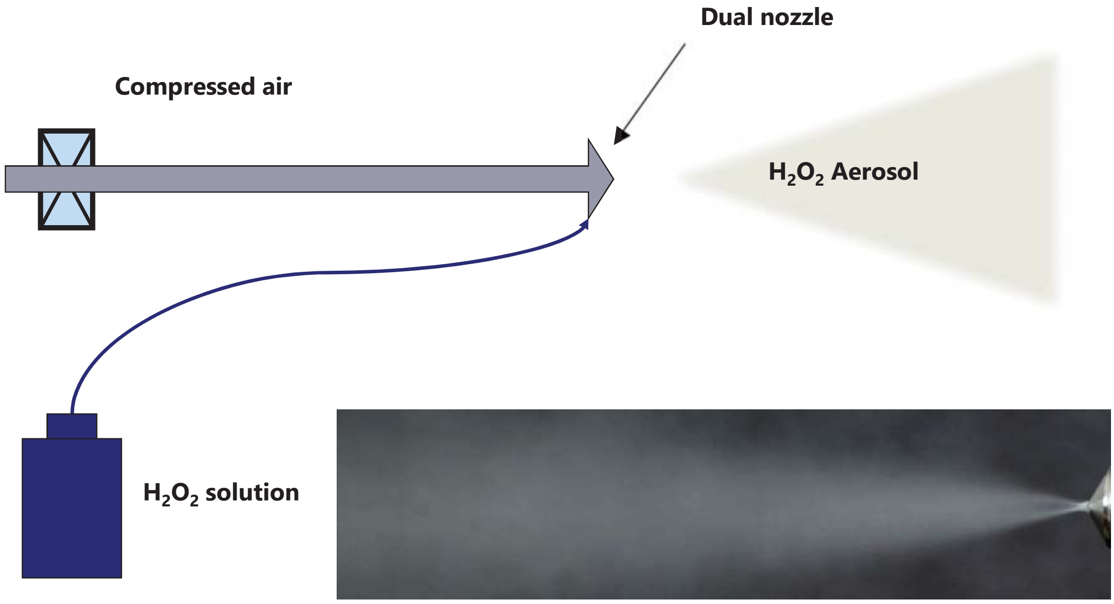
- Micro-nebulization of H_2O_2
- An embedded and proven system
- Minimized H_2O_2 consumption conforming to risk analysis (80% less than VHP)
- Fastest decontamination process (1 hour < 1 ppm)

SKANFOG® Principle



Principle of SKANFOG®

H2O2 Micro Nebulization - SKANFOG



H2O2 Micro Nebulization

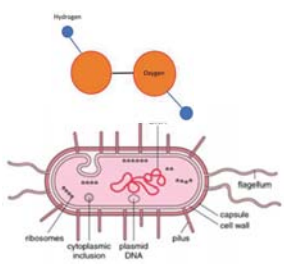
Micro nebulization of H_2O_2 solution into aerosol droplets

Evaporation of aerosol droplets until saturation

Micro-condensation on the surfaces

Inactivation effect

Damage of the Germ



Molecular Structure of H2O2

Droplet size and fast distribution

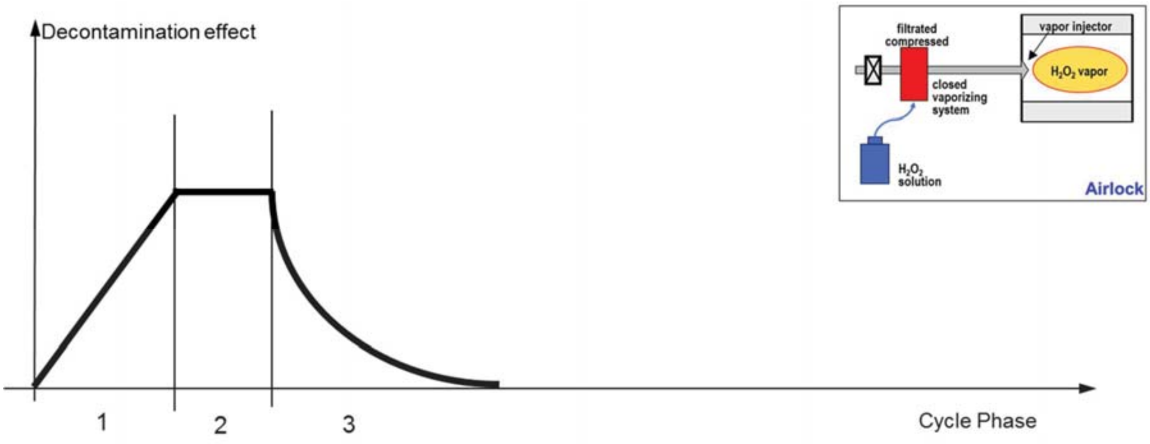
H2O2 Micro-Nebulization - Study

Room decontamination

From: P. Vanhecke, V. Sigwarth, C. Moirandat" **A Potent and Safe H_2O_2 Fumigation Approach"** *PDA J Pharm Sci and Tech* **2012**, *66* 354-370, Figure 14

Phases of Decontamination Cycle

Decontamination with H_2O_2 – SKANFOG®



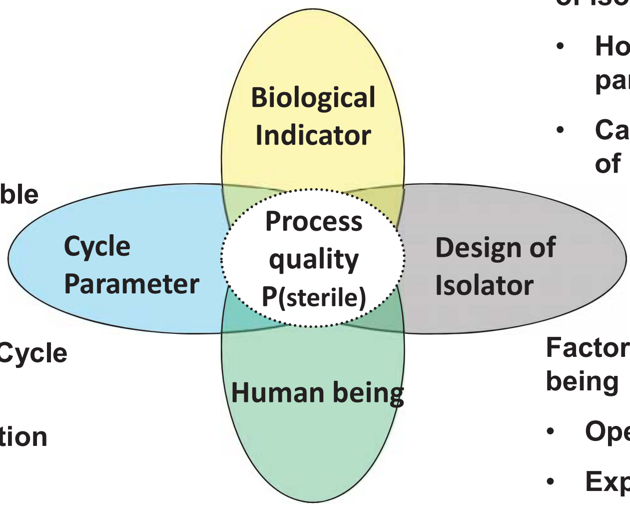
H2O2 Decontamination Parameters

Factor of Influence: Quality of BI

- Suitable for H_2O_2 decontamination
- Late positives
- Convenient, suitable resistance

Factor of Influence: Design of isolator

- Homogeneity of physical parameters
- Capacity and distribution of H_2O_2



Factor of Influence: Cycle Parameter

- achieved inactivation effect
- Stability of inactivation effect
- Duration of decontamination process

Factor of Influence: Human being

- Operator Training
- Expertise
- Behavior

Overview of current regulations and standards

– 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."

„ Current practice is to seek **six log reductions** of the biological indicator organism recommended by the manufacturer of the gas generator."

- FDA: ASEPTIC GUIDELINE

„ Cycles should be developed with an appropriate margin of extra kill to provide confidence in robustness of the decontamination processes. Normally, a four- to six-log reduction can be justified depending on the application. The specific BI spore titer used and the selection of BI placement sites should be justified."

→ …has to be understood as a total kill of BI inoculated at 10^4 to 10^6 spores / carrier

Overview of current regulations and standards


RESEARCH ARTICLE

Effect of Carrier Materials on the Resistance of Spores of *Bacillus stearothermophilus* to Gaseous Hydrogen Peroxide


A Potent and Safe H_2O_2 Fumigation Approach

- **FDA: ASEPTIC GUIDELINE**

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APPENDIX 1: ASEPTIC PROCESSING ISOLATORS

D. Decontamination

2. Efficacy

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. The characteristics of these agents generally preclude the reliable use of statistical methods (e.g., fraction negative) to determine process lethality (Ref. 13).

P.54 References

13. Sigwarth, V. and A. Stark, "Effect of Carrier Materials on the Resistance of Spores of Bacillus stearothermophilus to Gaseous Hydrogen Peroxide," PDA Journal of Pharmaceutical Science and Technology, Vol. 57, No. 1, January/February 2003.

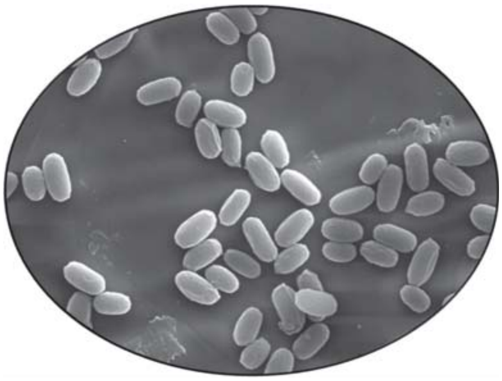
Overview of current regulations and standards

Process Expectations

- Reducing the microbiological contamination
- Decontamination process
- On the inner surfaces of the isolator system
- Sporicidal process
- Achieving a 4 to 6 spore log reduction
  - 6 log reduction ≠ Total Kill of BI inoculated with 10^6 spores
- No influence from inactivation process on products or tests

Biological Indicator

- Model of microbial reduction
- D-value determination
- Composition of biological indicators



Description of Biological Indicator

- Defined test organism — e.g. Geobacillus stearothermophilus
- Defined initial population — e.g. 1.0 x 106 [spores/carrier]
- Carrier material — e.g. stainless steel
- Primary packaging — e.g. Tyvek
- Inactivation method — e.g. gaseous H_2O_2

Basis and Selection of suitable BI as sensor for the inactivation process

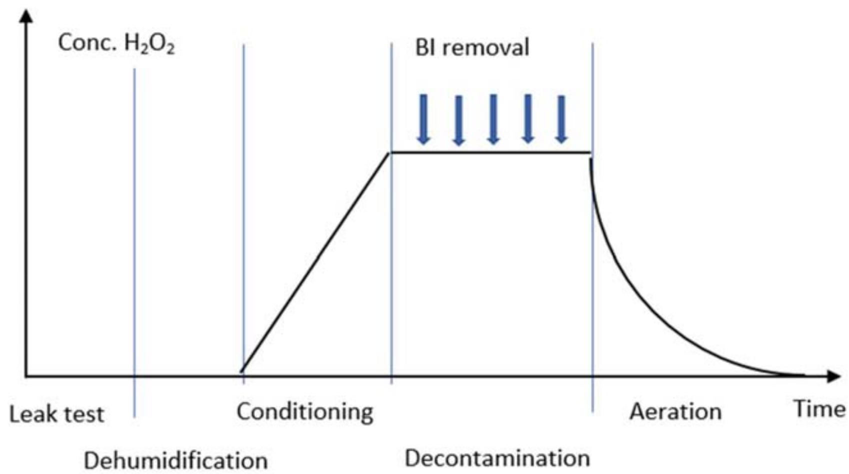
Definition D-value

- Statistical calculation based on the ratio of positive / negative BI at different time exposure during of a decontamination cycle
- Time in minutes to reduce the population by 1 log step, corresponding to 90% of the initial population
- Example:
  a D-value of 1.2 represents 1.2min for the population of one BI to be reduced from 10^6 to 10^5 spores/carrier

Use

- Information about the BI resistance – higher D-value representing a higher resistance (in reference isolator – characteristic of the BI)
- Information about the decontamination effect of an isolator – lower D-value representing a better decontamination effect (in isolator to be qualified – characteristic of the isolator)
- D-value from a BI lot depends on isolator → not a general statement

Cycle development with SIS 700



LSKM SIS 700

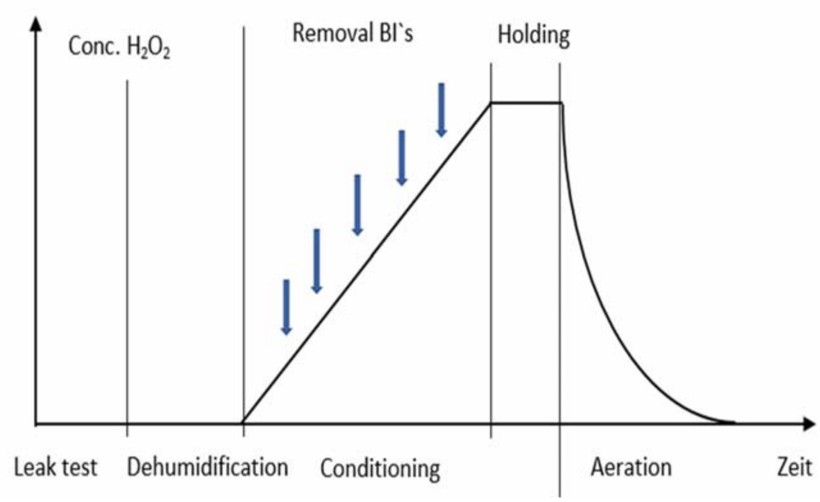
Limited Spearmen Karber Method

Group	1	2	3	4	5	6	7	Pos.	Neg.
Exposure time min	6.0	9.0	12.0	15.0	21.0	24.0	27.0		
1	+	+	+	+	0	0	0	+	0
2	+	+	+	0	0	0	0	+	0
3	+	+	0	0	0	0	0	n.a.	n.a.

\+ = Growth   0 = No growth

Cycle development with SKANFOG®

Definition of Total Kill Time (sample)



Principle of SKANFOG®

LSKM Fogging process

Limited Spearmen Karber Method

Group	1	2	3	4	5	6	7	8	Pos.	Neg.
Time	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00		
1	+	+	+	+	+	+	+	0	+	0
2	+	+	+	+	+	+	0	0	+	0
3	+	+	+	+	+	0	0	0	n.a.	n.a.

Basis and Selection of suitable BI as sensor for the inactivation process

Model of Microbial Reduction

- Initial Population [log-scale]
- Inactivation Time [min]
- D-value [min]
- Survival – Kill Window [min]

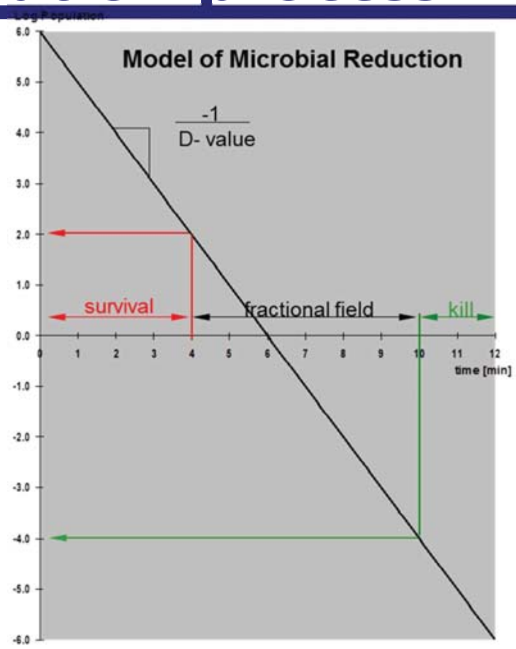
Survival Time [min]

≥ D-value x (log Population - 2)

Kill Time [min]

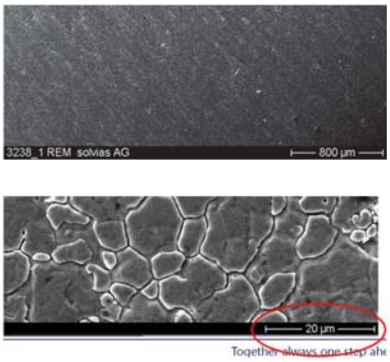
≤ D-value x (log Population + 4)

acc. to ISO 14161

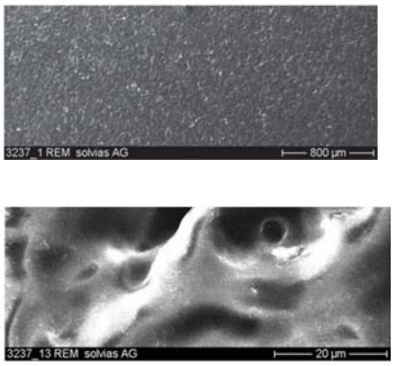


Influence of the Decontamination on different surfaces

Stainless steel not polished



Aluminium



Development and Quantification of Decontamination Cycles

Worst Case Study – SIS 700

Development and Quantification of Decontamination Cycles

Chemical Indicator Mapping (optional)

Qualitative evaluation of the homogeneity of the distribution of H_2O_2 everywhere in the isolator

Evaluation is made through the change of color of chemical indicator H_2O_2 sensitive

SKANFOG® Fix in Filling Lines

Baxter Halle, filling line

- Qualified 08/2015
- Entire cycle time < 70 min