Bio-Decontamination with H2O2 – Vapor in Pharmaceutical Industry

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Robert Bosch GmbH

SBM Expert's Congress 13th-14th of September, 2007

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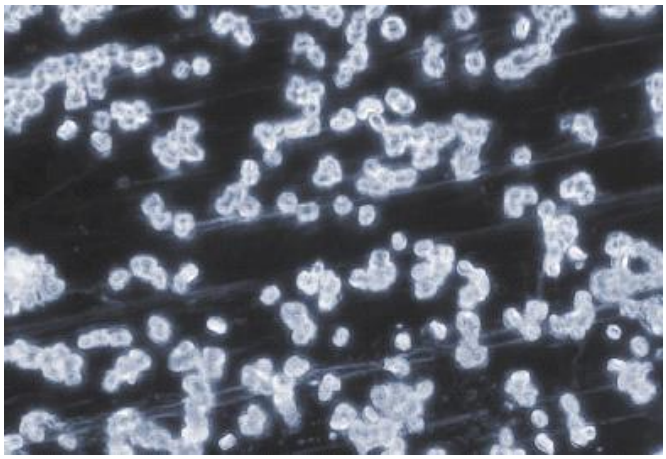
Bio-decontamination with H_2O_2 - Vapor

Structure

- Introduction
- "VHP" for Isolators
- Results
- More Applications
- Summary



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  - Chemistry / Biocidal Effect
  - Challenges
  - Regulatory
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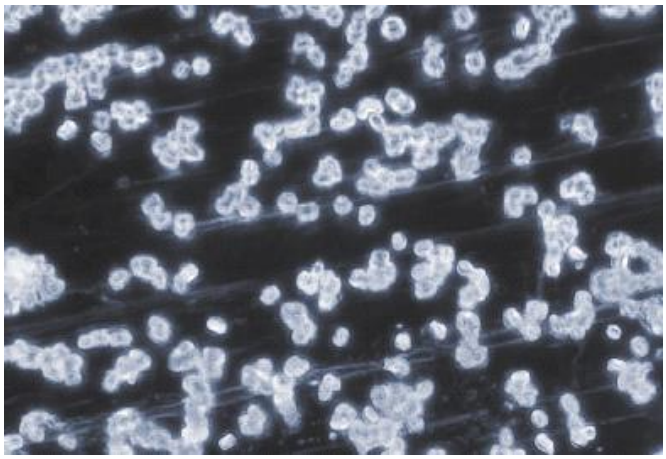


Bio-decontamination with H_2O_2 - Vapor

Introduction

- Hydrogen Peroxide is an old sterilant – well established in food industry, where liquid H_2O_2 is applied for disinfection of packaging material and plastic bottles.
- H_2O_2 has a broad antimicrobial activity spectrum and shows low toxicity.
- Residues of hydrogen peroxide decompose into neutral species, which underlines the environmental friendliness of this agent:

$$2\ H_2O_2 \leftrightarrows 2\ H_2O + O_2$$

- But: hydrogen peroxide can decompose with fast kinetics – under some circumstances it can explode at high concentrations.
- For complex geometries disinfection with liquid peroxide has limits. For this case H_2O_2 in the vapor state is widely used.

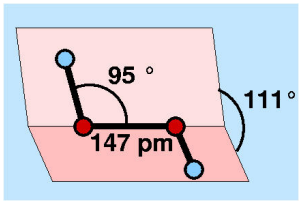
Chemistry / Biocidal Effect

- The hydrogen peroxide molecule has a unique geometry with a high energy angle, which makes splitting of O-O-bond easy:

  $H_2O_2 \leftrightarrows 2\ HO\bullet$

  $2\ HO\bullet \leftrightarrows H\text{-}O\text{-}H + \frac{1}{2}O_2$

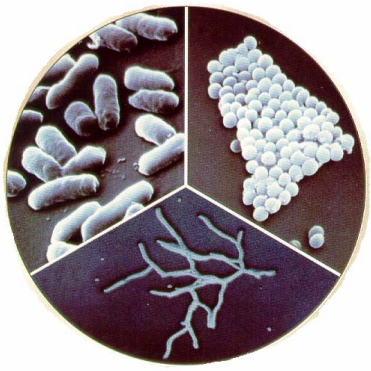
- The decomposition can be catalyzed by metallic surfaces (Cu, Pb, Mg...) – which can be used to decompose after use. On the other side this makes the need for noble surfaces in the equipment to be disinfected.



Bio-decontamination with H_2O_2 - Vapor

Chemistry / Biocidal Effect

- The biocidal effect of hydrogen peroxide comes from the oxygen atom/radical, which is released under influence of the enzyme catalase at the microbiotic surface. The oxidative power of oxygen radicals cause irreversible damage to enzymic systems and DNA.
- A minimum of humditiy at the surface to be treated helps to promote this meta-bolismism – especially bacterial spores need a basic humidity to show any bio-chemical activity.



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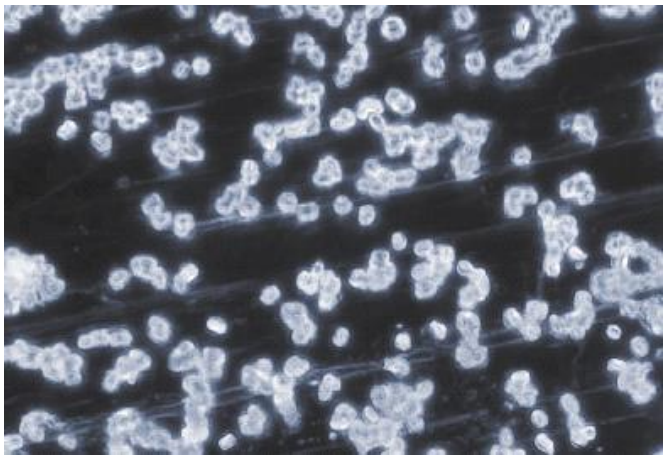
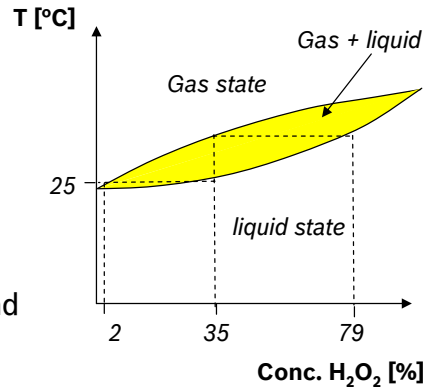


Challenges

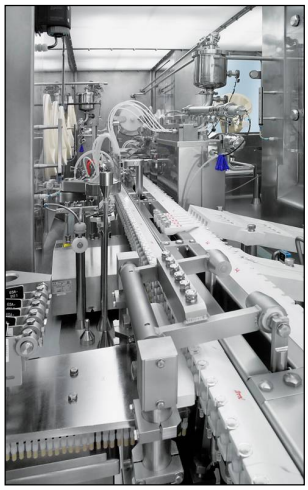
- Vaporized Hydrogen Peroxide is used to disinfect bottles and pharmaceutical equipment interior, such as isolators (mini-cleanrooms on top of machinery).
- Pioneer in that technique was AMSCO, later bought by Steris Co., with their VHP® technology back in the 80 ies.
- Disadvantage of vaporizing H_2O_2 are the two physical states present in the system, when using diluted H_2O_2 for evaporation. This results in different concentrations and thereby in different inactivation efficacy.

VHP®



Bio-decontamination with H_2O_2 - Vapor

Challenges



- Slow evaporation of e.g. 35% H_2O_2 separates the both components (”destillation”) during transition into vapor. Condensation on the surfaces makes the next separation (“concentration change”).
- Sterilisation means absence of viable microbiotics. In complex geometries this is a challenge, because homogeneous inactivation is required. This can be questioned with vapor/liquid mixtures.
- H_20_2 vapor is known as *bio-decontaminating, not sterilizing* surfaces – though 6 log inactivation can be achieved/proven.

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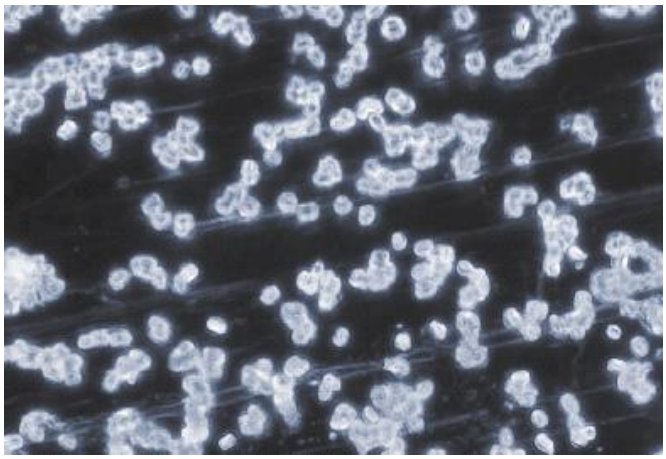
Bio-decontamination with H_2O_2 - Vapor

Structure



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Bio-decontamination with H_2O_2 - Vapor

Regulatory

- In "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" published by FDA in September 2004, within Appendix 1: Aseptic Processing Isolators the need for decontaminated surfaces is explained:

"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...."

Bio-decontamination with H_2O_2 - Vapor

Regulatory

- Continuation "Aseptic Guidance":

"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.... 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."

"E. Filling Line Sterilization
...Where decontamination methods are used to render certain product contact surfaces free of viable organisms, a minimum of a six-log reduction should be demonstrated using a suitable biological indicator."

Bio-decontamination with H_2O_2 - Vapor

Regulatory

- Continuation “Aseptic Guidance”:
  “E. Filling Line Sterilization
  …Where decontamination methods are used to render certain product contact surfaces free of viable organisms, a minimum of a six-log reduction should be demonstrated using a suitable biological indicator.”

- In EC GUIDE to Good Manufacturing Practice, Annex 1 a list of sterilization techniques (heat, moist heat, radiation, ethylene oxide…) does not include hydrogen peroxide. The description of sterilization/decontamination of isolators does not specifically discuss issues coming from bio-decontamination instead sterilization.

Bio-decontamination with H_2O_2 - Vapor

Regulatory

- In EC GUIDE to Good Manufacturing Practice, Annex 1 a list of sterilization techniques (heat, moist heat, radiation, ethylene oxide…) does not include hydrogen peroxide. The description of sterilization/decontamination of isolators does not specifically discuss issues coming from bio-decontamination instead “sterilization”.

Bio-decontamination with H_2O_2 - Vapor

Regulatory

- PIC/S Recommendation “Isolators used for Aseptic Processing and Sterility Testing”; Chapter “An expansion of the detailed points to be considered for the implementation of the principles to isolators subjected to a sporicidal process” collects 14 points for the sporicidal process. Point 9.4.1 mentions H_2O_2 bio-decontamination:

“…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.
… Peracetic acid, hydrogen peroxide and formaldehyde are used. …”

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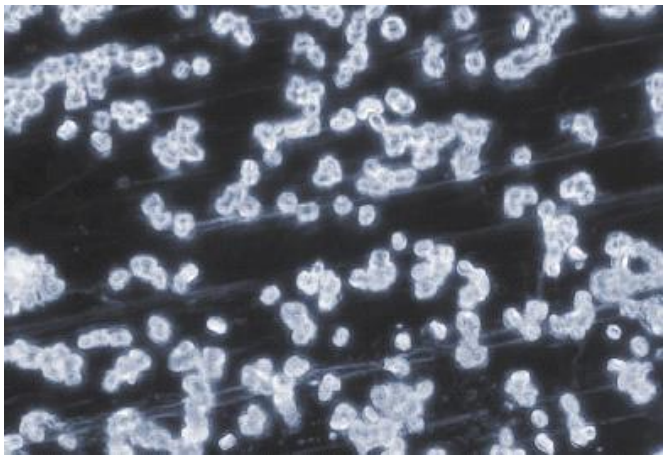

Bio-decontamination with H_2O_2 - Vapor

“VHP” for Isolators

- Vaporized hydrogen peroxide is widely used to decontaminate the inside of pharmaceutical isolators. The good old pioneering days applied a mixture of steam and H_2O_2 to be on the safe side, but validation was a nightmare.
- Nowadays several H_2O_2 gas generators are on the market – different philosophy, but more or less reliable technology.
- Cycle development and validation has become a routine job.

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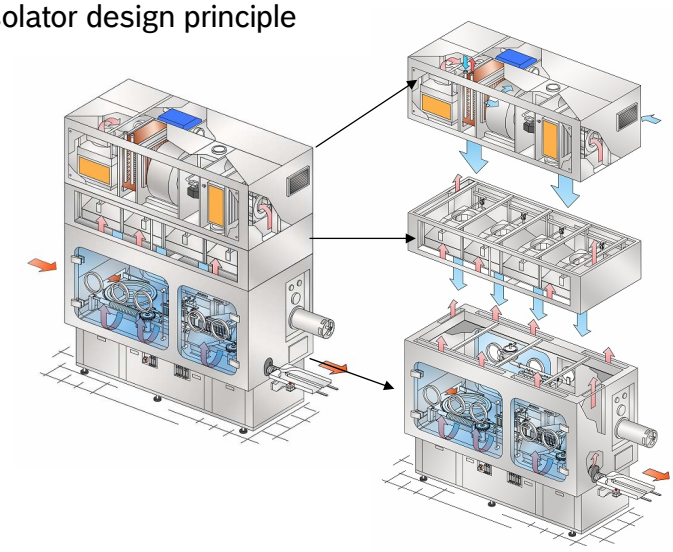
Bio-decontamination with H_2O_2 - Vapor

“VHP” for Isolators

- Isolator design principle



Air Management System (HVAC)

Unidirectional Air Flow Unit

Aseptic Processing Chamber

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Bio-decontamination with H_2O_2 - Vapor

“VHP” for Isolators

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Bio-decontamination with H_2O_2 - Vapor

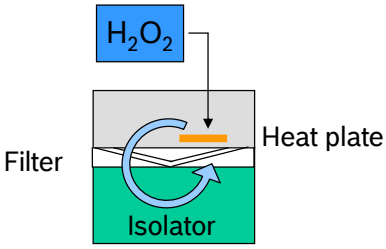
“VHP” for Isolators

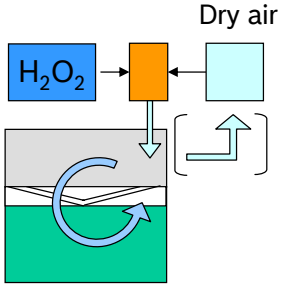
- Closed loop system:

  Liquid H_2O_2 is dropped on a heated plate inside the filter level of an isolator. Recirculation and continous injection of peroxide goes to saturation of atmosphere including strong visible condensation

- Open loop system:

  Liquid hydrogen peroxide is evaporated outside of the isolator in a gas generator; which carries the vapor with air into the isolator, where it is recirculated.
  Some o-l-systems perform “flash evaporation”.





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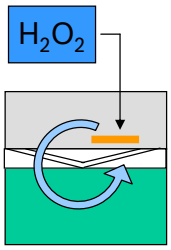
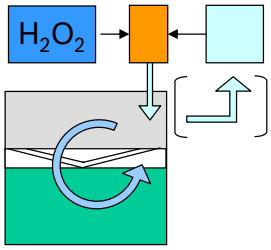
Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators

- Closed loop system:
  - Simple air management
  - Vapor passes filters first
  - Incomplete evaporation
  - Limited injection rate
  - Saturation/condensation soon



- Open loop system:
  - Complete ("flash") evaporation
  - Controlled atmosphere
  - Capability for high gas conc.
  - Air management more complex
  - More sophisticated generator



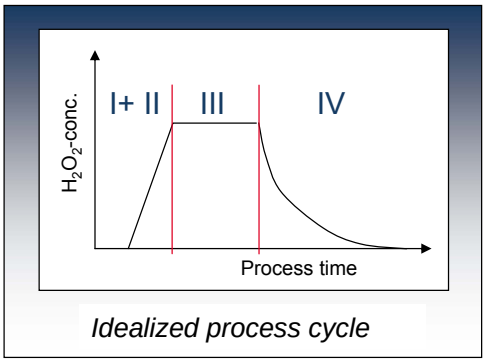
Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators

Preparation (Phase I)
- Expanding gloves, load monitoring goods
- Preparation of isolator atmosphere
- Preheating of peroxide duct work

Conditioning (Phase II)
- Injection of H_2O_2 with a high rate to achieve a high gas concentration

Biodecontamination (Phase III)
- Injection with a lower rate to replace inactivated peroxide and keep level



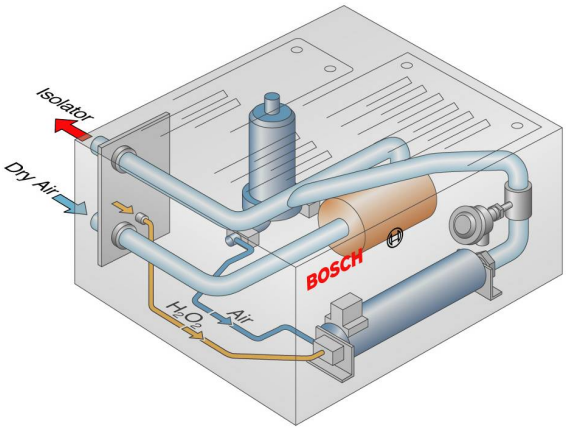
Idealized process cycle

Aeration (Phase IV)
- Removal of H_2O_2 from injection system
- Removal of peroxide from all isolator surfaces including filters.

Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators

- Bosch *SafeVAP* (open loop system)
  Features:
  - Venturi transport
  - 3-step evaporation
  - Inj.rates up to 80g / min
  - Controlled atmosphere



SafeVAP **=** ***Safe*** ***V***acuum ***A***ssisted ***P***eroxide Evaporation

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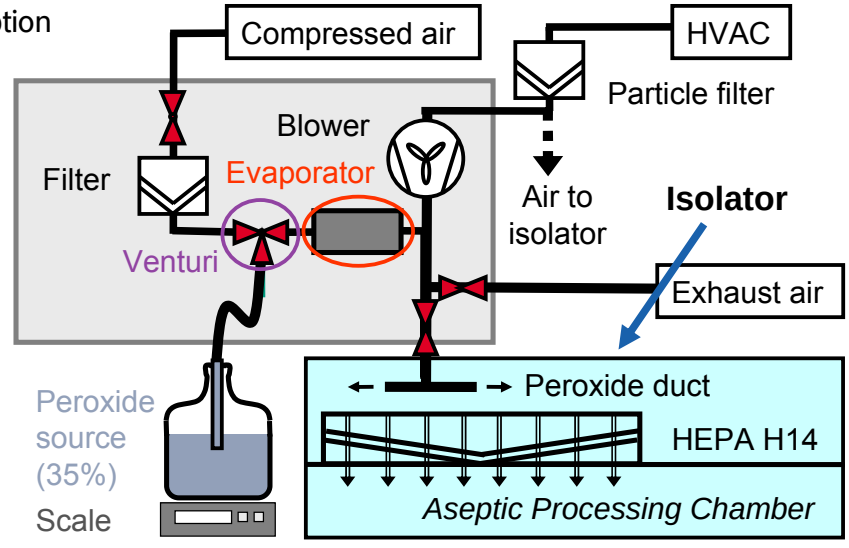
Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators

- Description



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Bio-decontamination with H_2O_2 - Vapor

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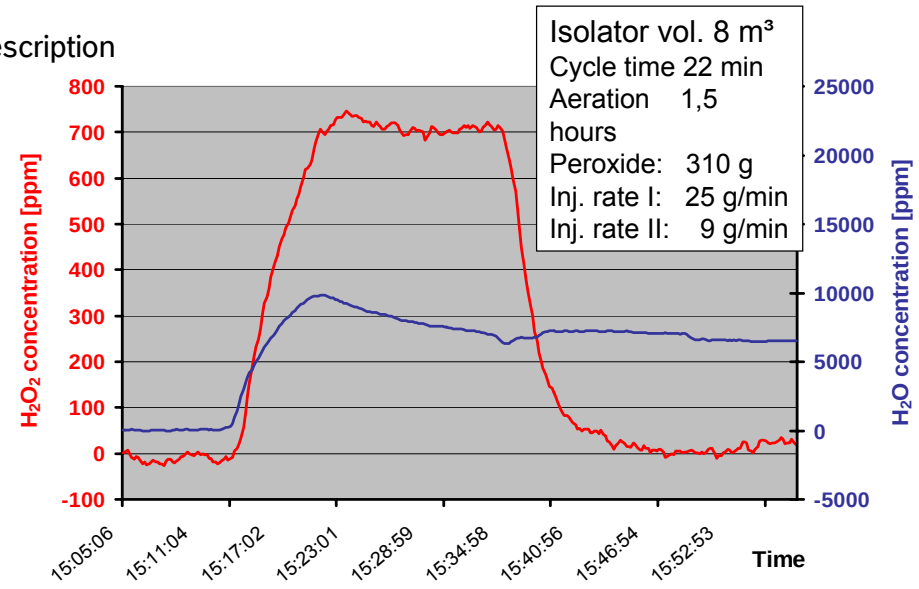

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Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators

- Cycle Development for H_2O_2 bio-decontamination include
  - OQ-studies
  - tests with chemical indicators (CI's)
  - Tests with bio indicators (BI's), which are stainless steel coupons inoculated with 6 log of the most resistant viable (spores of Geobacillus stearothermophilus).
- To ease handling (and to put an extra challenge on the biological test system), BI's wrapped in Tyvek became industrial standard.

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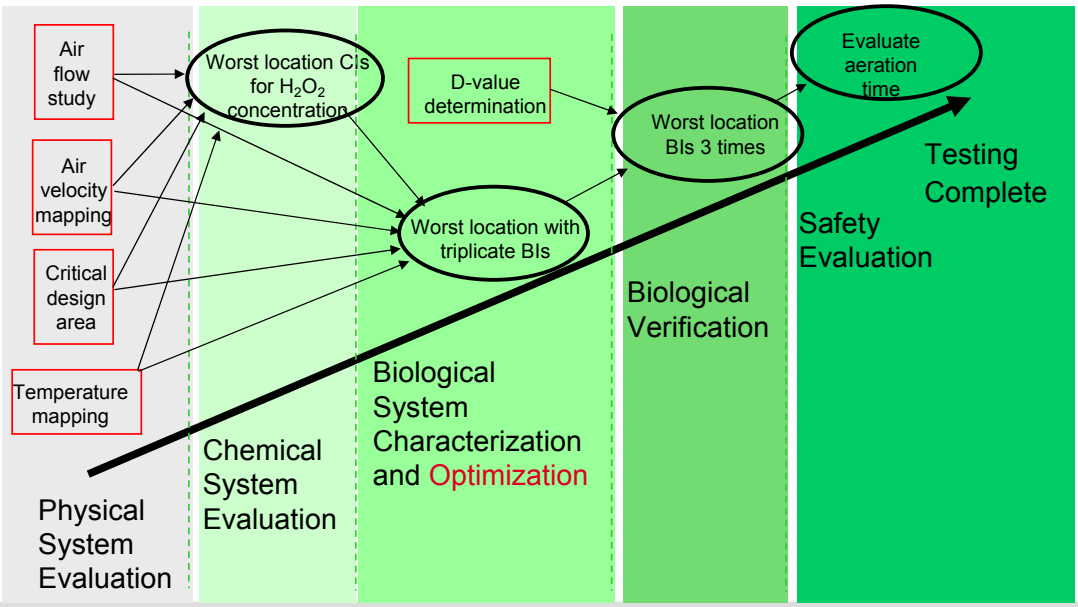
Bio-decontamination with H_2O_2 - Vapor

"VHP" for Isolators



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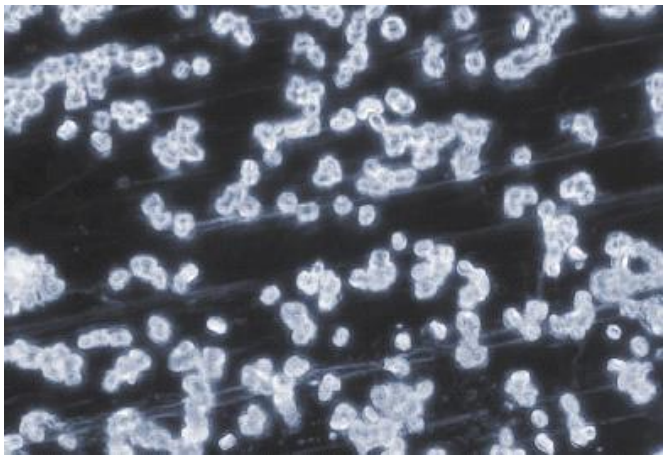

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Bio-decontamination with H_2O_2 - Vapor

Recent Studies

- Many studies were performed at Bosch during the last 3 years (PhD thesis). Basis for these studies was a reference isolator equipped with the SafeVAP system and placed in the Bosch PharmaLab.

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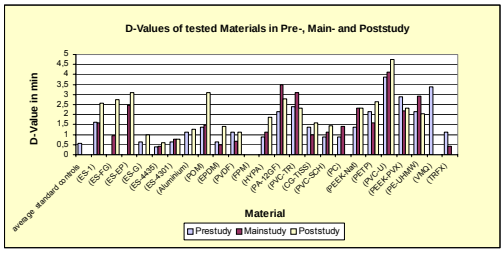
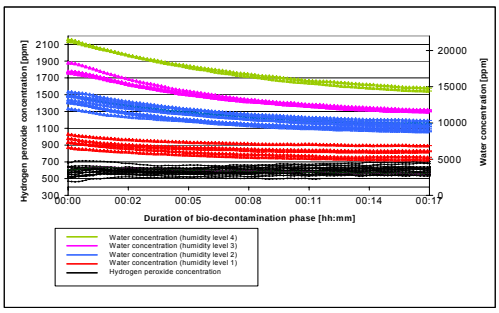
Bio-decontamination with H_2O_2 - Vapor

Recent Studies

- Material of Construction Study: Goal of this study was to learn the influence of different surfaces (material, finish) on inactivation efficacy of bioburden.
- Humidity Study
  Influence of relative humidity at different H2O2 gas con-centration levels was studied and compared with dew point analysis.





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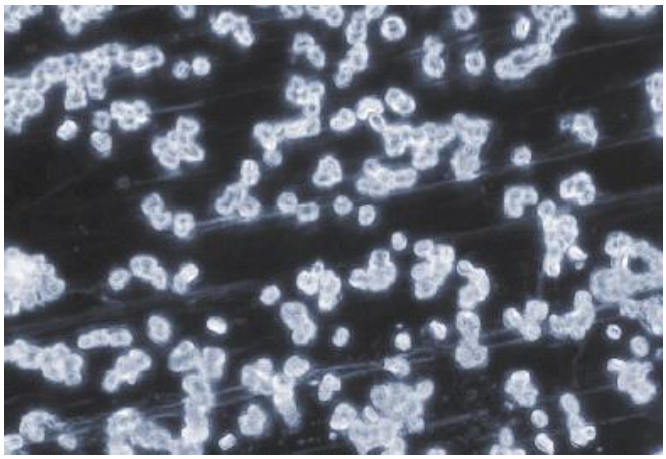
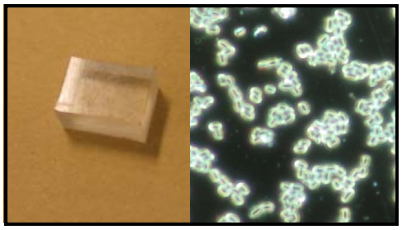


Bio-decontamination with H_2O_2 - Vapor

Results

Objective of material study:

- Examine influence of different construction material surfaces on inactivation of spores
- Determine variable kill kinetics (D-Value)
- Test organism: spores of Geobacillus stearothermophilus ATCC 12980 with population of > 1*106 spores per BI.

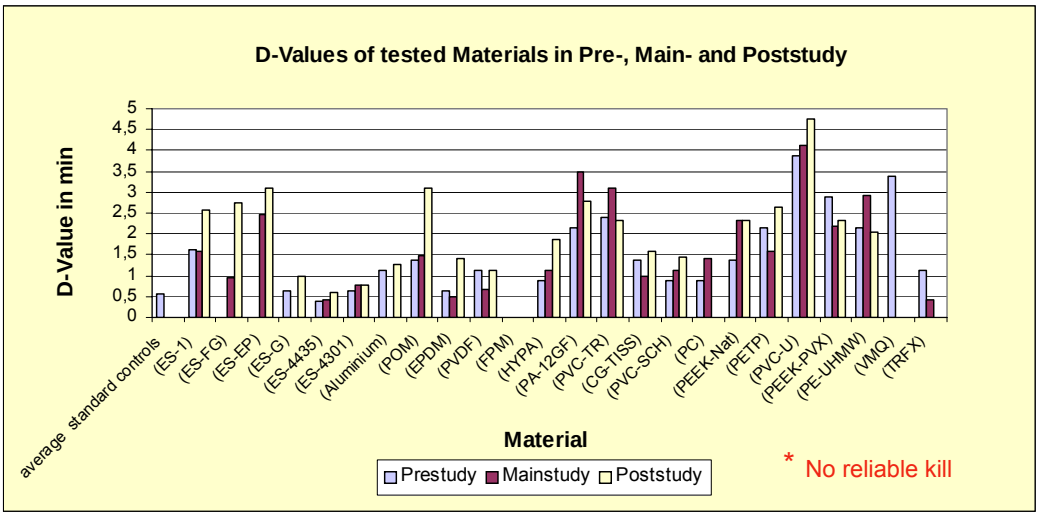


Exposure time [min]	0	5	10	15	20	25
Results	+	+	+	-	-	-
	+	+	-	-	-	-
	+	+	-	-	-	-
	Survival		Fractional	Killing		

Bio-decontamination with H_2O_2 - Vapor

Results

Results on some materials (50 different surfaces tested)



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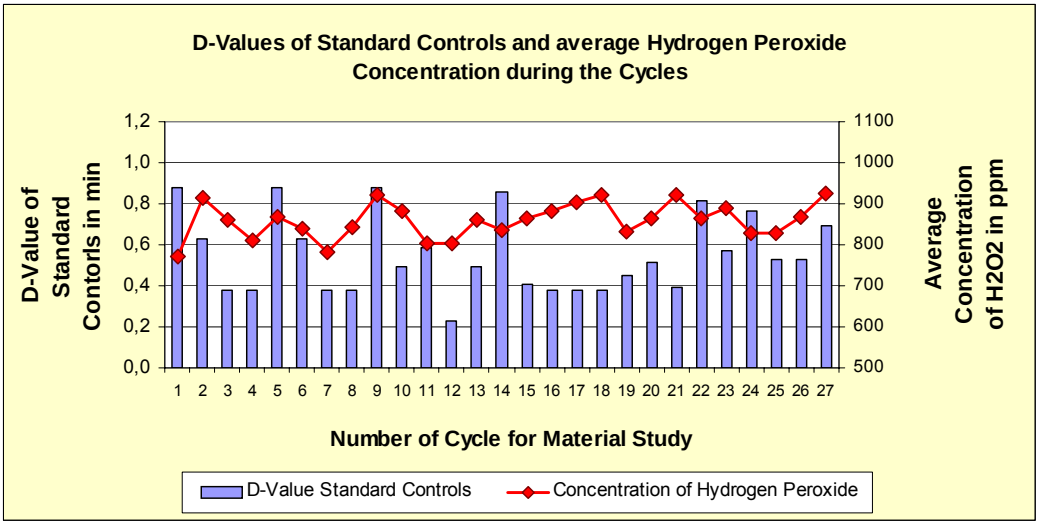
Bio-decontamination with H_2O_2 - Vapor

Results

Results on standard control (commercial Bio indicator made from SSL)



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Bio-decontamination with H_2O_2 - Vapor

Results

Summary of the study:

- Most materials tested show good inactivation properties.
- Plastic/elastomeric materials have generally higher D-values compared with stainless steel and glass.
- Standard commercial available BI's show a certain spread of D-values (0,2 min to 0,9 min – late positives included in the calculation), which represents microbiobolgical accuracy.
- A correlation between wetting properties, surface roughness and the entire D-values can be recognized.
- Critical materials of construction should either be replaced or need prolonging of the cycle time.

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Bio-decontamination with H_2O_2 - Vapor

Results

The results were recently published:

Suitability of Different Construction Materials for Use in Aseptic Processing Environments Decontaminated with Gaseous Hydrogen Peroxide

BEATRIZ UNGER,[1] UTA RAUSCHNABEL,[1] BERTHOLD DÜTHORN,[1] VOLKER KOTTKE,[2] CHRISTIAN HERTEL,[2] AND JOHANNES RAUSCHNABEL[1]

[1]Robert Bosch GmbH, Blaufelder Str. 45, 74564 Crailsheim, Germany, Phone: +49 7951 402-471, Fax: +49 711 811-5180358, E-mail: beatriz.unger@de.bosch.com; [2]University of Hohenheim, 70599 Stuttgart, Germany

PDA journal, Vol. 61, No. 4, July-August 2007

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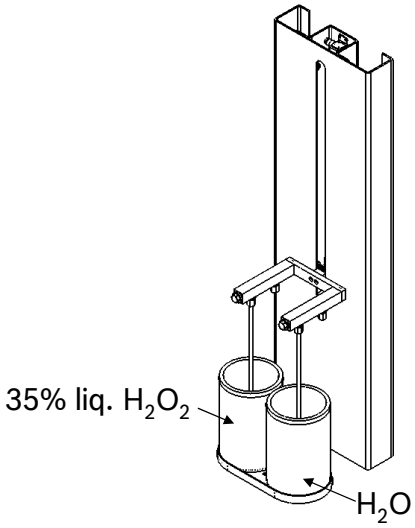
Bio-decontamination with H_2O_2 - Vapor

Results

Procedure for Humidity study:

- Separate evaporation of water and hydrogen peroxide (35%)
- Control of humidity level with NIR probe, dew point sensor and standard humidity sensor
- D - value determination of commercial BI's (SSL)
- Investigation on inactivation in hindered surfaces with high aspect ratio



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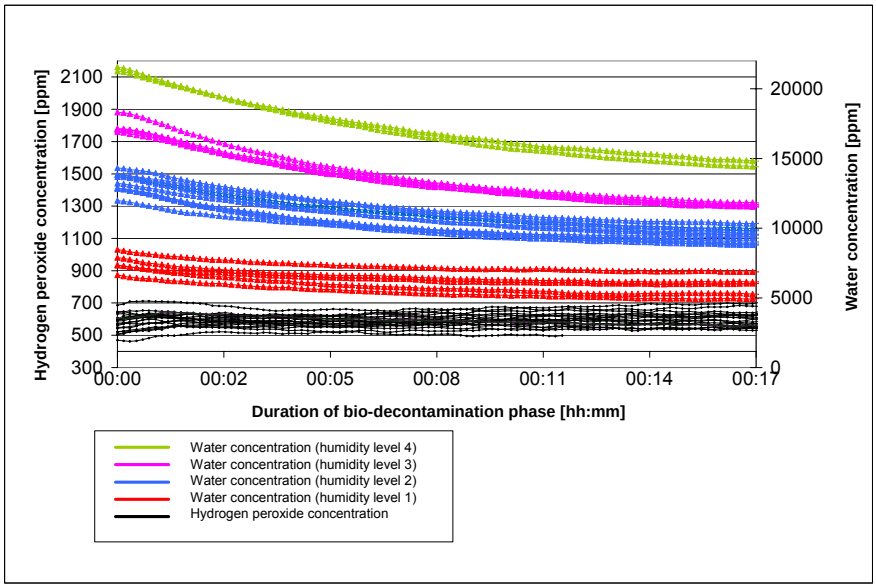
Bio-decontamination with H_2O_2 - Vapor

Results

Details:



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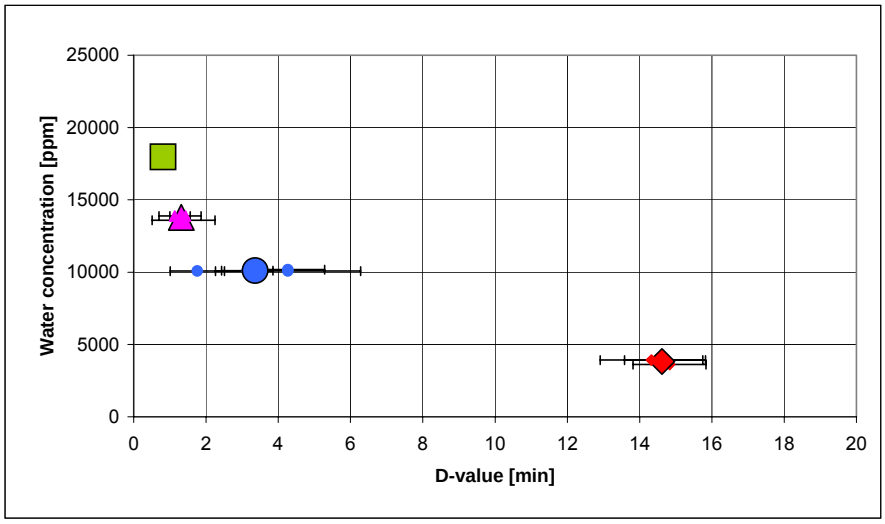
Bio-decontamination with H_2O_2 - Vapor

Results

400 ppm:



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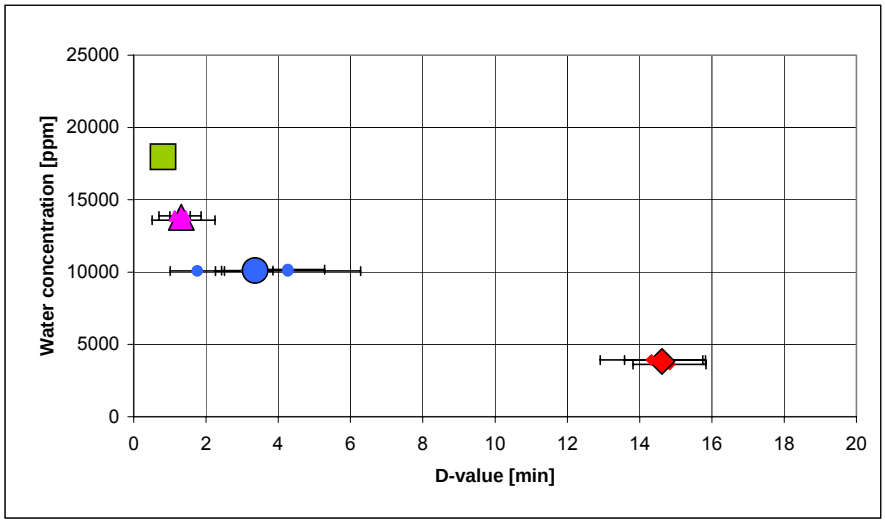
Bio-decontamination with H_2O_2 - Vapor

Results

600 ppm



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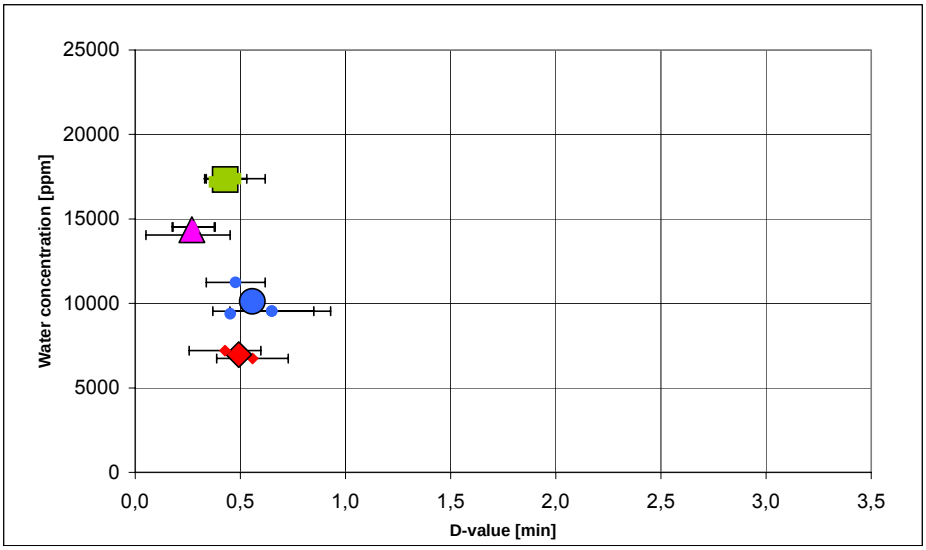
Bio-decontamination with H_2O_2 - Vapor

Results

800 ppm:



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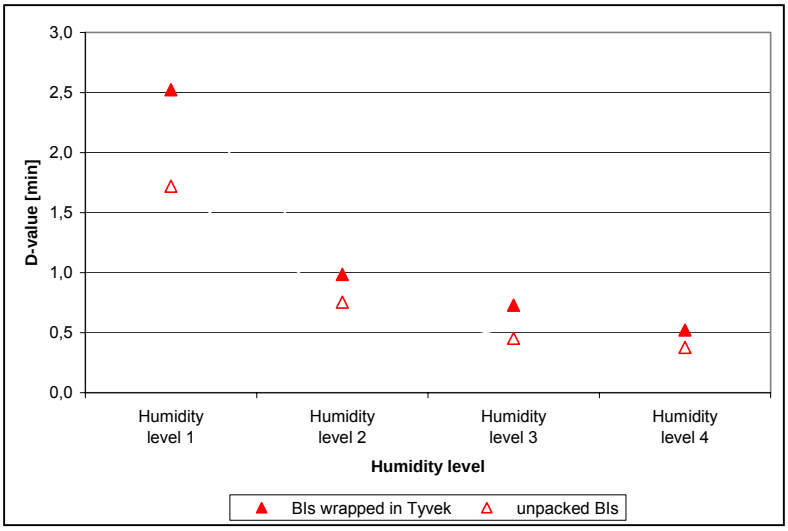
Bio-decontamination with H_2O_2 - Vapor

Results

Comparison
Wrapped vs.
Nude BI's :



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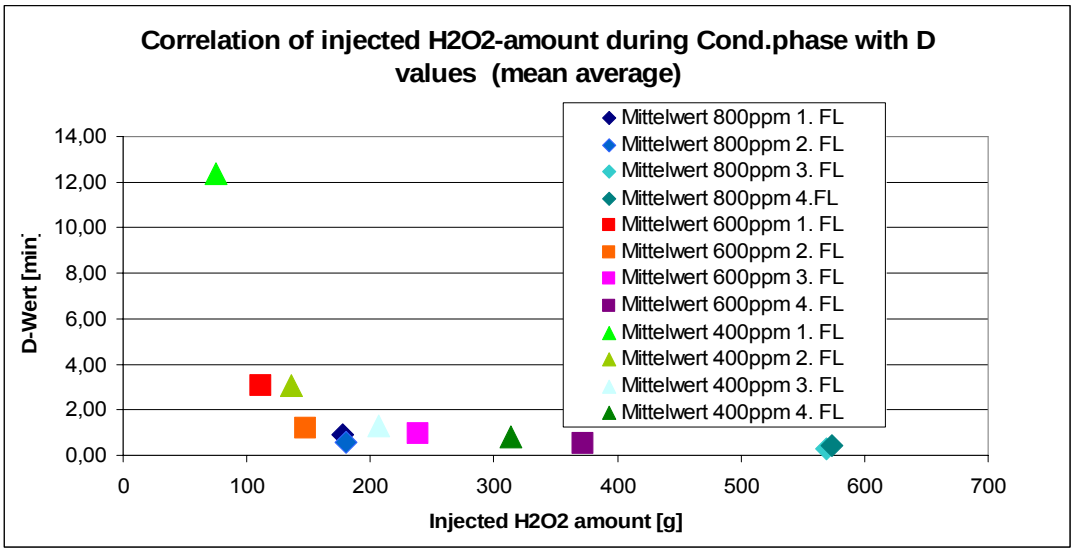
Results



Bio-decontamination with H_2O_2 - Vapor

Results

Summary:

- The higher the cgas phase concentration, the more independent is the inactivation effect from the humidity level.
- At lower concentrations the same kill as at higher concentration can be achieved with higher humidity (condensation)
- The faster the concentration rises during conditioning phase (flash evaporation), the less peroxide is needed to achieve a good kill.
- (Nano/micro) condensation occurs at all humidity levels. Visible concentration is not needed to get short inactivation times.

Structure

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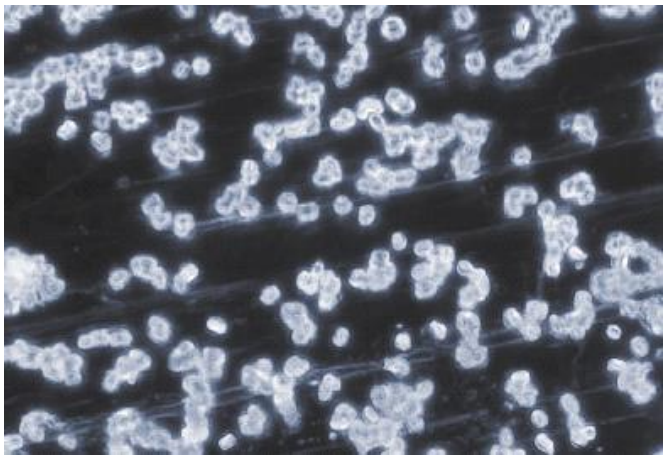
- "VHP" for Isolators
- Results
- More Applications
- Summary



More Applications

- Vaporized H_2O_2 is applied with all kinds of isolators: fill/finish isolators, sterility testing isolators, hospital isolators…
- A new trend is fumigation of cleanrooms and animal testing facilities with hydrogen peroxide vapor.
- H_2O_2 in vapor state could potentially replace alcoholic spray&pray procedures in material transfer chambers and material locks for thermolabile products.
- Bio-decontamination of tubs with presterilized, nested syringes can also be performed with H_2O_2.

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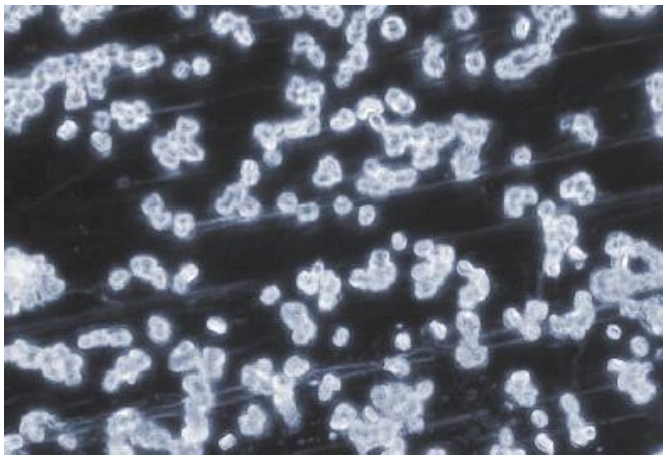

Summary

- Hydrogen peroxide vapor is widely used in pharmaceutical industry. One major application is disinfection of isolator interior.
- Closed and open loop systems are established in the market, which are technically robust and validatable.
- Inactivation effect on bioburden differs depending on the material of construction (material and finish).
- Gas concentration and humidity effect dominate the kill efficacy: high gas concentrations through flash evaporation help to achieve efficient processes.
- New applications of H_2O_2 vapor include cleanroom fumigation and decontamination of thermolabile materials in transfer chambers,

Bio-decontamination with H_2O_2 - Vapor

BOSCH