Vaporized Hydrogen Peroxide (VHP®) Gaseous Decontamination :

'GREEN' Technology for the Highest Level of Microbial Control within a Pharmaceutical Facility

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ISPE Boston Area Chapter
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Agenda – Part 1

- Overview of the VHP Process: efficacy, safety, regulatory landscape, environmental properties and material compatibility
- VHP Technology and Equipment
- VHP Biodecontamination Field Applications
- VHP Services and Project Planning
- Case Studies

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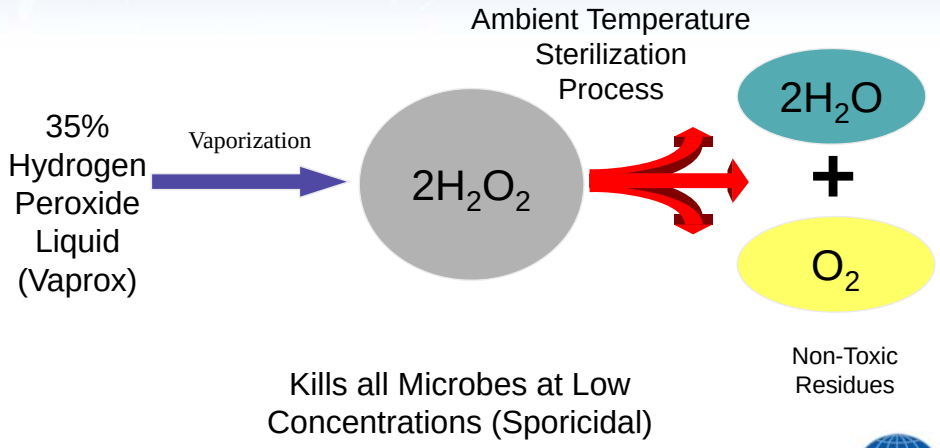
Why Gaseous Decontamination?

- Contamination remediation
- Pre-occupancy new or renovated facility
- Preventative periodic bio-burden reduction
- Product/population change
- Equipment transfer
- Facility decommissioning
- Equipment maintenance, i.e. BSCs, HEPA housings, etc.

VHP: Background and History

- VHP process developed mid-1980s, utilizing patented closed-loop, low concentration “dry” process
- VHP process patent issued in early 1990s
- Over 1,200 VHP systems in use world-wide in pharma, med device, LAR, bio-containment fields
- 15+ years of validated use in pharmaceutical manufacturing
- Large scale VHP facility applications applied for remediation during 2001 anthrax attacks
- 2007 VHP contract service offering available to industry

VHP: the Process



Kills all Microbes at Low Concentrations (Sporicidal)

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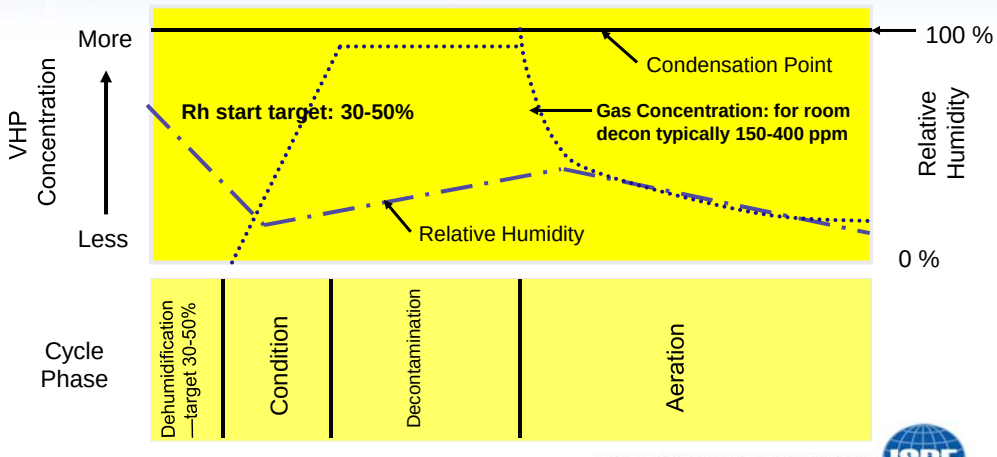
"Typical" VHP Biodecontamination Cycle



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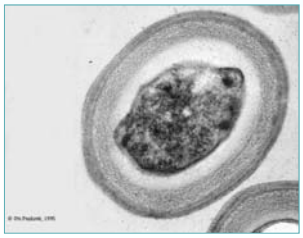
Variables Affecting Efficacy

- Temperature and humidity affect how much hydrogen peroxide (HP) can be generated in the gas state, start Rh typically 30-50%
- Concentration—typically 150-400 ppm room applications
  - (injection rate/ air flow) * wt. % of HP
- Saturation
  - Inject as much as possible but below dew-point
  - Humidity is good for microbial kill
- Distribution—may be facilitated with fans
- Materials which can reduce VHP concentration, cellulosic material (i.e. cardboard, paper), galvanized steel, standing water

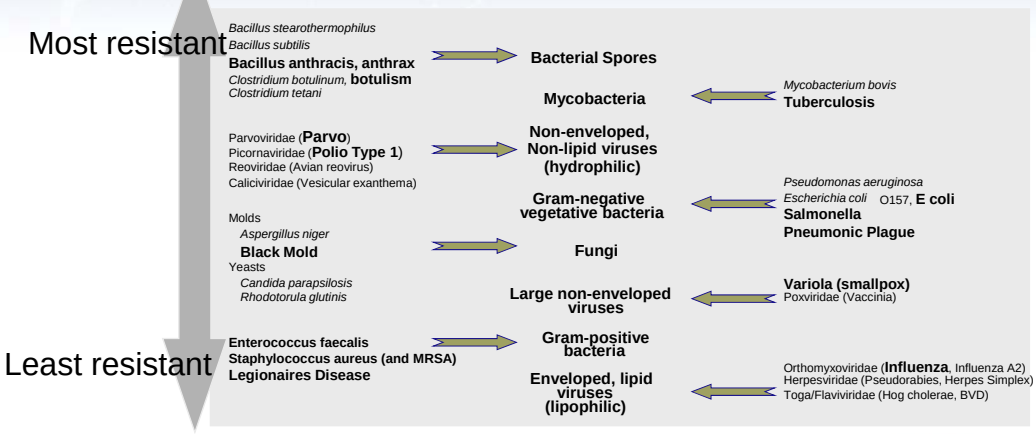
Why H_2O_2 Vapor? <u>Sporicidal at Low Concentrations</u>

- Bacterial Spores - Most Resistant Organism to VHP
- Highly sporicidal even as low as 0.1 mg/l
- Broad kill spectrum
- 35% H_2O_2 Registered EPA sterilant
- As per EPA label short "contact" times, **six log reduction: 30-90 minutes @ 250-400 ppm**



Geobacillus stearothermophilus Cross section

Resistance to VHP for Biological Organism Classes

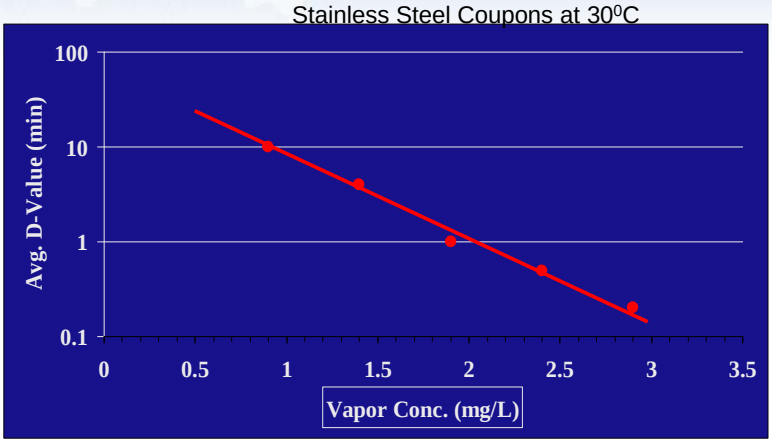


Why H_2O_2 Vapor? Efficacy Testing and Monitoring

- Biological Indicators - Most VHP Resistant *geobacillus stearothermophilus* typically 4-6 log
- Chemical Indicators – Qualitative instant feedback
- Real-time monitoring with electro-chemical sensors

VHP Kill Matrix

Geobacillus stearothermophilus spores inoculated on Stainless Steel Coupons at 30^0C



Bacterial Spores Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Bacillus anthracis*
- *Bacillus cereus*
- *Bacillus circulans*
- *Bacillus pumilus*
- *Geobacillus stearothermophilus*
- *Bacillus subtilus*

- *Clostridium botulinum*
- *Clostridium sporogenes*
- *Clostridium tetani*
- *Clostridium difficile*

Mycobacteria Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Mycobacterium smegmatis*
- *Mycobacterium terrae*
- *Mycobacterium bovis*
- *Mycobacterium tuberculosis*
- *Nocardia lactamdurans*

Non-enveloped, Non-lipid Viruses Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Parvoviridae (Feline and Canine parvovirus)*
- *Picornaviridae (Polio Type 1, Swine Vesicular, Rhinovirus 14)*
- *Reoviridae (Blue Tongue, Avian reovirus)*
- *Caliciviridae (Vesicular exanthema)*

Gram-negative Vegetative Bacteria Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Burkholdia cepacia*
- *Pseudomonas aeruginosa*
- *Serratia marcesens*
- *Escherichia coli*
- *Proteus vulgaris*
- *Salmonella choleraesuis*

Fungi, Molds, and Yeasts Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Aspergillus niger*
- *Aspergillus terrus*
- *Candida parapsilosis*
- *Rhodotorula glutinis*
- *Fusarium oxysporum*
- *Penicillium chrysogenum*

- *Candida parapsilosis*
- *Saccharomyces cerevisiae*
- *Rhodotorula glutinis*

Large Non-enveloped Viruses Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Adenovirus (Adenovirus 2)*
- *Poxviridae (Vaccinia)*

Gram-positive Bacteria Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Enterococcus faecium*
- *Enterococcus faecalis*
- *Staphylococcus aureus* (MRSA)
- *Lactobacillus casei*
- *Listeria monocytogenes*
- *Legionella pneumophilia*

Enveloped, Lipid Viruses Evaluated for Their Resistance to Hydrogen Peroxide Gas

- *Orthomyxoviridae (Avian Influenza)*
- *Paramyxoviridae (New Castle)*
- *Herpesviridae (Pseudorabies, Herpes Simplex)*
- *Rhaboviridae (Vesicular stomatitis)*
- *Toga/Flaviviridae (Hog cholerae, BVD)*

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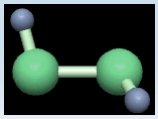
Why H_2O_2 Vapor? Safety Profile



Hydrogen Peroxide	Chlorine Dioxide	Formaldehyde
Skin/eye irritant	Severe irritant	Human carcinogen
PEL 1.0 ppm	PEL 0.1 ppm	PEL 0.75 ppm
IDLH 75 ppm	STEL 0.3 ppm	STEL 2 ppm
	IDLH 5.0 ppm	IDLH 10 ppm

PEL - Permissible Exposure Limit (8 hours)
STEL - Short-term Exposure Limit (15 min.)
IDLH - Immediately Dangerous to Life or Health

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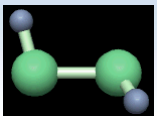
Why H_2O_2 Vapor?
Safety Profile



Typical Decontamination Concentrations:

VHP	Chlorine Dioxide	Formaldehyde
150-400 ppm	500-1,500 ppm	8,000-10,000 ppm

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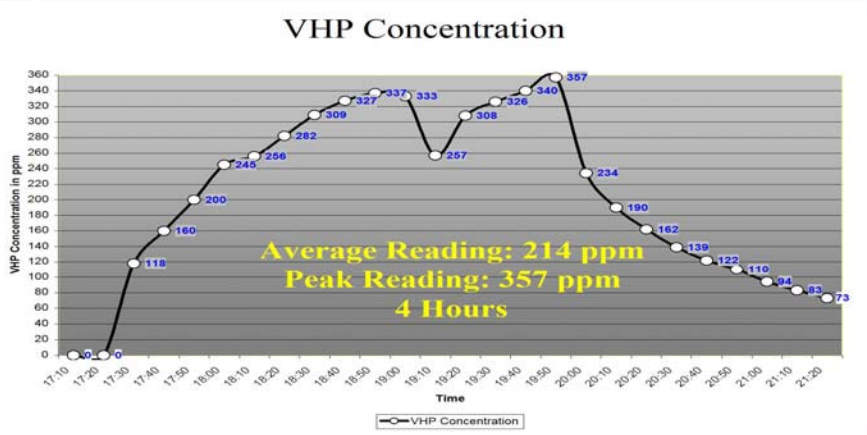
Why H_2O_2 Vapor?
Safety Profile, VHP Degradation: real-time monitoring



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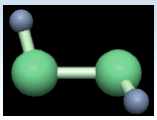
Why H_2O_2 Vapor? Safety Profile



When considering VHP typical use concentrations, degradation and migratory properties and OSHA exposure limits, VHP offers less exposure risk to personnel and animals where small leaks occur.

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Why H_2O_2 Vapor? A Green Solution

Non-toxic byproducts

$2H_2O$ + O_2

No post-decon wipe down

EPA: “no risks to the environment are expected from use of pesticide products containing hydrogen peroxide because 1) the substance readily decomposes to water and oxygen gas, leaving no residue; 2) it is effective at low concentrations where no toxic effects are expected” www.epa.gov

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Material Compatibility*

Metals

Aluminum Excellent
Anodized Aluminum Good
Brass Good
Copper Good.
Stainless Steel – all grades Excellent
Steel Good
Titanium Excellent

Stainless Steel – all grades Excellent
Steel Good
Titanium Excellent

Plastics

ABS Excellent
Aflas Excellent
CPVC (chlorinated polyvinylchloride) Excellent
Kel –F Excellent
Nylon Fair
PMMA Excellent
Polyethersulfone (**PES**) Excellent
PolyethyleneTerephthalate (**PET**) Good

Polyacetal (**Delrin**) Excellent
Polycarbonate Excellent
Polyetherimide (**Ultem**) Excellent
Polymethylepentene Excellent
Polyphenylene oxide Excellent
Polyetherketone (**PEEK**) Excellent
Polyethylene (**HDPE, LDPE UHMWPE**) Excellent

Elastomers

Buna N Fair
Butyl Rubber Good
Chem Raz Good
EPDM Fair
Viton Excellent

Hypalon Excellent
Polyurethane Excellent
Silicone Rubbers Excellent
Kelrez Excellent

*Compatibility is defined as the materials ability to undergo exposure to VHP with no significant changes in physical, or chemical properties (i.e. no changes in strength, flexibility, chemical composition, color etc.).

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Why H_2O_2 Vapor?
Material and Component Compatibility Pharma Project
Pilot Field Test

- laptop computer (turned on)
- LCD monitor (turned off)
- telephone (on)
- electronic scales (on)
- various electronic sensors
- stainless steel clamps, fittings, and connectors
- rubber grommets and washers
- rubber hoses
- plastic funnel and containers

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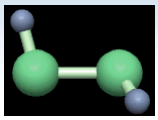
Why H_2O_2 Vapor?
EPA-registered, FIFRA compliant



In compliance with Federal Insecticide, Fungicide and Rodenticide Act, all anti-microbial agents must be EPA registered.
35% hydrogen peroxide
EPA reg. no. 58779-4

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Why VHP? A Summary of Advantages

- Rapid decontamination at ambient temperatures and low concentrations
- Strong history of use and efficacy data, easily validated with BIs
- Strong comparative safety profile—detectable well below IDLH, no “trapped gases”
- Non-toxic by-products-a “green” solution
- No lengthy aeration
- No residue
- Strong material and component compatibility profile
- EPA Registered—FIFRA compliant

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VHP Pharmaceutical Facility Applications

Rapidly Increasing in Popularity, Common Applications Include:

- Aseptic Manufacturing Rooms and Pilot Production Rooms: pre-occupancy new or renovated facility, remediation of know contaminant, periodic preventative
- Tissue Culture Rooms, Cold Rooms, Warm Rooms
- Lab Animal Research Procedure, Cage Change and Equipment Transfer Rooms
- Biological Safety Laboratories Level 3 (BSL-3)
- Biological Safety Cabinets, Incubators, Enclosures

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VHP Generation Technology

- Mobile VHP
- Installed VHP
- Facility integrated VHP
- EPA-registered 35% HP
- For Room Applications with ARD use, for 3,500 ft^3 room, typically 1 machine will achieve six-log kill in 2 hours or 7,000 ft3 in 4 hours

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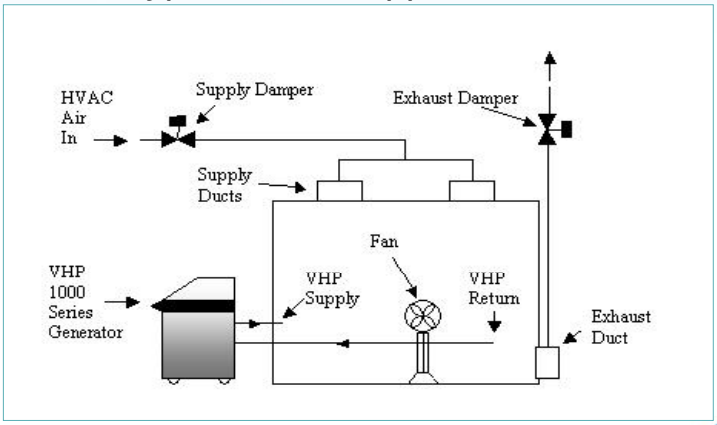
Methods of VHP Injection

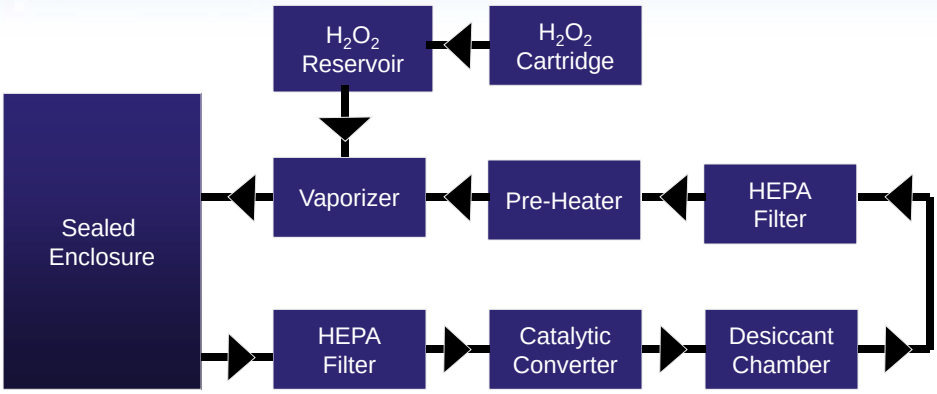
- External via integrated ports
- External via installed Plexiglas panels
- In room, solo or daisy-chained
- Via AHUs (can include ductwork decontamination)

VHP Room Decontamination

Typical Room Application



Flow Diagram



VHP Service Project Planning

- Fumigation management plan (FMP) project document
- Define purpose and scope of decontamination
- Identify the team players including stakeholders and support personnel (area managers and PIs, EH &S, facilities engineering, security, etc.) and assign responsibilities
- Review site schematics, perform site visit, evaluate HVAC and electrical capabilities
- Review personnel/authority notification, site control and security, site signage

VHP Project Planning contd.

- Review area preparation: pre-cleaning, material/equipment transfer, HVAC control/support, smoke detector disengagement responsibilities, sealing of space
- Establish safety buffer zone, project safety plan and external monitoring plan
- Review post decontamination area clearance and equipment/material retrieval procedures
- Define acceptance criteria, establish BI quantity/mapping where applicable
- Establish the final project schedule, task sequencing and responsibilities

VHP Project Execution

- Upon arrival to job site equipment, material and personnel transfer commences in accordance with site requirements (gowning, equipment transfer protocols)
- Target area is prepared for decontamination: BI, CI, VHP generator, fan, emergency signage placement
- Smoke detectors disengaged/ HVAC isolated
- Final pre-go walk-thru/assessment with client to confirm area readiness
- Upon client authorization/clearance VHP injection commences
- Real-time internal and external monitoring of VHP
- Following injection commensurate with project requirements, aeration commences to bring VHP levels in area to below PEL 1.0 ppm
- Following area clearance, equipment, and BI/CI retrieval
- Upon completion of independent third-party BI analysis, report issued

Case Study 1:
Pharmaceutical Manufacturing Facility

- Project scope: 240,000 ft^3 manufacturing space including bioreactor rooms
- Issue: bacterial remediation emergency
- Remote (AHU) and terminal ceiling HEPA filtration
- AHU and local VHP injection

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VHP Case Study 1 continued

- 65 rooms, 48 hours
- 56 liters of Vaprox 35%
- 165 biological indicator locations
- 95 Chemical Indicators
- VHP injection 12 g/min
- VHP average concentration 242 ppm

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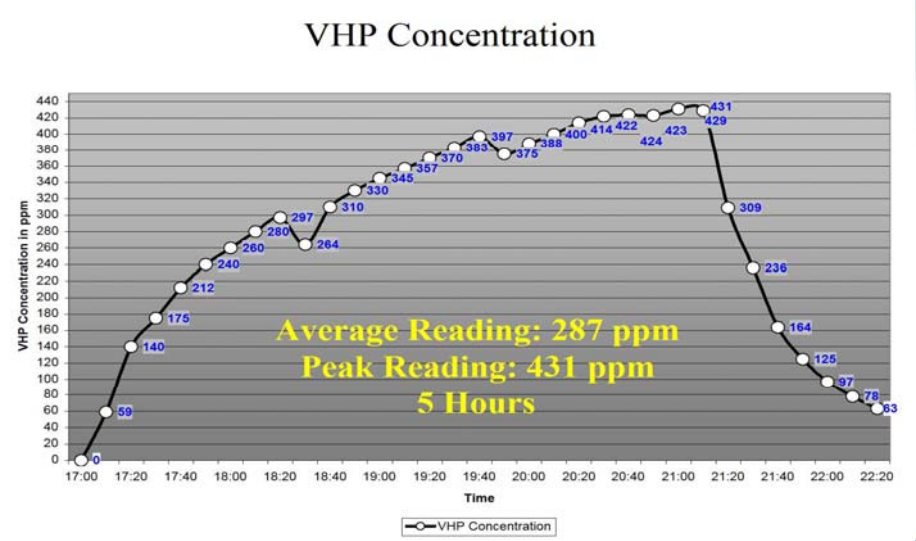
VHP Case Study 1 continued



VHP Case Study 1: Results

- All CIs changed color
- 96% BIs ≥ 6 log kill, with remaining ≥ 5 log kill
- External monitoring VHP concentration < 1.0 ppm throughout safety perimeter

Case Study 2:
Pharmaceutical Manufacturing Facility

- Project Scope: 84,000 ft^3 pilot production facility
- Issue: Preventative during shutdown
- Remote (AHU) and terminal ceiling HEPA filtration
- Local VHP injection

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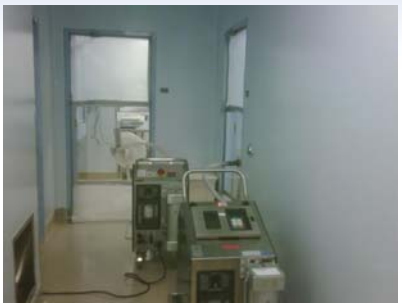
VHP Case Study 2 continued

- 28 rooms, 24 hours
- 22 liters of Vaprox 35%
- 65 biological indicator locations
- 28 Chemical Indicators
- VHP injection 12 g/min
- VHP average concentration 282 ppm



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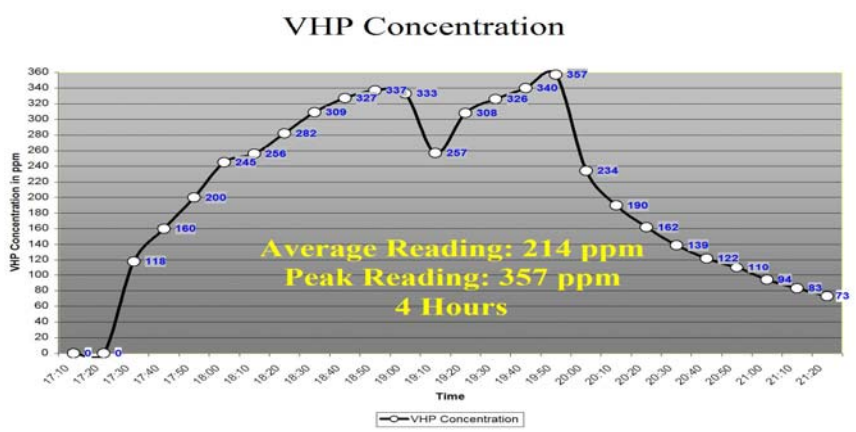
VHP Case Study 2 continued



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VHP Case Study 2 continued

- All CIs changed color
- Six-log kill all 65 BIs
- External monitoring VHP concentration < 1.0 ppm throughout safety perimeter

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Questions and Project Discussion

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Agenda – Part 2

- H_2O_2 - Vapor vs. Condensate
- Portable or Modular?
- Installation of Modular VHP Systems
- Modular VHP Case Studies
- Final Thoughts

Vapor or Condensate?

Boiling Points:
H_2O 100°C
H_2O_2 150°C

…if you can see it, it's not a vapor

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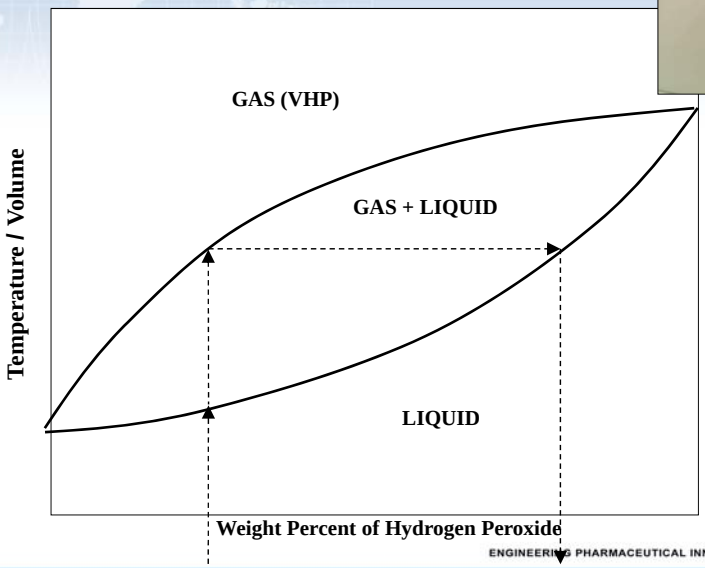
Vapor (300ppm) vs. Condensate (700,000ppm)



Effect of improper application

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VHP Flexibility

- Maximum flexibility – multiple enclosure types
- Rooms, product or package handling equipment
- Integrations with Chambers, Washers and Autoclaves

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Which VHP System?

Portable

- ✓ Spaces not yet defined
- ✓ Uses in different buildings
- ✓ Typically less than 10,000ft3
- ✓ Cycle time not a constraint
- ✓ Use of fans not an issue
- ✓ Less frequent use

Modular

- ✓ Large and small spaces up to ~80,000 ft3
- ✓ Same enclosures repeatedly
- ✓ Frequent use (chamber)
- ✓ Short cycle times
- ✓ Automated sequenced decontamination of multiple rooms

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Why Modular?

Keep Equipment Outside Space

- Save space within room / Pass Through
- Avoid cross contamination
- Keep maintenance activities outside

No Set Up

- Decon at the Press of a Button
- Run Sequential Decons via BMS*
- Reduced Handling of Peroxide Excellent Distribution

Cost

- Less expensive than multiple portables
- Save on labor
- The easier to use – the more frequent the use -the cleaner the space

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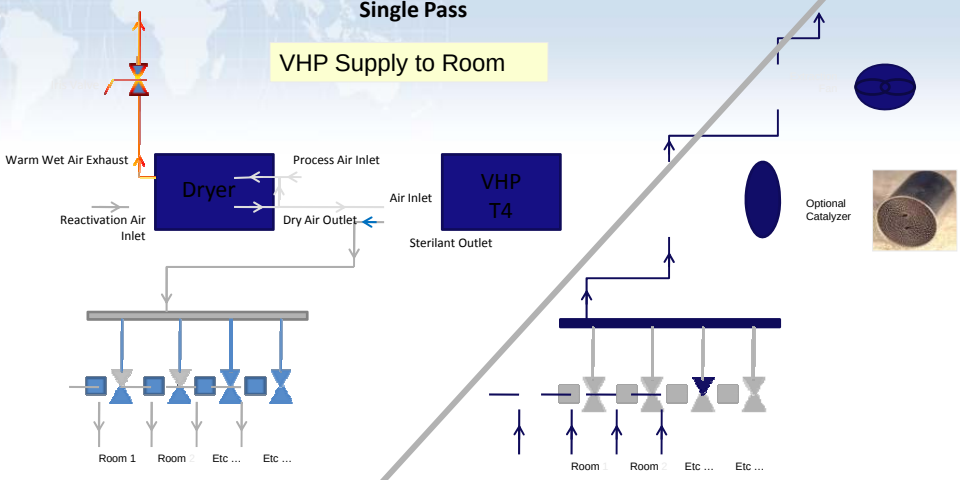
*BMS = Building Management System

VHP Modular Integration Schematic

Single Pass

VHP Supply to Room



VHP Exhaust from Room

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VHP Emissions

- No EPA Limit
- Uniform Fire Code
  - ½ IDLH emergency conditions for “toxic” gases
  - Local regulations ? Check.

Exhaust is rarely if ever an issue.

Why?

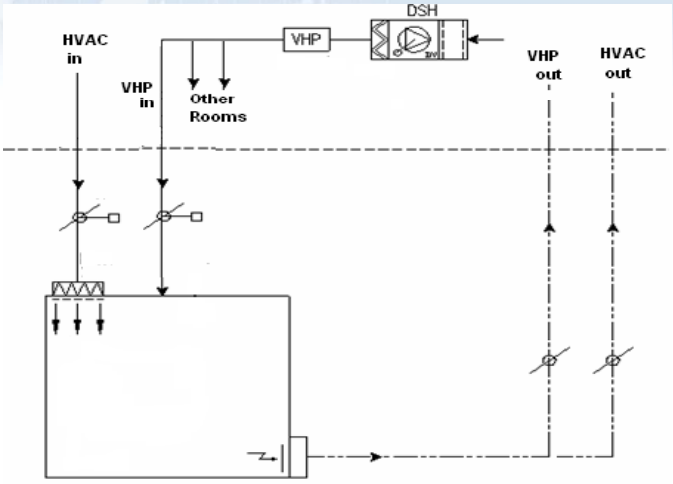
- Dilution
- Break down (galvanized ductwork)
- Easy to install catalyst

There are 2 options for integration...

Airflow	Single Pass	Recirculating
Typical Applications	BSL, Lab Animal	Clean Room, RABS
Dehumidification	HVAC	HVAC
VHP Supply	Dedicated each room	HVAC
Pressure control	Dedicated blower	HVAC
Aeration	HVAC	HVAC

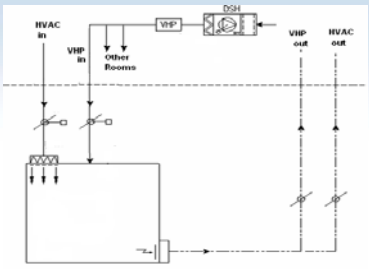
T4

Single Pass System

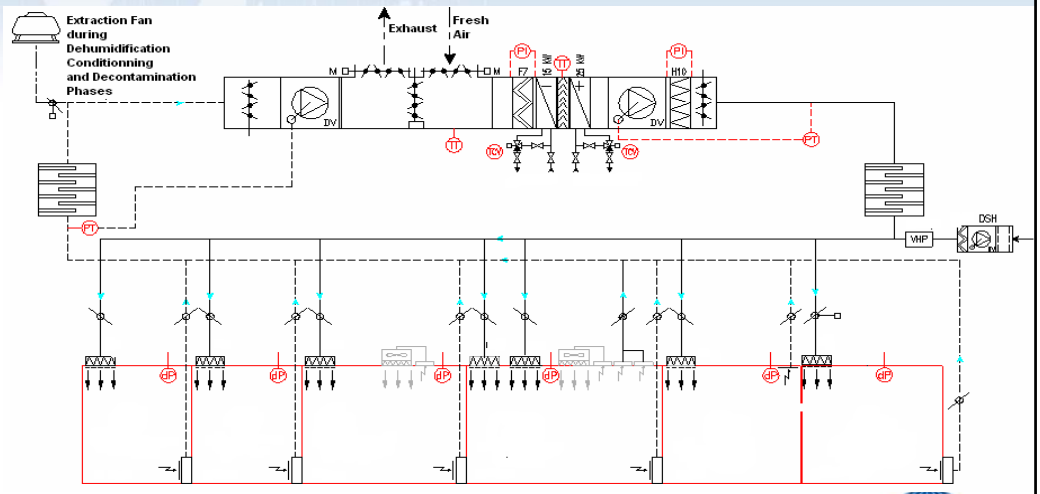


Single Pass System

- VHP Pipes
  - Made of CPVC or PP
  - Insulated (supply only) but not traced
- Cycle Phases
  - Dehumidification via HVAC
  - Decontamination phase
    - HVAC is stopped
    - Leaktight dampers are closed
    - Gas flows into and from the rooms at specified rates via pre-set butterfly valves
  - Aeration Phase
    - HVAC restarted (VHP - exhausted to outside)
- Pressure Control (Positive or Negative)
  - Possible during decontamination cycles
  - On small and/or leaktight rooms
  - By variable speed exhaust fan



Recirculating System (Clean Room)



Recirculating System

- VHP Pipework
  - Made of CPVC or PP.
  - Section to central supply insulated but not traced
- Ductwork / HEPAs
  - Must be air-tight
  - Materials - PVC coated, galvanized, Aluminum , Stainless Steel but no bare copper
  - VHP will penetrate and decontaminate HEPAs
- Cycle Phases:
  - Dehumidification/ Injection Phase
    - Runs closed loop only , with no fresh air.
    - Recirculation allows an even distribution of the gas concentration in all the rooms .
    - Cooling and heating of the HVAC will be stopped .
  - Aeration: the maximum of fresh air is admitted during the Aeration Phase

Large Room Biopharmaceutical Fermentation Suite

Volume: 32,000ft³ (900m³)

Ceiling height: 28ft (8,5m)

Single pass, No fans

6-log reduction

Cycle time 6 hours

New construction

Cycle Phase	Time min.	Airflow	Injection g/min
Dehumidification	30	6 A.E./ hour	-
Condition	30	120 cfm	96
Decontamination	90	120 cfm	60
Aeration	210	40 A.E./ hour	-

A.E. = Air Exchange

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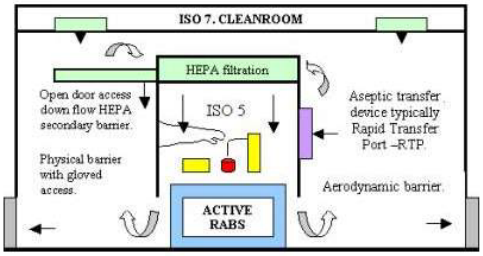
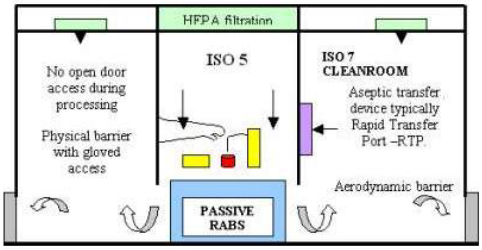
RABS – (Restricted Access Barrier Systems)

Modular VHP systems can rapidly decontaminate both Active & Passive RABS and the surrounding rooms.





Source: Pharmaceutical International

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Pass-Through Chambers / Transfer Hatches / Material Air Locks

Shown above

Enclosure v Volume ft3	Enclosure surface material	Injection rate Condition g/min.	Injection rate Decon g/min.	Decon time Min 6 log	Decon airflow ft3/min	PPM	Aeration airflow ft3/min	Total Cycle Time min.
460 (6x8x9.5'L)	Stainless	32	23	12	**120**	1000	**765**	45
175 (4x6x7'L)	Epoxy paint	12	9	8	**40**	950	**1750**	30

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HEPA Filter Decontamination

Exhaust

Inlet

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BSL Lab & BSC Decon
Single Pass

Simultaneous Decon of Primary Containment

A2 type biosafety cabinets can be decontaminated together with the room

- Exhaust dampers above cabinets are closed
- Cabinet blowers left on

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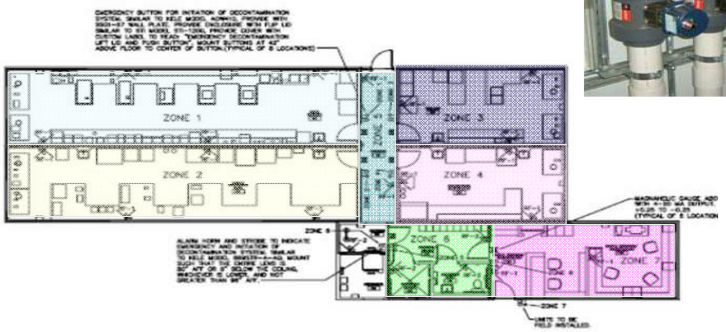
Automated Sequential Zone
BSL-3 Lab Decontamination
Single Pass



Zone
1
2
3
4
5
6
7

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Task List

Vendor	General Contractor
✓Parts	✓Parts
VHP Generator	Ductwork (piping)
Dehumidifier (Munters)	Dampers (airtight)
Bulk Fill apparatus	Booster Fan (if needed)
Extra Controllers (remote)	✓Labor
Sensors/ Monitors	BMS Integration
✓Consulting / Labor	Ductwork Installation
System Selection / Layout	
VHP Air Supply Balance	
Cycle Development	
Interface with BMS	
IQ/OQ and commissioning	
VHP Unit Installation	

Selected Installations

Pharma / Animal Health

- GSK
- Intervet
- Fresenius
- Sanofi
- Merial
- Alcon
- Pfizer
- Fort Dodge

Public Health Labs

- Indiana
- New Jersey
- West Virginia

Others

- Tripler- US Army
- Univ. Nebraska
- Lawrence Livermore National Labs
- INRS

Why VHP?

- **Environmentally Safe**
  - ✓ Excellent Material Compatibility, Even with Sensitive Electronics, and Low Toxicity
- **Residue-Free**
  - ✓ Quickly Breaks Down into Water Vapor and Oxygen.
- **Ideal for Cleanrooms**
  - ✓ Integrated as a user-friendly Utility
- **Use Registered with EPA**

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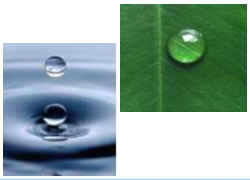
Why VHP?

- ✓ Consistency & Distribution
  - ➢ Wet surfaces / minimal contact times -not an issue
  - ➢ Passes through HEPA filters
  - ➢ Decontaminates biosafety cabinets and HEPAs during room decon
  - ➢ Rapidly kills airborne and surface microbes
- ✓ Labor
  - ➢ Minimal labor required
  - ➢ Hundreds of validation applications



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Thank you!

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