H_2O_2 Bio-Decontamination Process and Aseptic Transfer of Heat Sensitive Materials

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Presentation Outline

- Surface bio-decontamination drivers and available technologies;
- Surface bio-decontamination drivers;
- QbD, risk assessment & mitigation overview;
- Surface chemical bio-decontamination cycle;
- Cycle validation approach;
- Conclusions.

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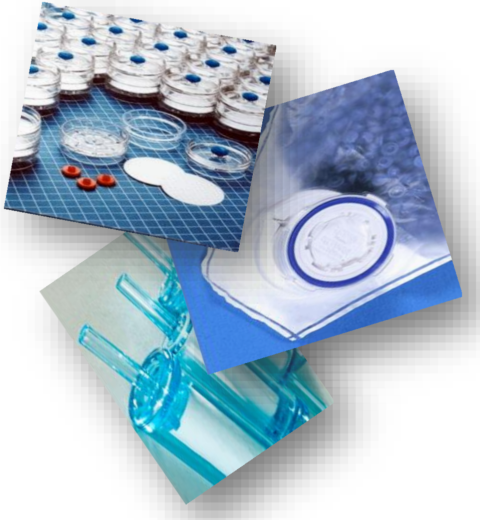
Surface bio-decontamination drivers

- Plastic Single Use devices more and more used for Aseptic Processing ➔ less cleaning and downtime;
- Primary containers, stoppers, clean room garments etc. outsourcing;



- Material transfer of heat sensitive items might magnify the risk of viable contamination delivery into the sterile suite;
- HPV surface bio-decontamination can mitigate this risk.

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Available technologies

- Nothing plus interlocked doors
- Spray & wipe & pray
- LAF and UV irradiation
- HPV transfer hatch
- Dry mist
- CD gas
- ND gas

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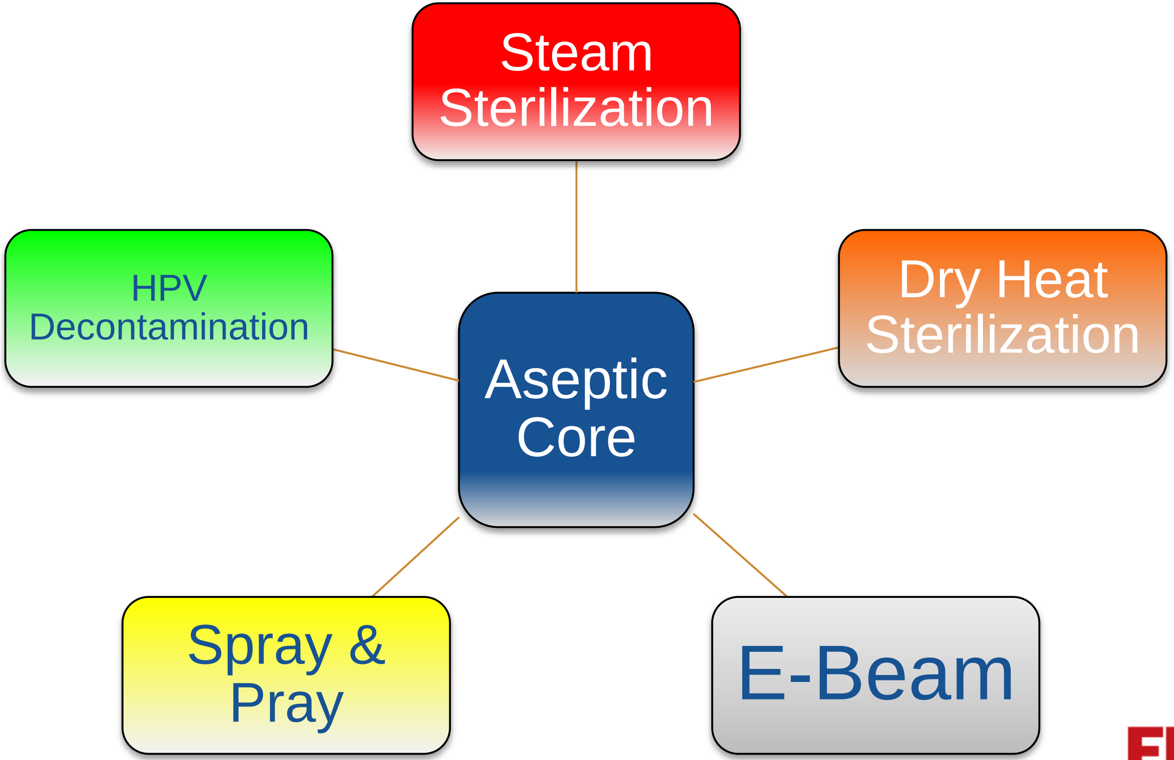
Material transfer routing



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Load patterns examples

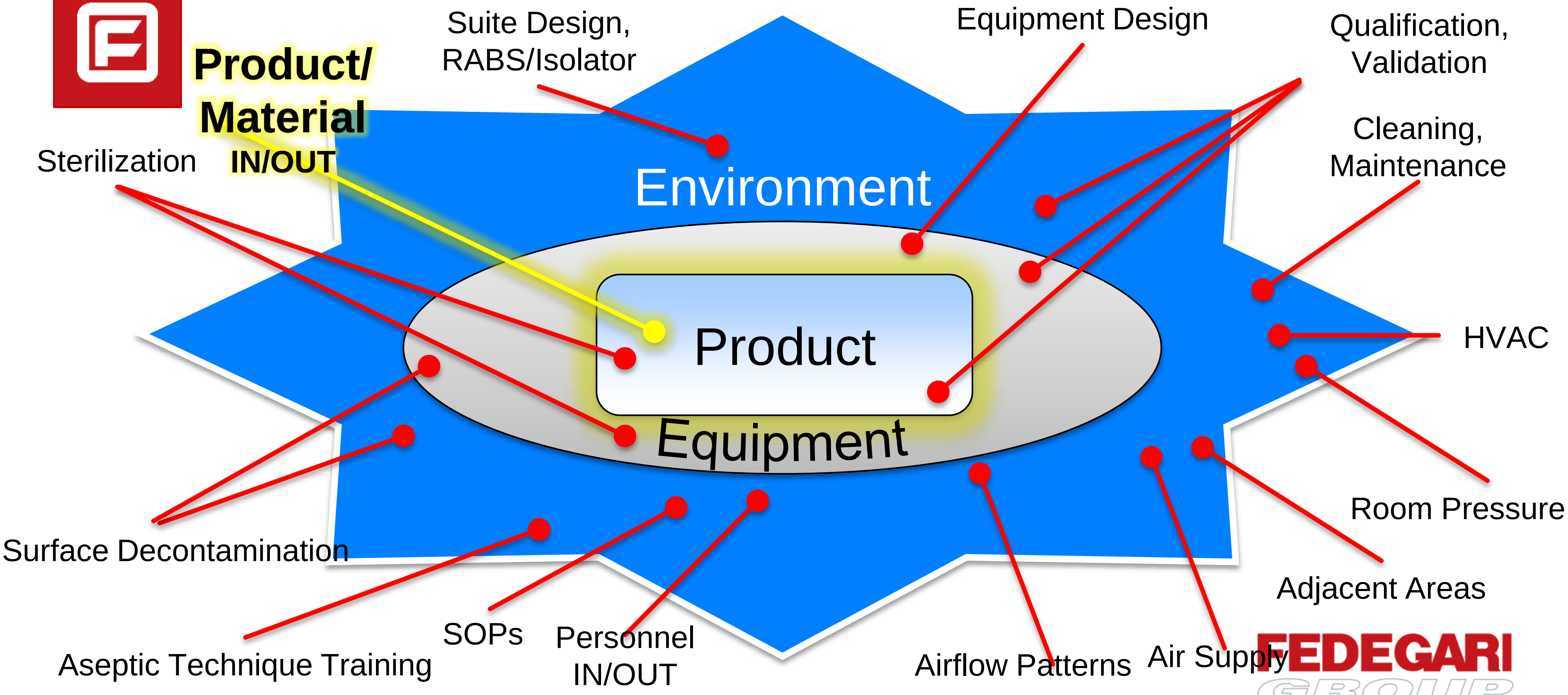
Risk assessment approach

What are the risks involved in an uncontrolled material transfer process?

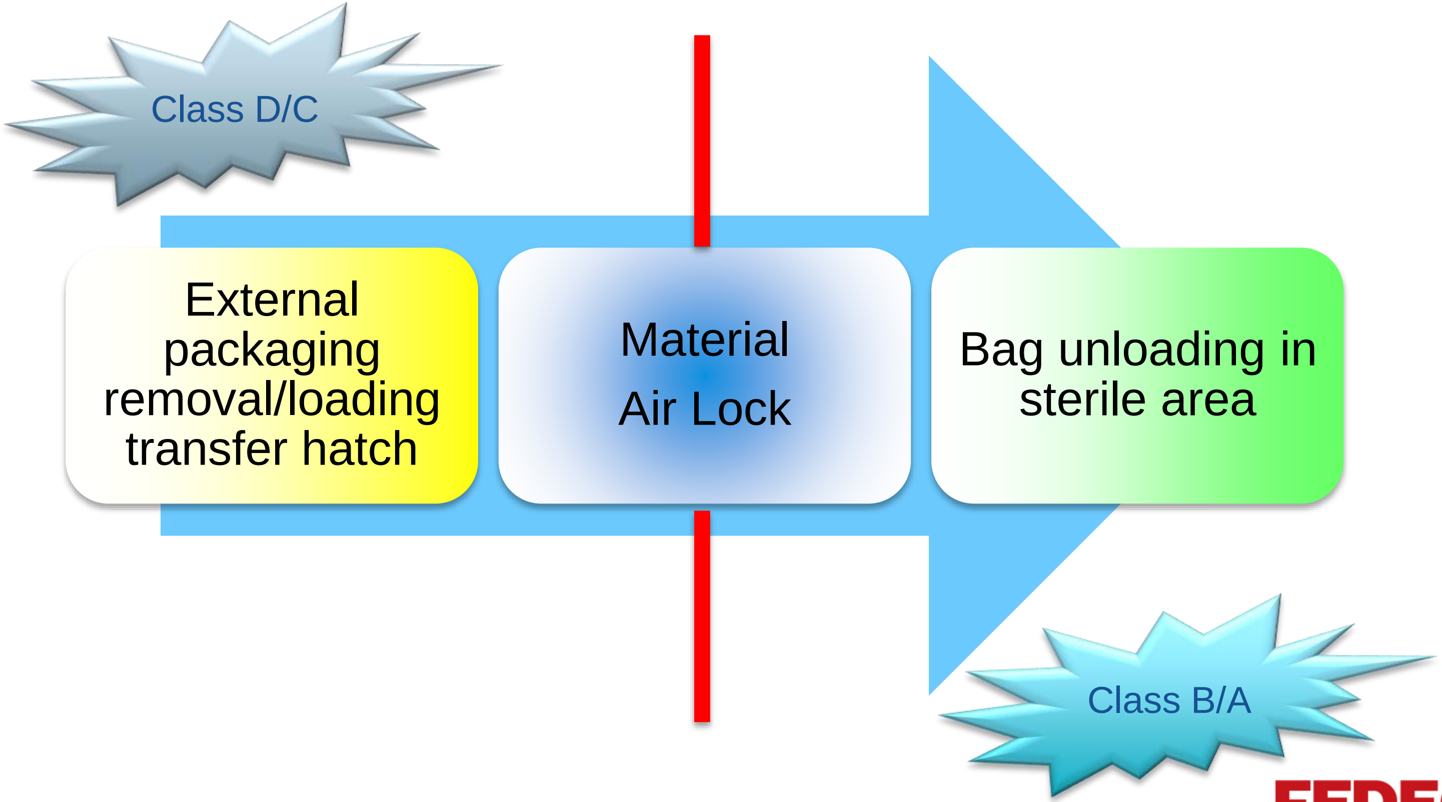
- Health damage by supplying a contaminated product;
- Batch product rejection;
- Product shortage;
- Increased production downtime;
- Inspection failure.

These are the risks not having a good system

Risk in aseptic processing



Case study: stopper bag transfer



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Risk Mitigation

-16%

-80 %

Risk=AxBxCxD=
1,5x1,25x1,5x1=
2,81

Spray & Pray...

Risk=AxBxCxD=
1,5x1,25x1,25x1
= 2,34

UV+LAF

Risk=AXBXCXD=
1,5x1,25x0,25x1=
0,46

HPV

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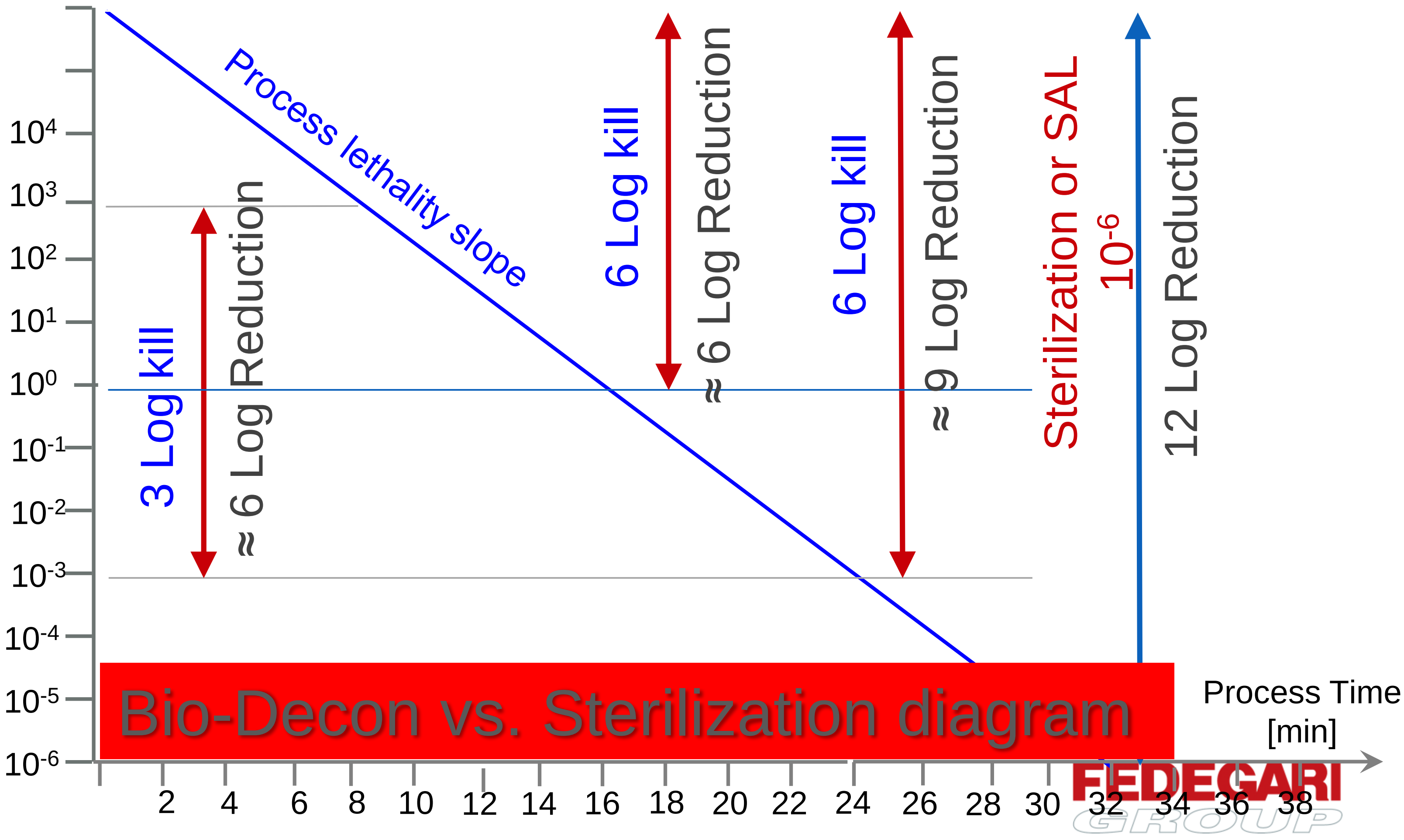
Bio-Decon vs. Sterilization diagram



What is an effective decon?

- Homogeneous distribution of the biocide within the enclosure and the load;
- Thorough and complete penetration;
- Validated biocide contact time to get the required Log Reduction of the bioburden concentration.

Any decontamination method requires a complete and thorough distribution of the biocide to get an effective decontamination.

Decon MAL key features

- Equipment air tightness – leak test
- Turbulence HPV/Air mixture distribution
- Biocide concentration monitoring
- Equipment Chamber aeration through HEPA Filter
- Chamber positive differential pressure (15 Pa aeration and stand-by phases)
- Monitoring of Biocide effective removal below TLV requirements
- Robustness of the unit control system

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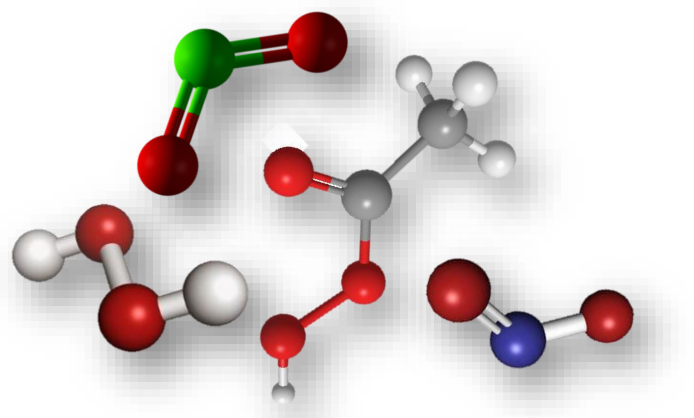
Most used biocides

- Hydrogen Peroxide vapours/mist, HPV;
- Proxy Acetic Acid dry mist, PAA;
- Chlorine Dioxide gas;
- Nitrogen Dioxide gas.



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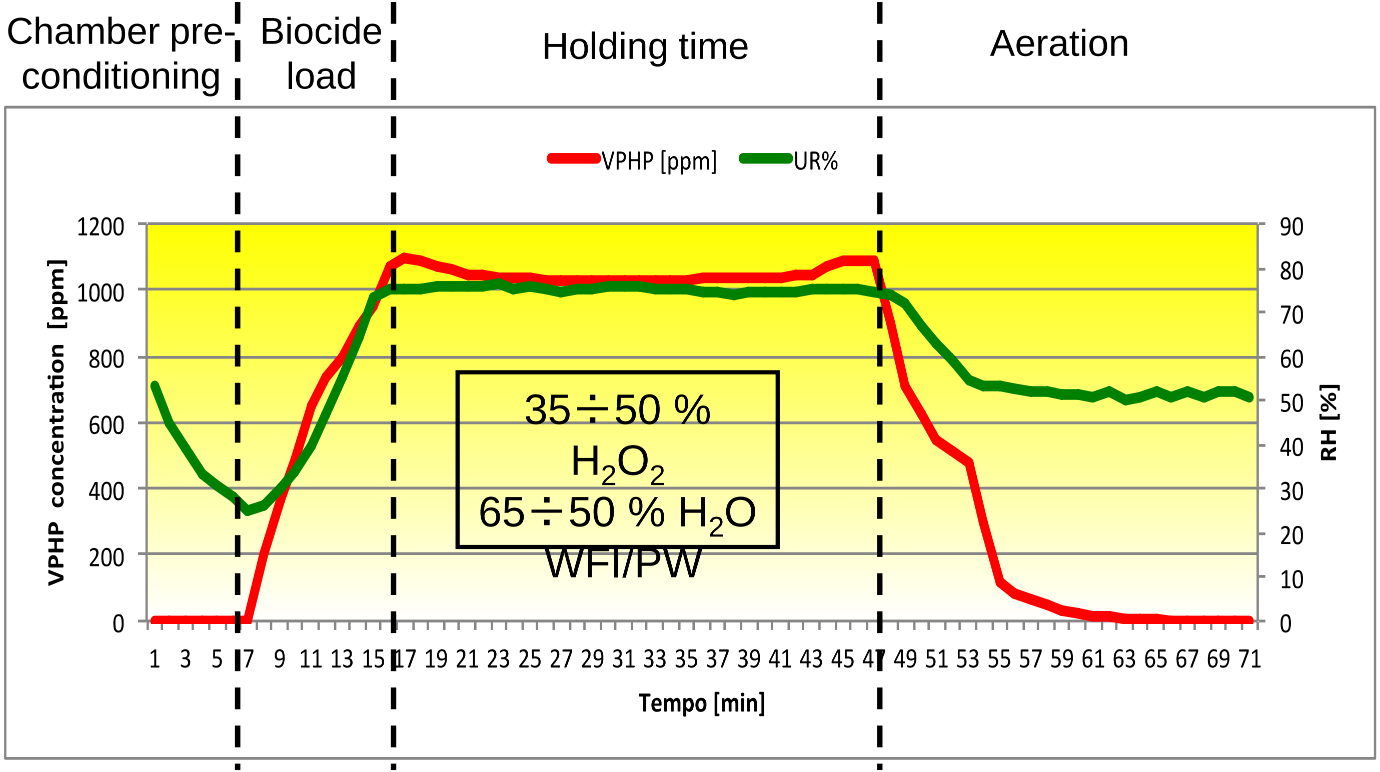
Decontamination cycle

A 4 phases decontamination cycle

1. Chamber pre-conditioning
2. Load of the Biocide
3. Holding time
4. Aeration

Decontamination cycle



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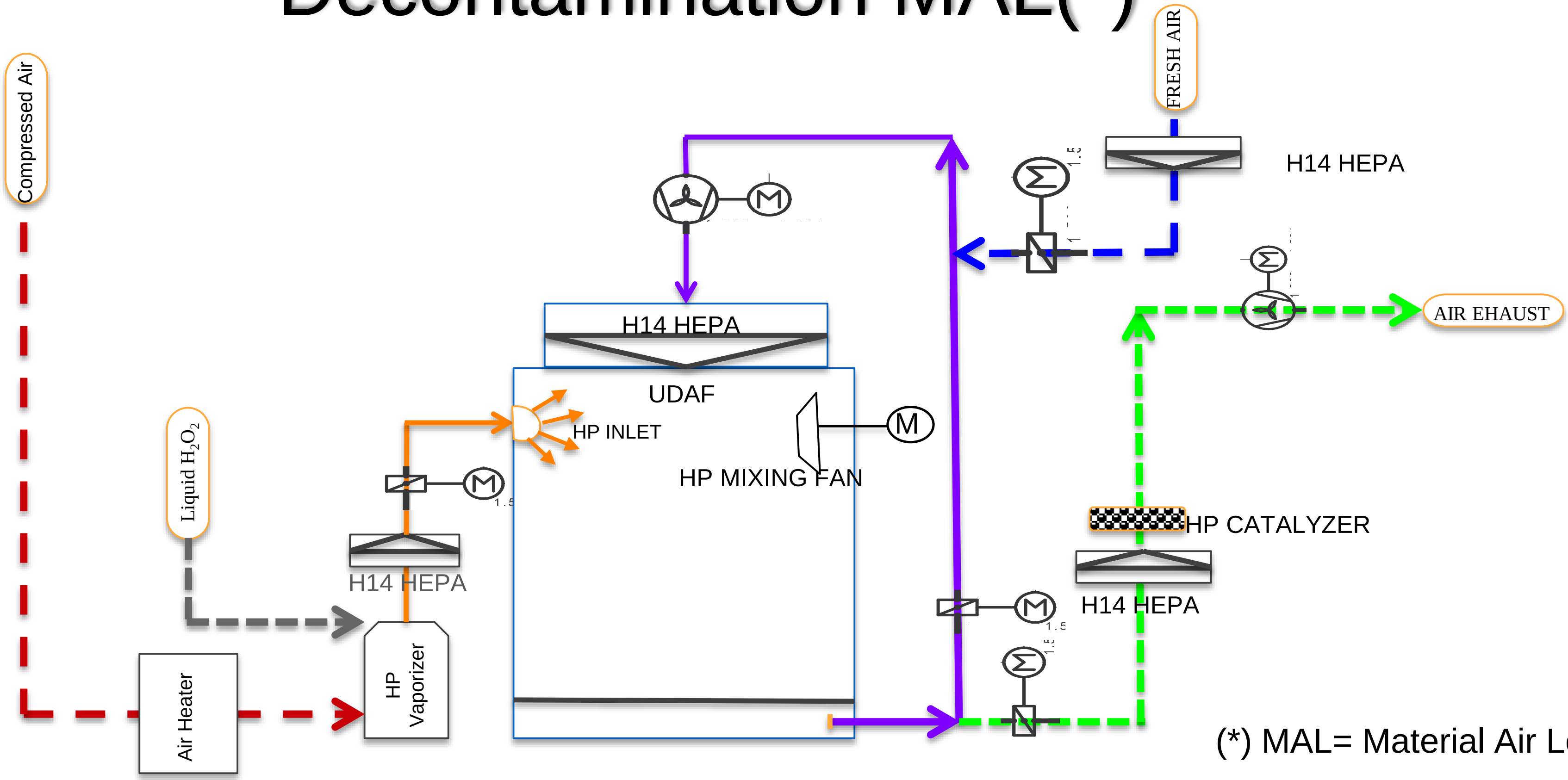
Unidirectional airflow integrated into a Decontamination MAL(*)



(*) MAL= Material Air Lock

MAL units examples

Surface bio-decontamination transfer hatch for heat sensitive products to be delivered into a Class A sterile suite from a Class C area.

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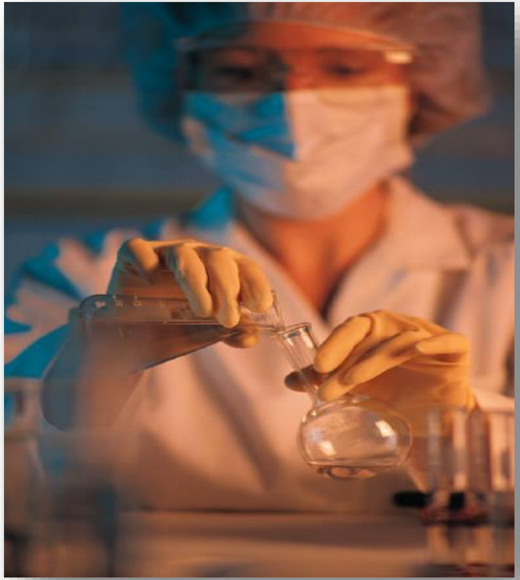
Key Factors

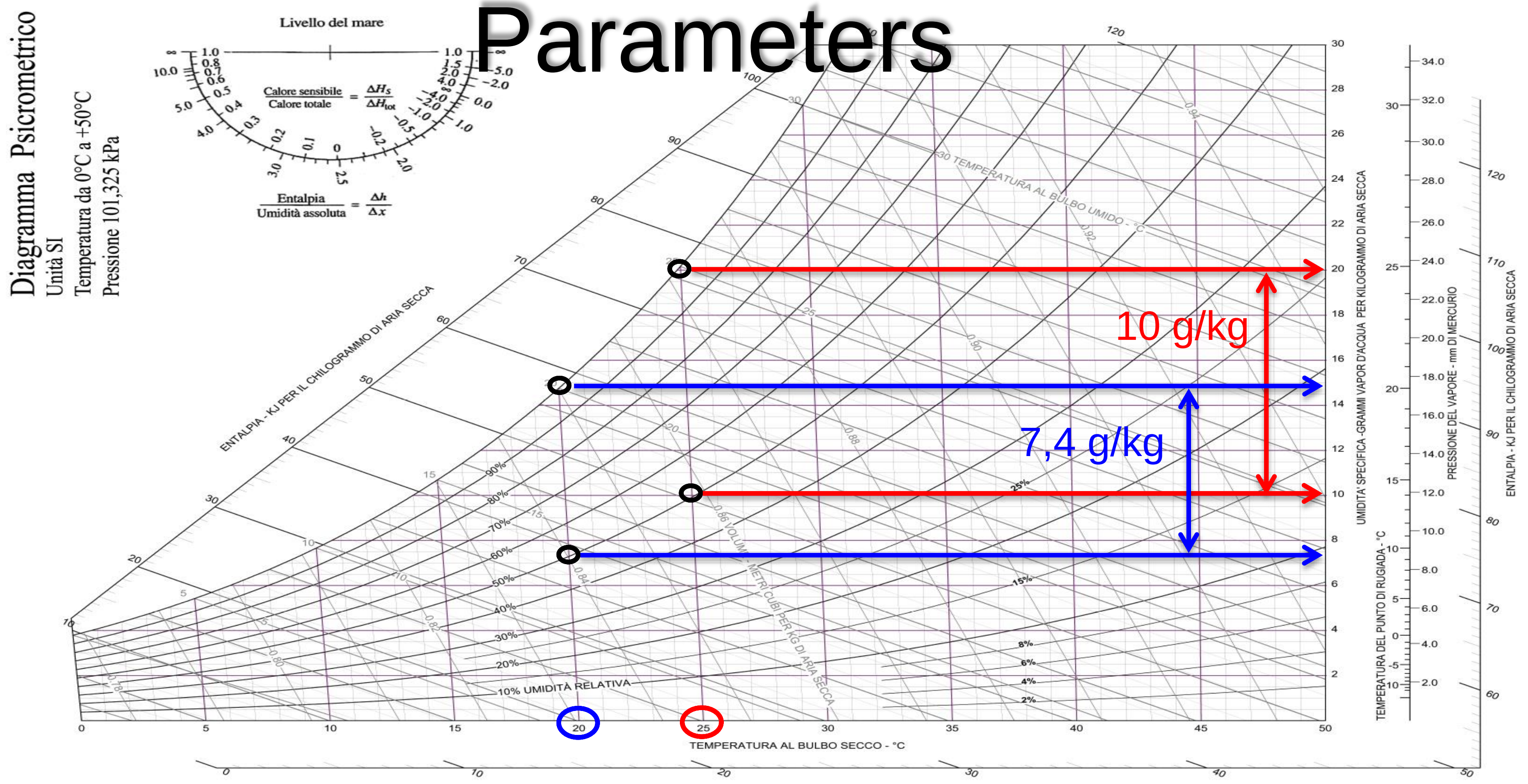
The right recipe to achieve a process robustness

The ingredients of our recipe are the followings:

- Material and chamber surfaces clean and dry;
- Relative Humidity;
- Temperature;
- H_2O_2 concentration;
- H_2O_2 distribution uniformity;
- Process lethality and holding time;
- H_2O_2 absorption/desorption;
- Aeration.

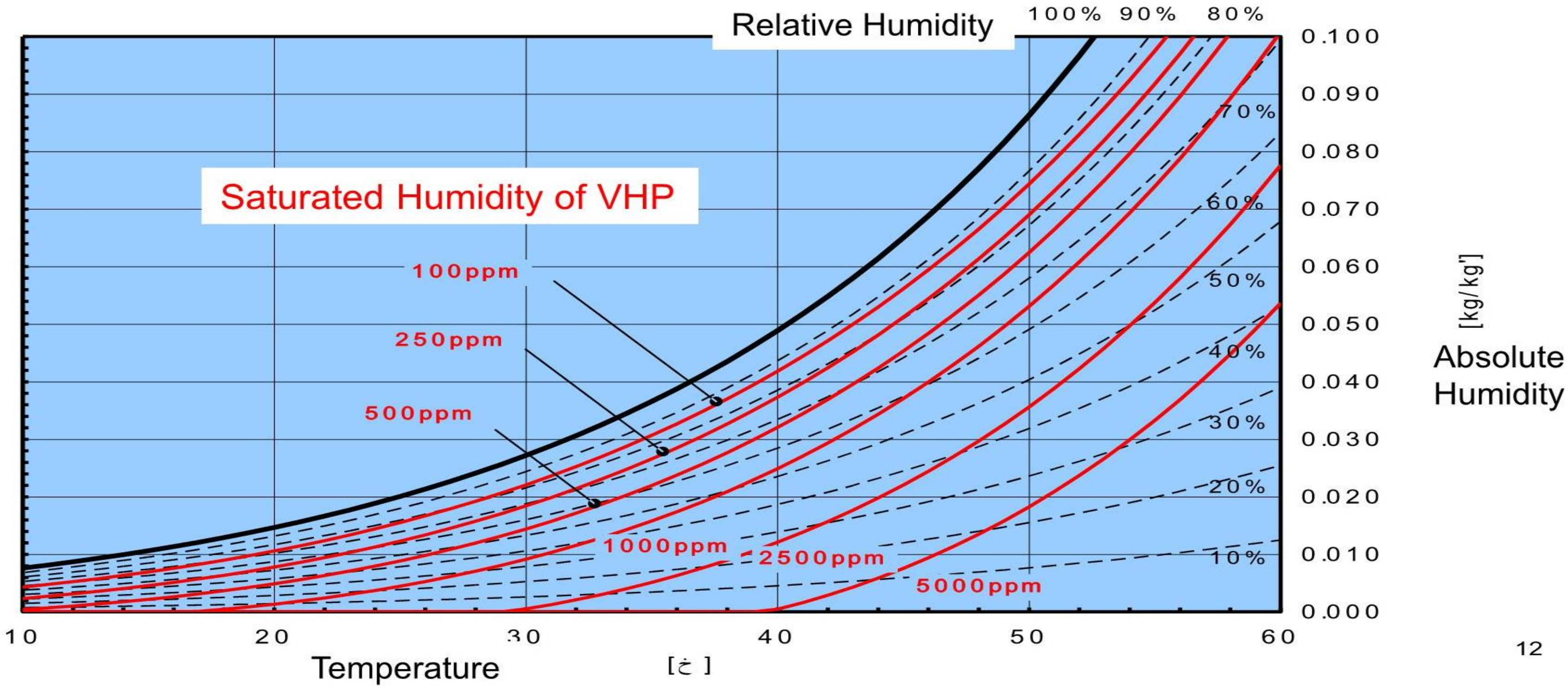


Parameters



TEMPERATURE/ RELATIVE HUMIDITY

Parameters



SOURCE: PDA Europe, Pro-conference Workshop, Daikichiro Murakami, February 11, 2013

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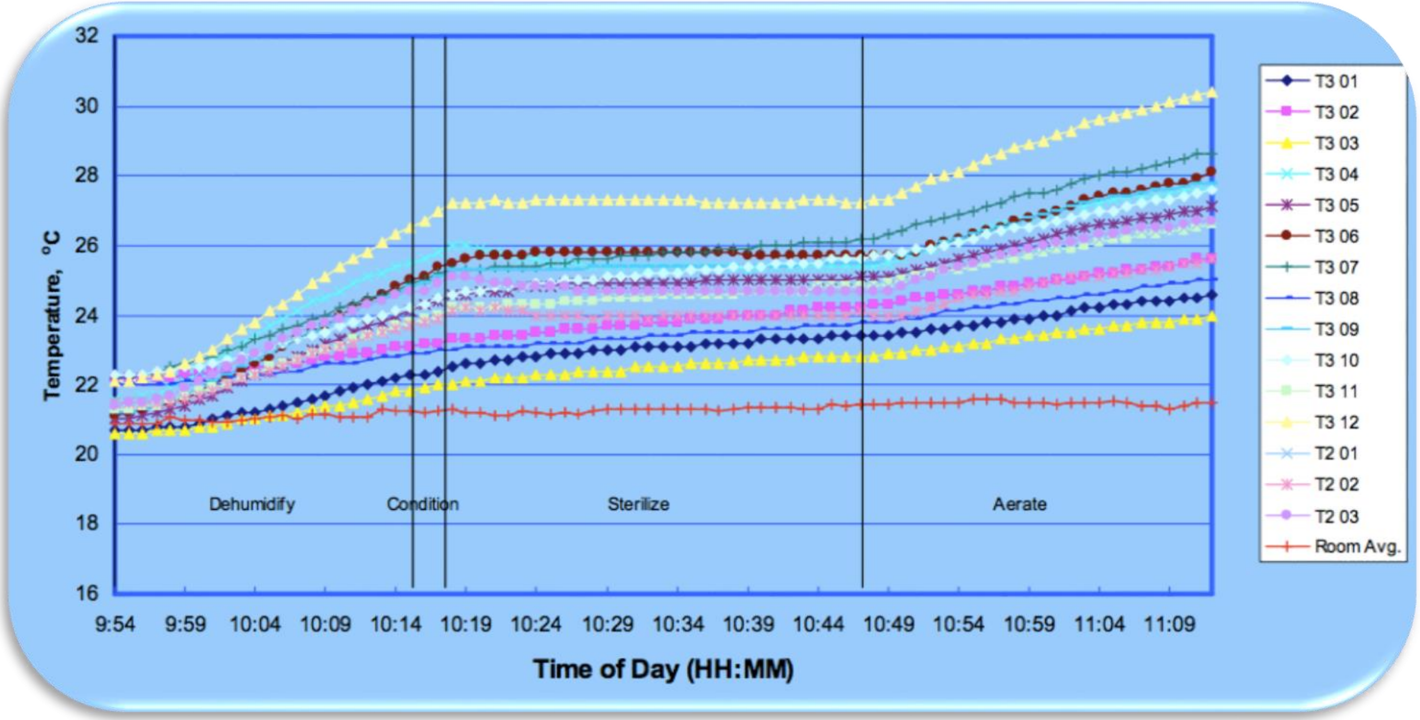
Temperature mapping



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Biocide concentration

Most of the H_2O_2 generator available on the market are **controlling** the biocide concentration delivered to the chamber enclosure **by weight/volume rate per time**;

A new vaporiser was implemented and controlled according to the **instantaneous concentration** of the biocide in the vapour phase.

A PID feedback control loop adjust the concentration within the chamber in a very narrow range.

Better robustness, repeatability and decon process design according to different loads.

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New generation H_2O_2 Vaporizer

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H_2O_2 monitoring and control: two sensors

High concentration

Low concentration

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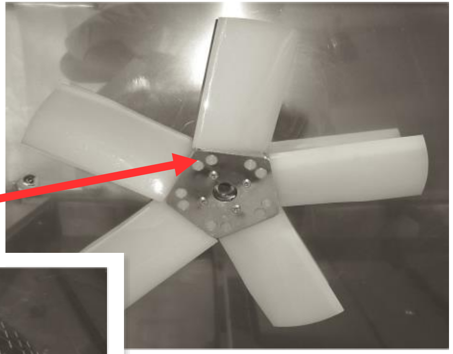
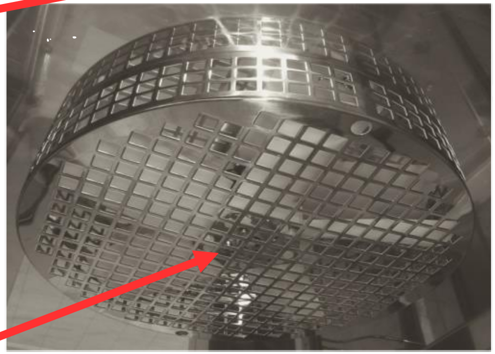
Biocide concentration

Getting rid of stratification

- Same conditions within chamber volume;
- Uniform material decontamination;
- Avoiding cold spots.

Magnetic coupling propeller





Vertical inlet

Side delivery

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Aeration

Air make up

- **Dilution** of the H_2O_2 concentration with **fresh air** to strip out the biocide from material surfaces;
- **Dilution rate** is based on **150 ÷ 300** air exchanges per hour;

RH and T

- Dry and warm air supplies the required **energy to desorb H_2O_2** from the porous loads;
- The **desorption is temperature dependent** and overcomes of the adhesion energy of the H_2O_2 molecules to the surface;
- **Below 2 ppm** it worth to **cool down** the chamber and **rise the RH** for the final aeration step **below 1ppm**. Future application with large molecules of biological products will require H_2O_2 residual below 50 ppb.

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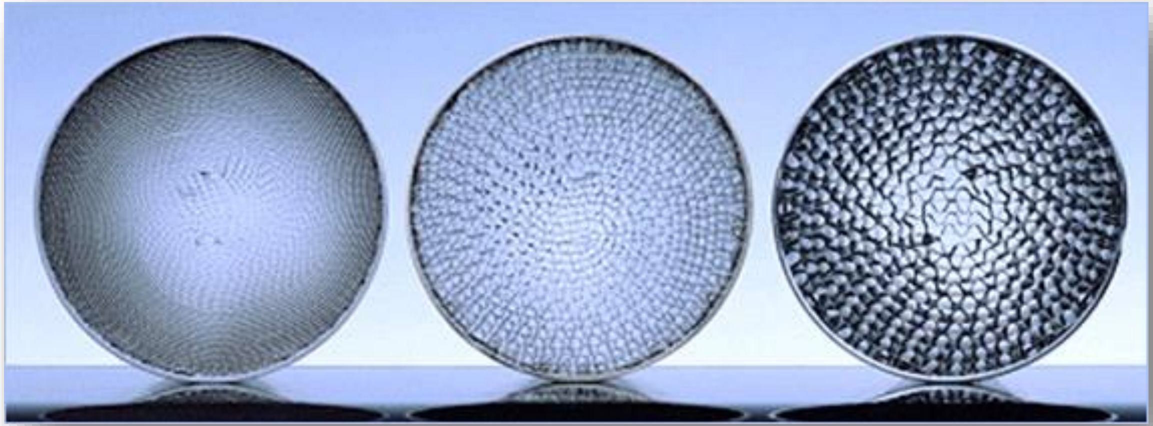
Catalytic Converter

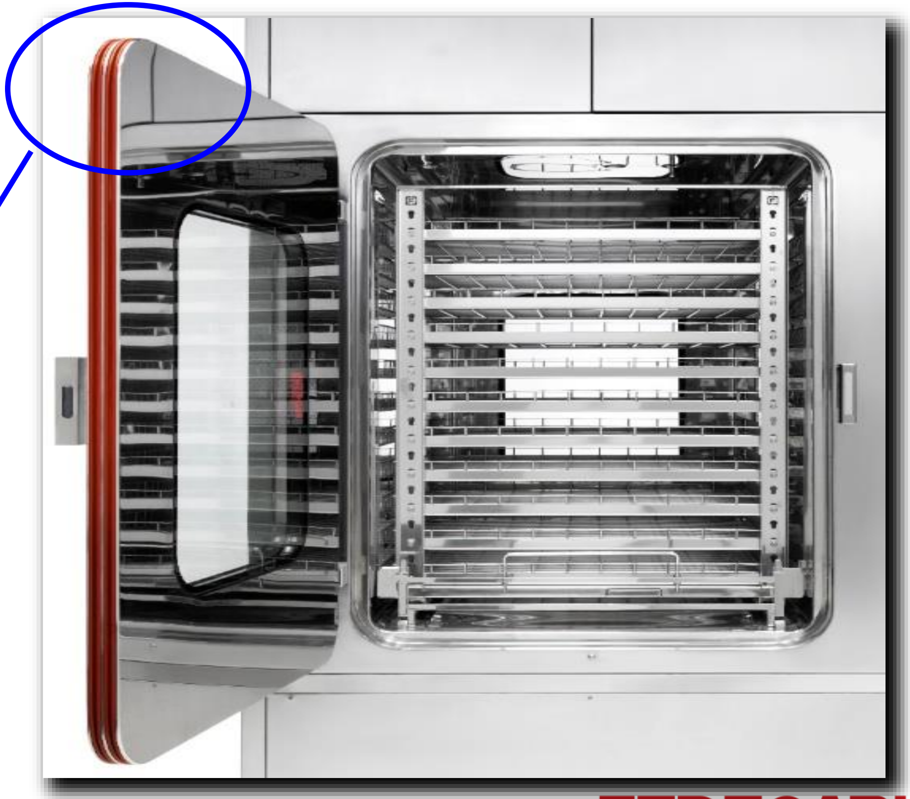
The size and expense of the HVAC system and the energy required to condition the fresh air become limiting factors and therefore air recirculation trough a catalyzer bank is often required to improve the energy sustainability.



Adsorptive materials

- The higher the H_2O_2 adsorption rate of the materials, the longer the desorption and aeration time;
- Materials with higher adsorption properties can not always be avoided like Tyvek, critical issues with wet loads, paper and nylon;
- The selection of the materials influences the cycle length to the desired residual concentration;
- HEPA filters are typically an example of adsorptive material and have a real impact in the aeration time.

Chamber tightness



Pressure decay test cycle start / cycle end

Dual Inflatable gaskets with integral integrity testing

DEFLATED

INFLATED

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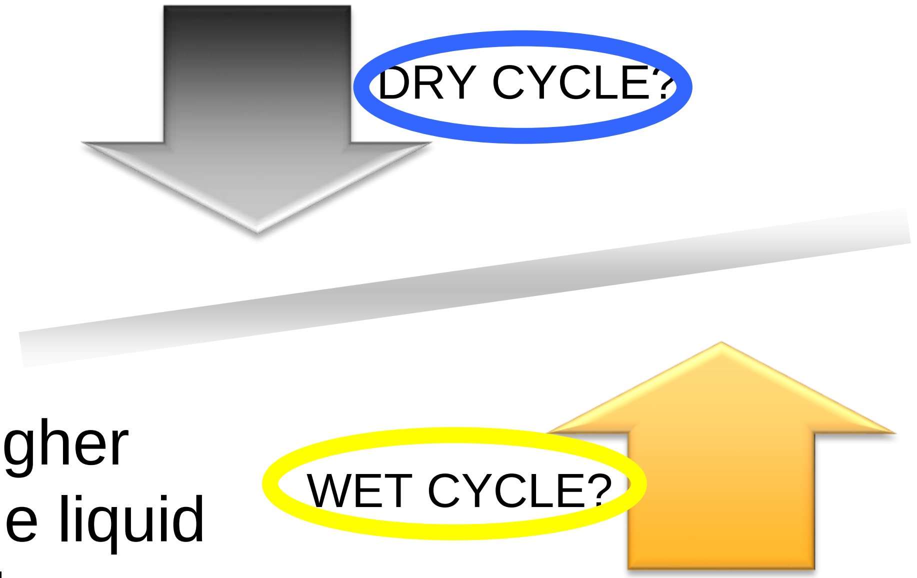
Dry Cycle vs. Wet Cycle

What is the difference?

Even H_2O_2 distribution in the enclosure;
Lower aeration time.



Micro condensation – higher H_2O_2 concentration in the liquid phase and shorter D values;
RH close to the dew point.

Dry Cycle vs. Wet Cycle

Pros & Cons

Wet cycle pros:

Higher concentration of H_2O_2 in the liquid phase, lower D-value, lower contact time;

Wet cycle cons:

Longer aeration time due to the “bounce back” of H_2O_2 concentration in the vapor phase;

Material compatibility to higher H_2O_2 concentration in the liquid phase;

Dry cycle pros:

More repeatable and robust process;

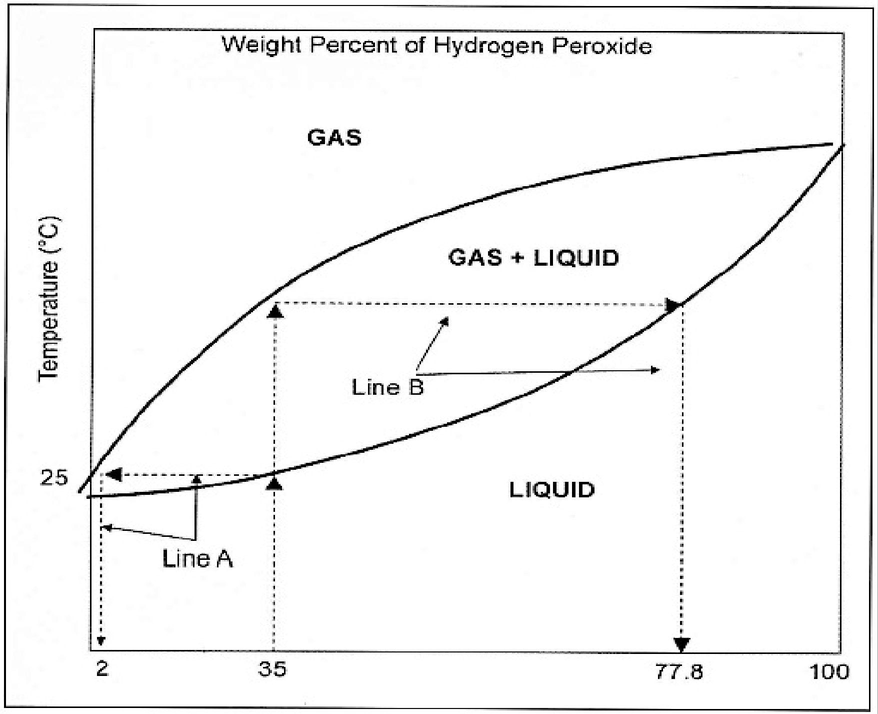
Even contact of H_2O_2 with all exposed surfaces;

Lower aeration time;

Dry cycle cons:

Sensible to surrounding environment T/RH variation;

Vapor phase stratification within the enclosure.



Source: Pharmaceutical Engineering 2007

VALIDATION PACKAGE

Enclosure evaluation

- Load pattern study
- Air distribution study
- Enclosure pressure decay test
- Enclosure T/RH mapping
- HEPA filters leak test
- Particle counting

Biocide uniformity evaluation

- Enclosure T mapping with biocide
- Biocide stratification
- CIs worst location

Biological system evaluation & Optimization

- 3 BI's per location
- Enclosure D-value calculation
- BI' worst location identification

Biological Performance Qualification

- 3 time BI's exposure per worst location

Cycle safety evaluation

- Aeration time study
- Biocide TLV analysis

Conclusions

- Nowadays heat sensitive disposable materials are becoming widely used in aseptic manufacturing;
- Material transfer has to be design to mitigate the risk of microbial contamination.
- Quality by Design and risk assessment approach has to be applied;
- Traditional Material Air Lock cannot guarantee a safe and validated transfer into an aseptic suite and cannot be accepted anymore;
- Surface chemical bio-contamination is now the front edge of the transfer technology;

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Thank you for your attention

And now ready for your questions…

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