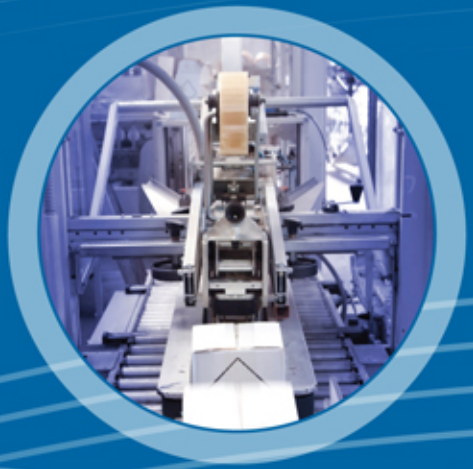
PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

Challenges with Decontamination



Thanks!

- PDA and the program planning committee for the invitation
- Getinge La Cahlène (NO_2 process built into isolators)

- Noxilizer Japan – Building the decon. systems and testing
- Team in Baltimore – Testing with H_2O_2 and NO_2
  - Jeff Soreide
  - Tom Bujold
  - Michael Maust
  - Erica Raudenbush

Goal: Reduce Contamination

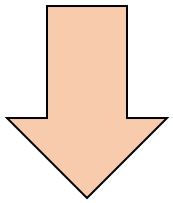
- Evaluation of isolators and transfer air locks:
  - Testing with NO_2 and H_2O_2 was completed
  - Same isolator, same aeration air flow settings, same filters (glass fiber media), … only the decontamination source changed.
  - D-values measured, cycles validated, BIs tested, aeration studied, … etc.
- What can cause problems?
  - Biological Indicators (BIs)
  - HEPA Filters
  - Syringe tubs
  - Dead-legs, gaps, etc.

Agenda

- Biological Indicators (BIs)
- Filters
- Syringe tubs
- Dead-legs, gaps, etc.

Rationale for Using BIs

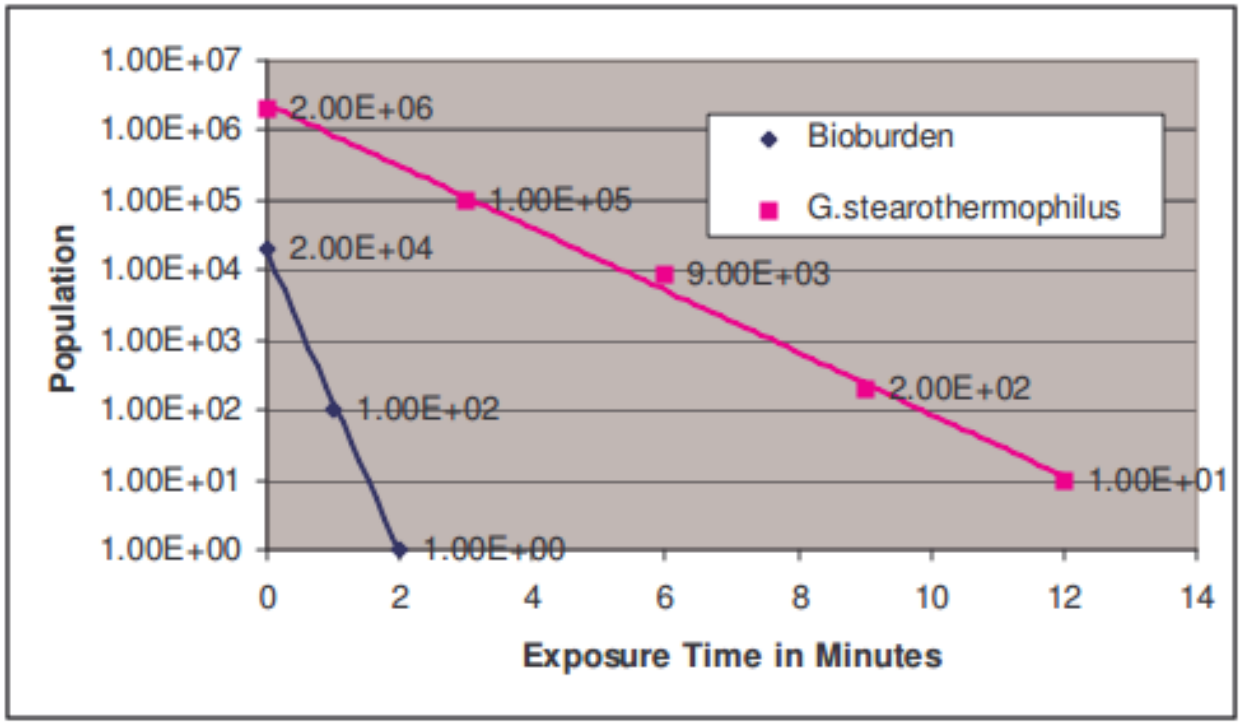
- We want to have low probability of contamination
  - ➢Bioburden is relatively weak and has low population



- We will use a BI as an indicator
  - ➢Highly resistant organism (i.e., *G. stearothermophilus*)
  - ➢High population (> 10^6)

- Can we do things that decrease our success with this rationale?

Inactivation Curves



MesaLabs

base sterilization cycles on the resistance of other organisms?

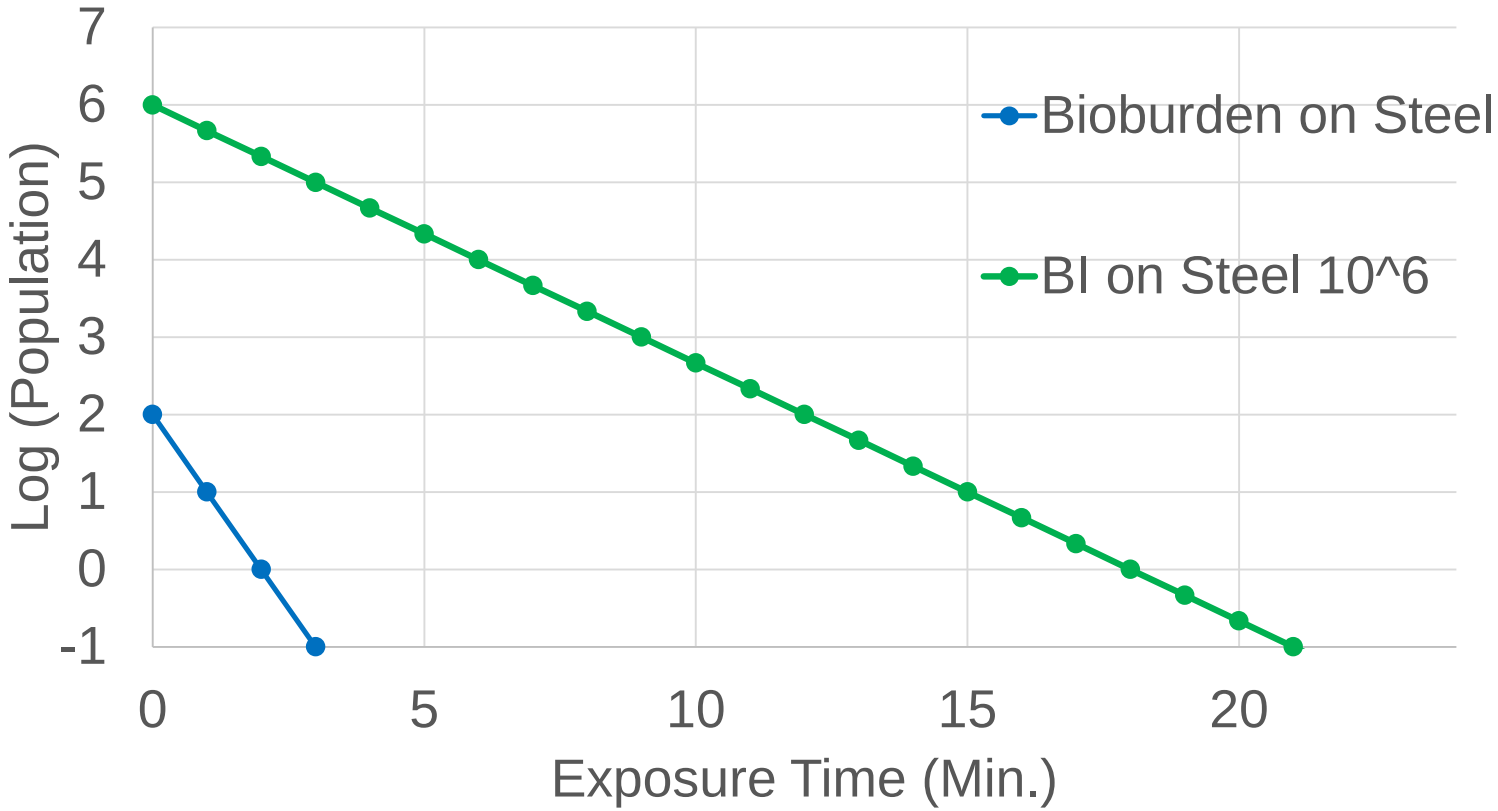
Spore News

Volume 1 , Number 3
June 2004

PRODUCT D-VALUE STUDIES: A CRITICAL TOOL
WHEN DEVELOPING A STERILIZATION PROCESS

Inactivation Curves

- The familiar comparison of bioburden and the BI



BI vs. Bioburden

- In this example, BI inactivation requires 18 minutes and the bioburden is dead in 2 minutes.

- This is good ….

  … if there aren't complicating factors.

Materials Change D-values

- What if the bioburden is not on steel or glass?
  - D-values vary with substrate or BI carrier material
  - Examples for H_2O_2 process are shown below* (but similar for NO_2, etc.):

Material	D-value
Stainless Steel	1.0
PVC, Hard	1.0
PTFE	1.3
Tyvek	2.0
PVC, Soft	4.3
HEPA Filter Media	3.6
Paper	>17

~~These will be discussed~~

*Values taken from SKAN paper: "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 Journal, Vol. 57, No.1 January / February 2003

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3 x D-value safety margin lost.

But, we still have the 6 log population of the BI organism!

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Materials with the same name can have different D-value.

Test all formulations!

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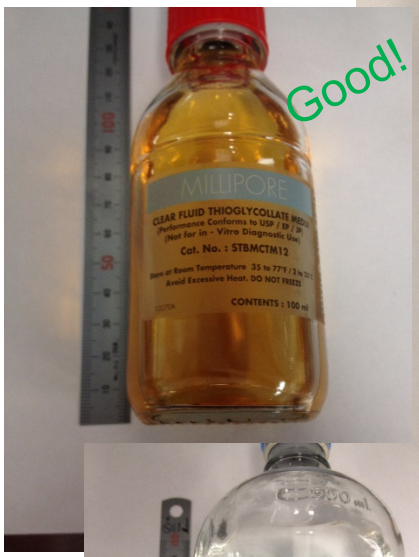
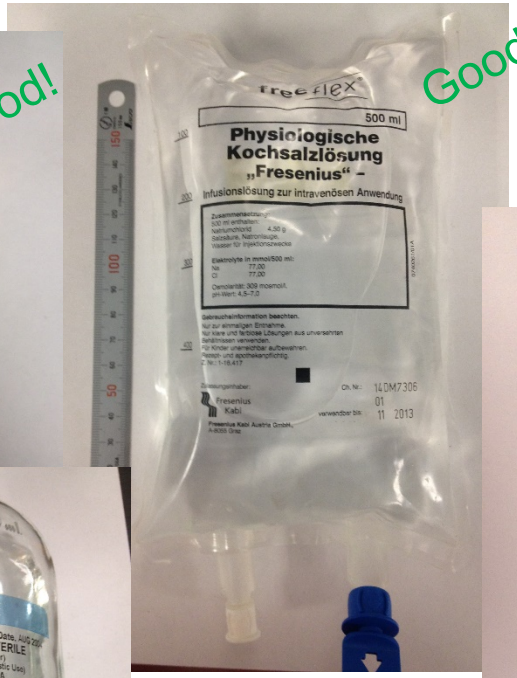
What Is Decontamination?

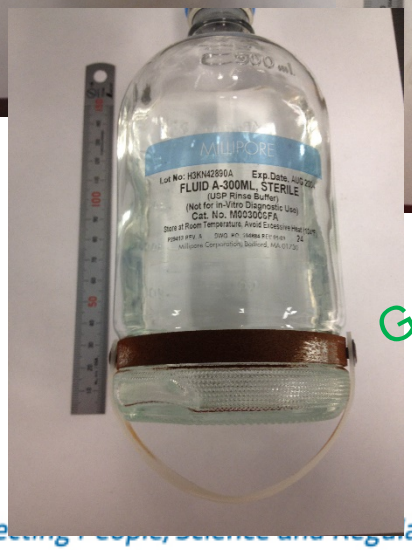
Items presented for decontamination!



Good!



Good!



Good!

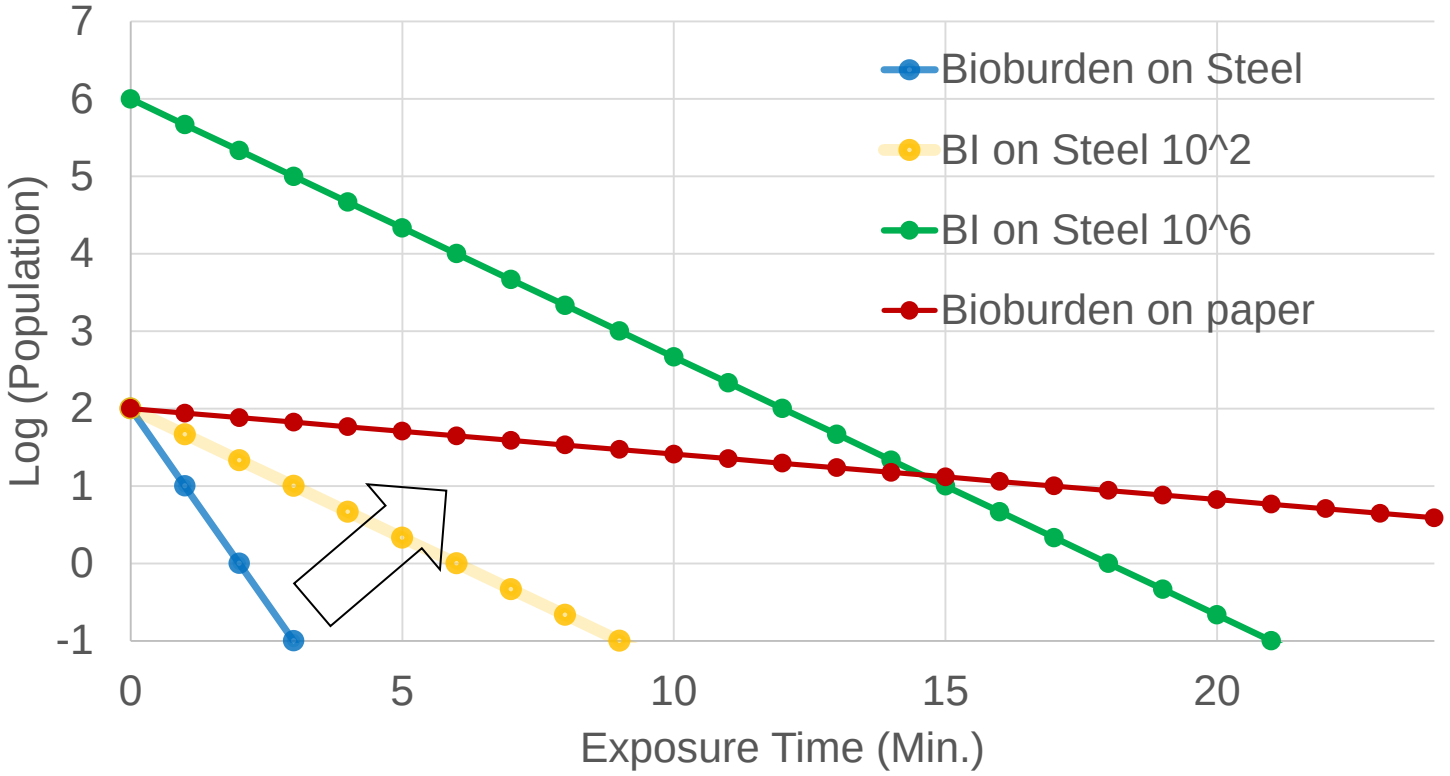
Paper!

Paper!

Paper!

BI vs. Bioburden

Carrier Material	D-value
Stainless Steel	1 min.
Paper	> 17 min.



BI vs. Bioburden Summary

- The BI provides a rigorous challenge
- However,
  - Materials change D-values

- Understand and evaluate each load
  - Materials, orientation, etc.
  - (and don't put paper in the H_2O_2 or NO_2 systems)
  - Location in the volume being treated

- No paper labels on items going into Transfer Air Lock
- Industry trends to shorter cycles times make evaluations critical

Agenda

- Biological Indicators (BIs)
- Filters
- Syringe tubs
- Dead-legs, gaps, etc.

HEPA Filters

- http://www.picscheme.org/pdf/29_pi-014-3-recommendation-on-isolators.pdfasdf

PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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.

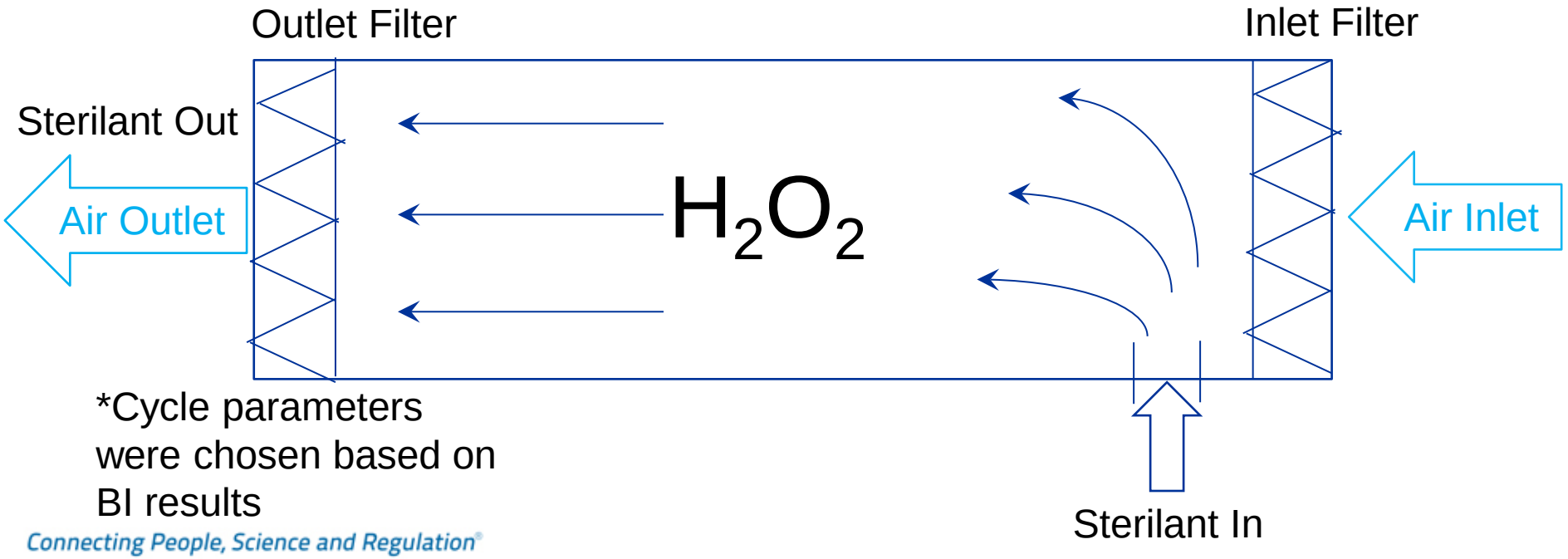
014-3
September 2007

7.4.6 … All inlet and outlet filters associated with the isolator should be exposed to gas or sterilized.

ISOLATORS USED FOR ASEPTIC PROCESSING AND STERILITY TESTING

Isolator Configuration for Testing

- 'Validation Cycle' used:
  - The outlet filter is exposed to sterilant gas
  - The inlet filter is only passively exposed to the sterilant gas.
  - The inlet filter presents the greatest risk.



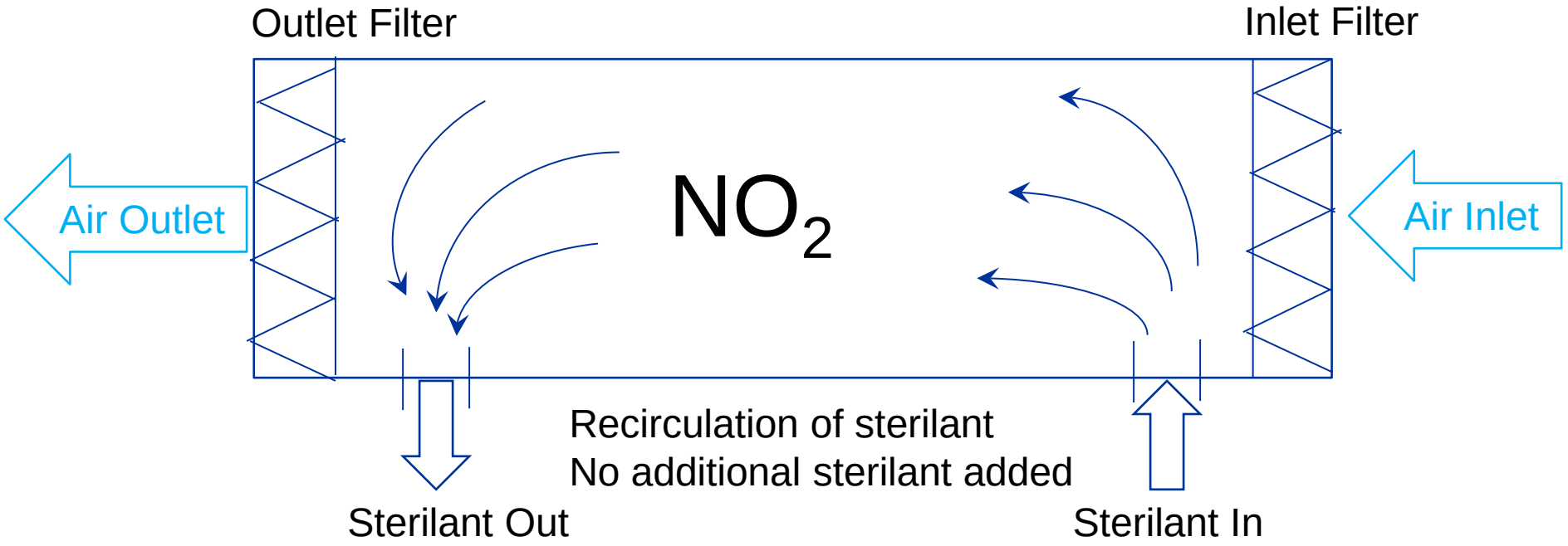
*Cycle parameters were chosen based on BI results

H_2O_2 Lethality on the HEPA Filter

- BIs were placed on the interior face of the filters

Isolator Configuration for Testing

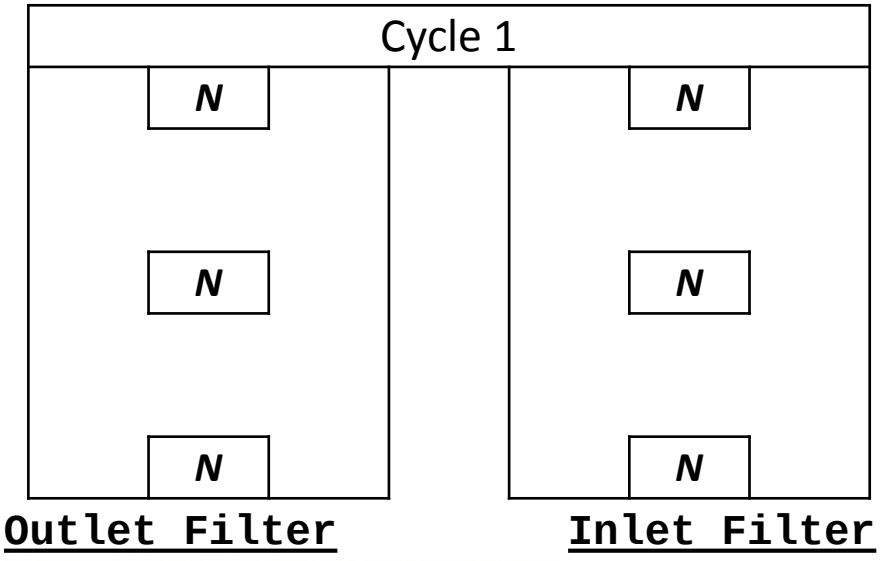
- Isolator has an inlet filter and an outlet filter
- Sterilant is recirculated to reduce interaction with the filters
- The inlet filter is used for fresh air during aeration

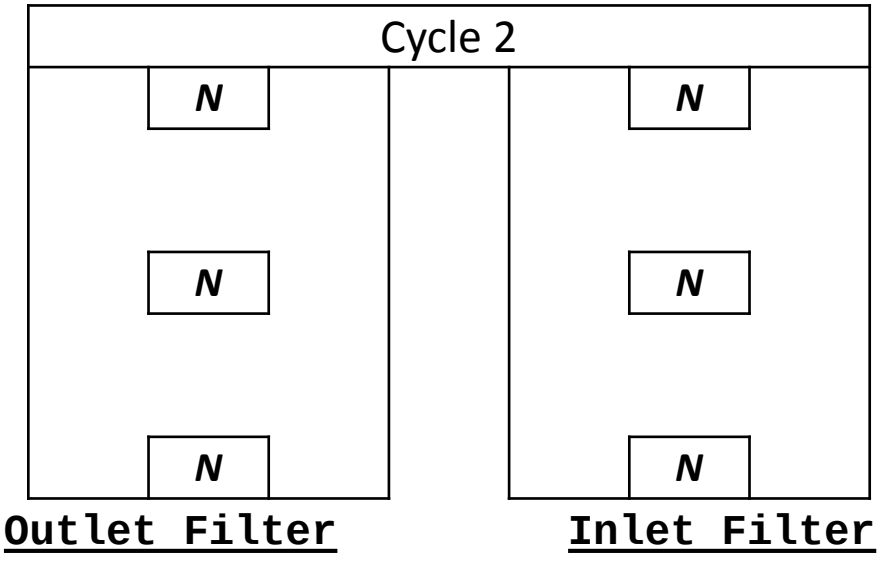


NO_2 Lethality on the HEPA Filter

- BIs were placed on the interior face of the filters

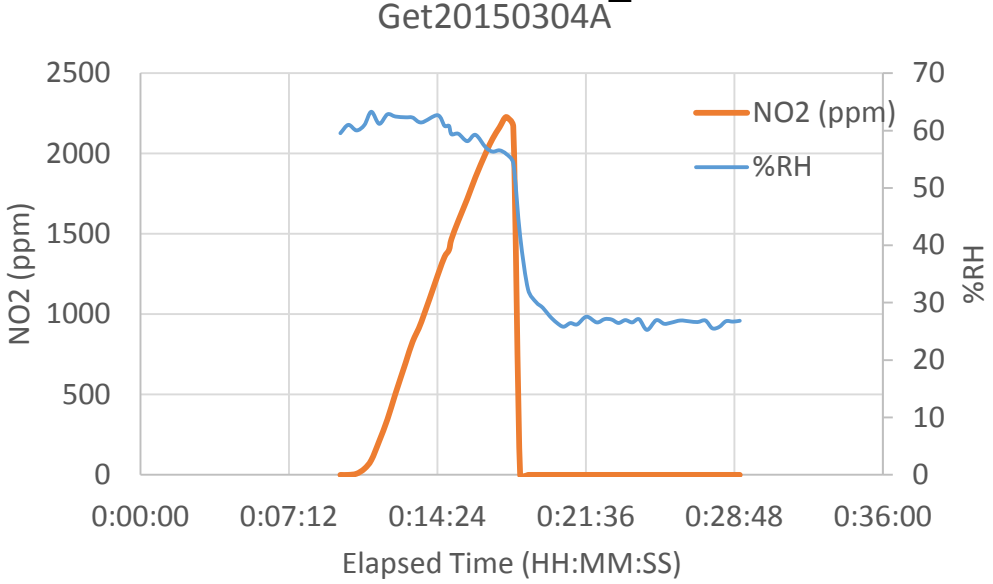
N = Sterile ***P*** = Not Sterile





NO_2 Penetration Through Filter

- The graph shows that NO_2 penetrates through the filter.
- Average lethality outside of outlet filter was 4.5 log reduction
- Note: this is NO_2 diffusing through the filter



75% RH
15mg/L NO_2
8 minute Dwell
5 minute Aeration

Filter Decontamination Summary

- The NO_2 process penetrates into the filter media
- The H_2O_2 filter process killed most BIs on the filter surfaces, inside the isolator
  - More time is needed for BIs inside the isolator
  - Little or no spore log reduction was observed on the outside surface of the outlet filter (supersaturated gas doesn't pass through the filter?)

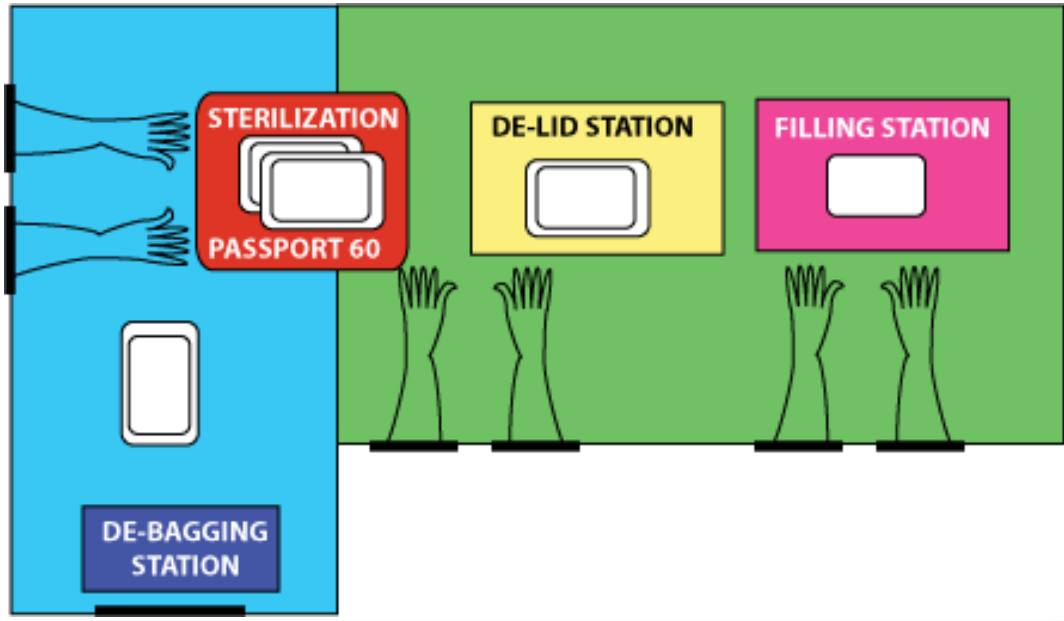
➢ Apparently, the filter surfaces are a hard-to-kill location and should be part of testing/validation!

Agenda

- Biological Indicators (BIs)
- Filters
- Syringe tubs
- Dead-legs, gaps, etc.

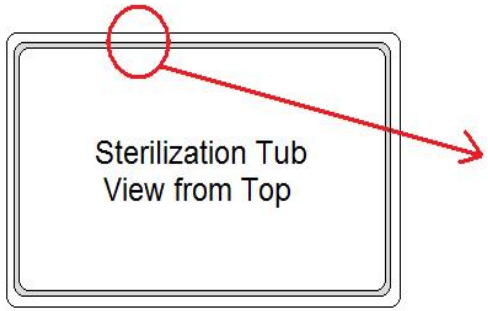
Syringe Tub Decontamination

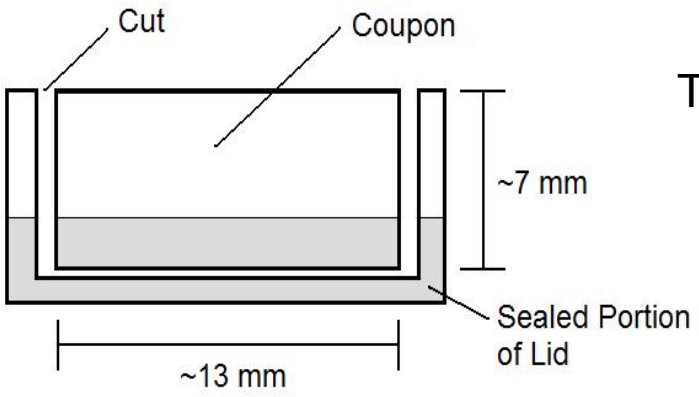
- Transfer air lock for introducing work items into a small, manual filling line (Noxilizer's PassPort concept)
- Sized for the application, small (60 L volume, large enough for two syringe tubs) to 300 L (for up to 16 syringe tubs)
- System Specifications:
  1. 13 minute process
  2. Six log BI reduction
  3. Aerate to < 1 ppm
  4. No residuals

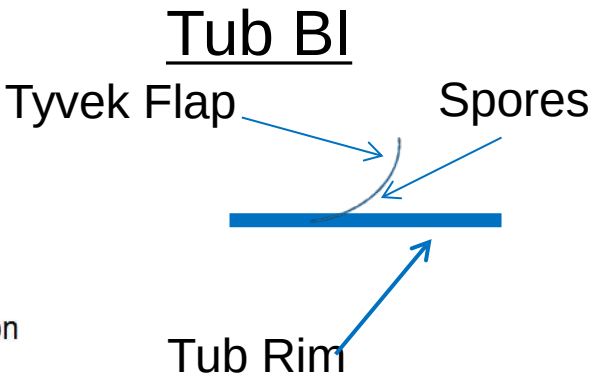


Tub Decontamination

- BI's are made from the tub rim
- The Tyvek flap is lifted and inoculated with spore suspension and allowed to dry
- 10^4 Spores







H_2O_2 Decontamination Data

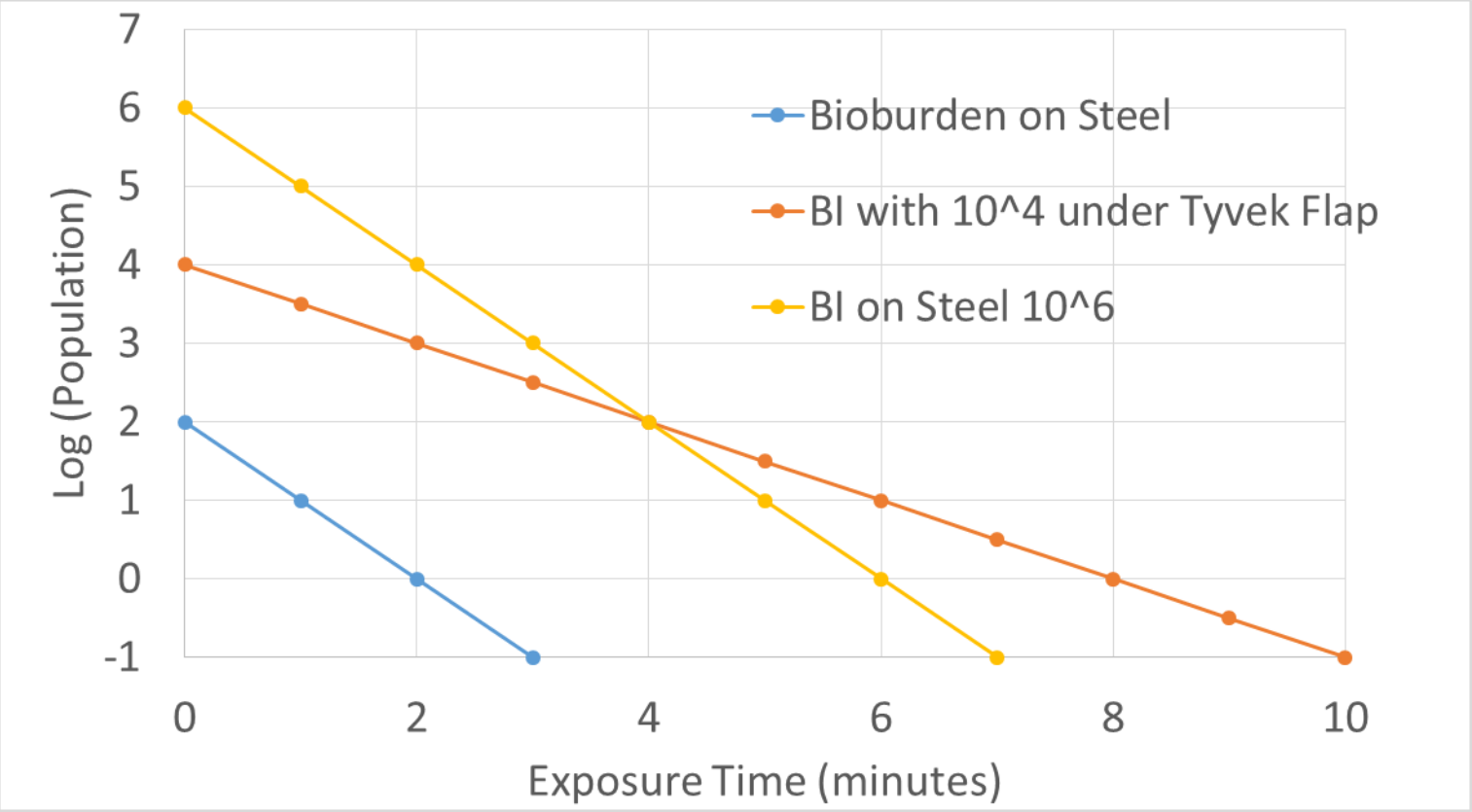
N = Sterile	***P*** = Not Sterile

HPV Tub BI Data

	Sample No.		1	2	3	4	5
8 min.		**Tub**	***N***	***P***	***P***	***N***	***P***
6 min.		**Tub**	***N***	***P***	***N***	***N***	***P***
4 min.		**Tub**	***N***	***P***	***N***	***P***	***N***
2 min.		**Tub**	***P***	***P***	***P***	***P***	***N***

- Longer cycles might work
- 8 minutes was used for validation of airlock chamber
- Longer exposures needed for consistent results

Tub BI Data with H_2O_2



- The packaging poses a challenge to the process
- 10^4 is still a rigorous challenge

NO_2 Decontamination Data

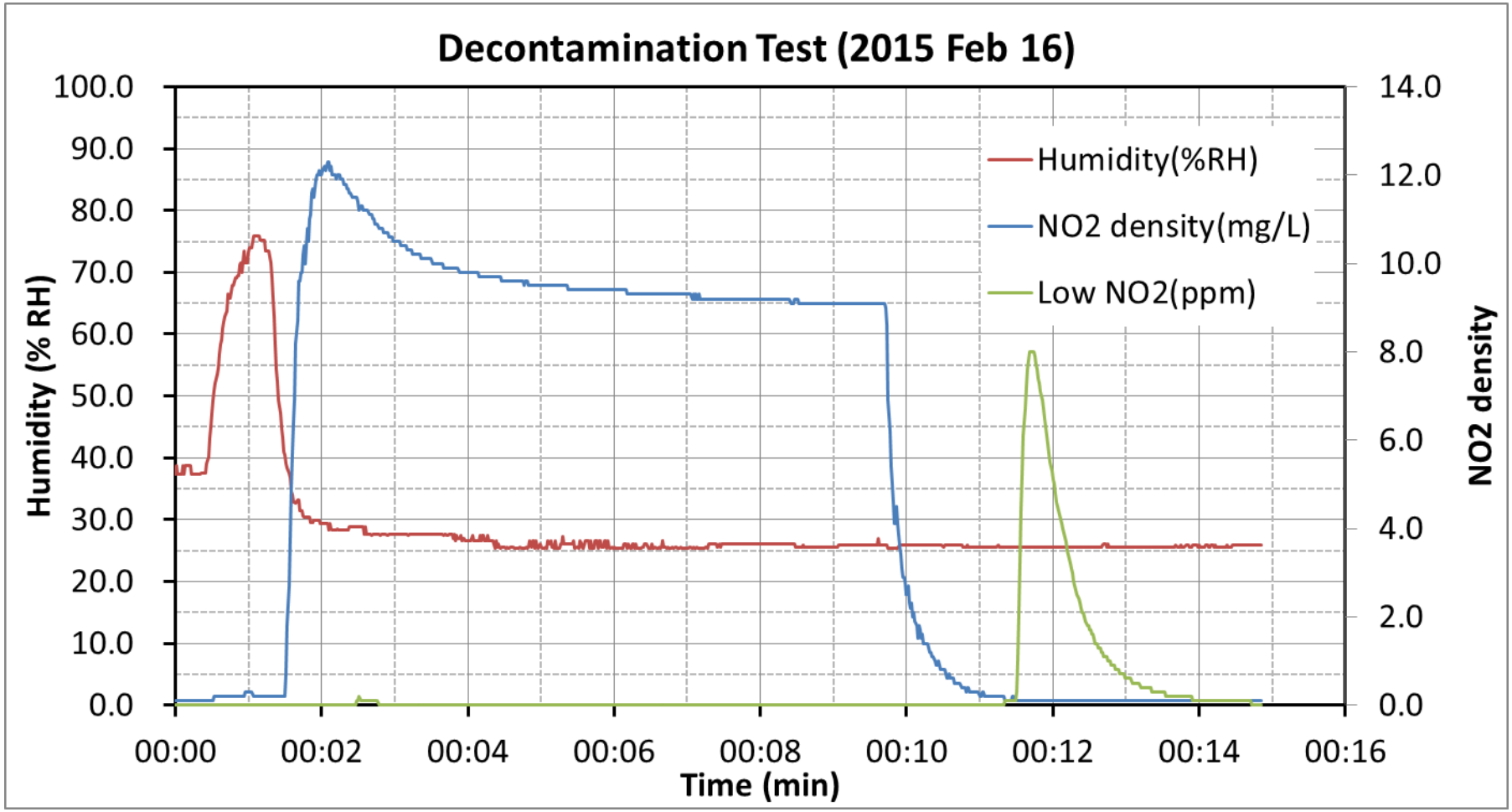
N	= Sterile	***P***	= Not Sterile

NO2 Tub BI Data

	20 mg/L, 6 min.	**Tub**	***N***	***N***	***N***	***N***	***N***
	50%						
	10 mg/L, 4 min.	**Tub**	***N***	***N***	***N***	***N***	***N***
	70%						
	10 mg/L, 4 min	**Tub**	***N***	***N***	***N***	***N***	***N***
	75%						
	10 mg/L, 2 min.	**Tub**	***N***	***N***	***N***	***N***	***N***
	75%						

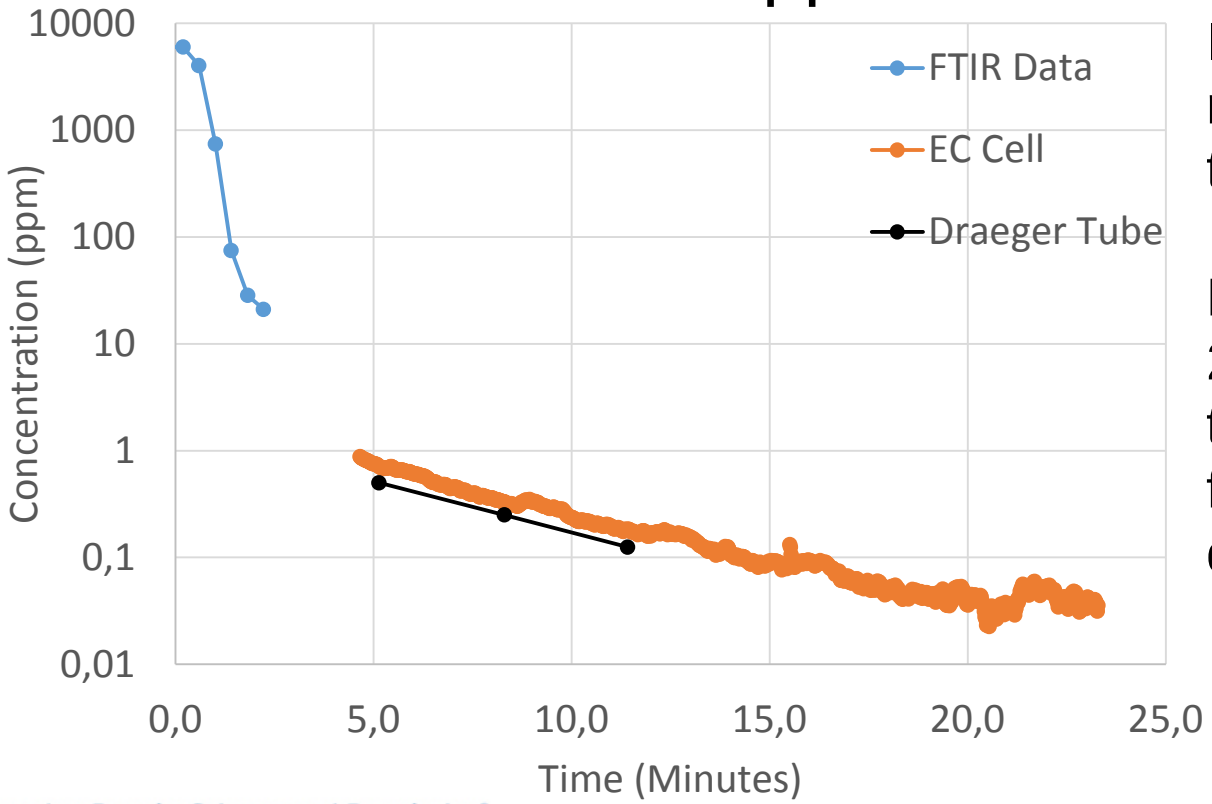
- Results are consistent
- Short cycles are demonstrated

NO_2 Cycle Used



Fast Aeration

- In transfer air lock (and in 1000 L isolator!):
  - 5 minutes to 1 ppm
  - 13 minutes to 0.1 ppm



In filling lines that require H_2O_2 aeration to less than 30 ppb:

NO_2 ambient levels are 20 to 40 ppb. Aeration to 100 ppb is sufficient for filling sensitive drugs.

Syringe Tub Summary

- Packages have flaps (outside of the seal) that are hard-to-kill locations (Syringe tubs are just and example).
  - These portions of the packages will be handled or manipulated in the aseptic areas
  - These locations should be tested during the develop of cycle parameters

- The H_2O_2 cycle at 8 minutes killed the BIs during cycle development
  - The geometry, tub material, or gas available at the inoculated locations could be elongating the lethality process by a small amount.

Agenda

- Biological Indicators (BIs)
- Filters
- Syringe tubs
- Dead-legs, gaps, etc.

Hard-to-Kill Locations

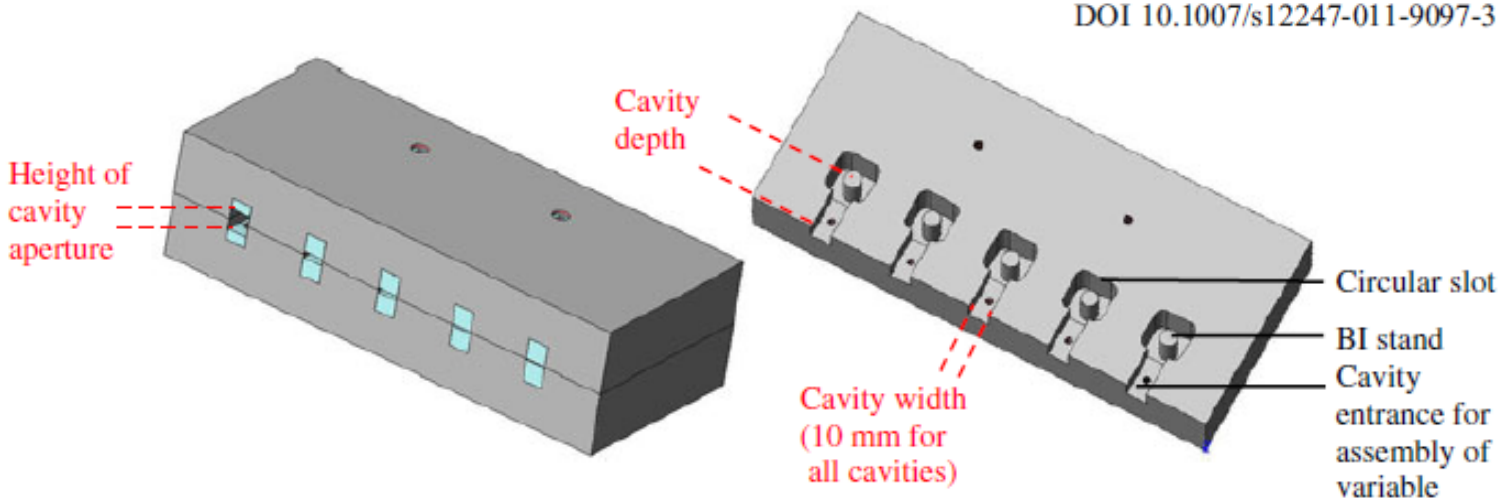
- The sterilant gas must kill in the hard to reach locations
  - Between transfer air lock load items
  - In small gaps or dead-legs
  - Around filling line components
- Testing can result in guidelines for filling line designers
- Greater diffusion of the sterilant can mean less filling line disassembly during decontamination

Sterilant Penetration

Hydrogen Peroxide Vapor Penetration into Small Cavities during Low-Temperature Decontamination Cycles

Beatriz Unger-Bimczok · Thomas Kosian · Volker Kottke · Christian Hertel · Johannes Rauschnabel

J Pharm Innov (2011) 6:32–46
DOI 10.1007/s12247-011-9097-3



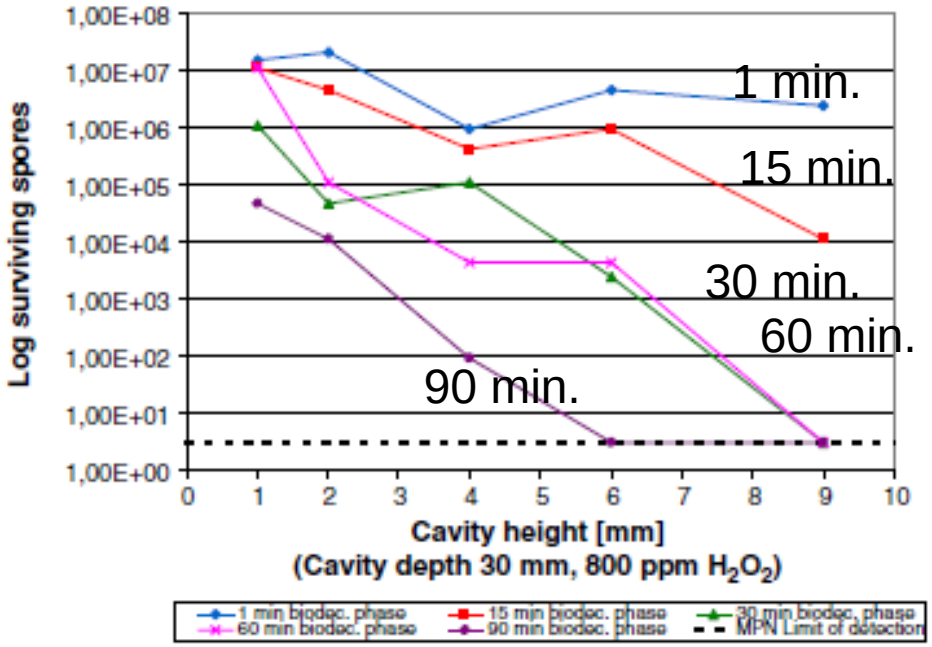
Stainless test steel block assembly with five parallel variable height cavities

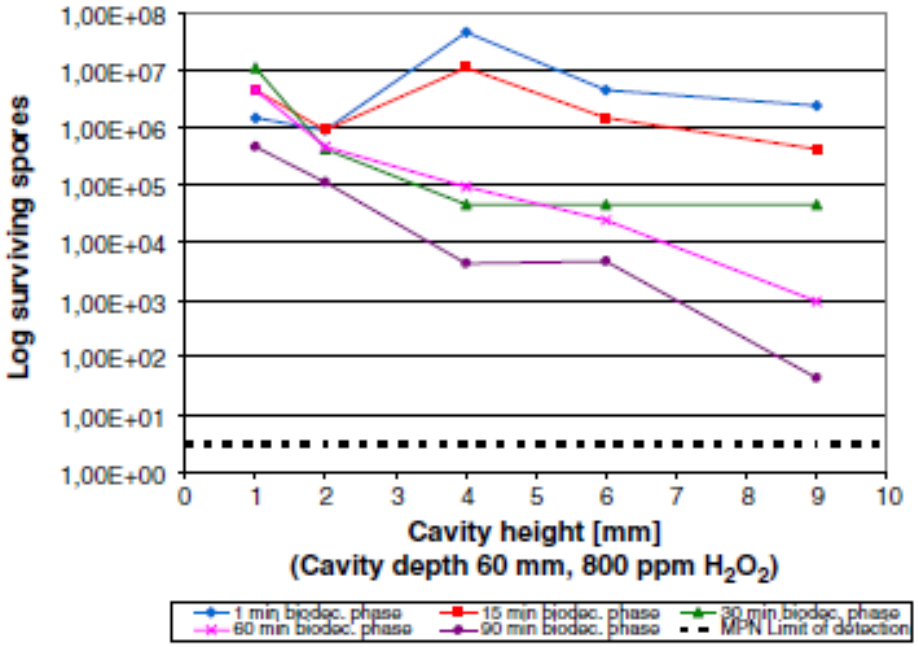
Bottom half of the test block assembly

Penetration of Sterilant

Results of Unger-Bimczok, et al., research

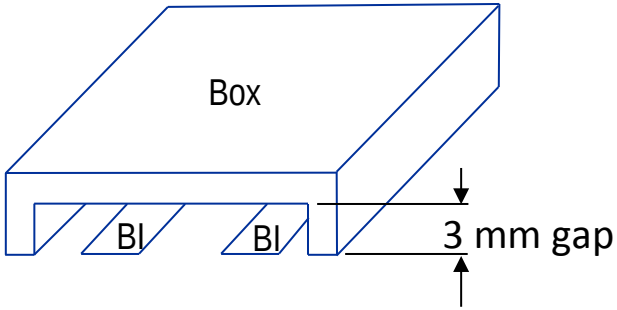
- Lethality in 3 cm deep, 9 mm gap requires 30 min.
- 4 mm gap did not show lethality after 60 minutes

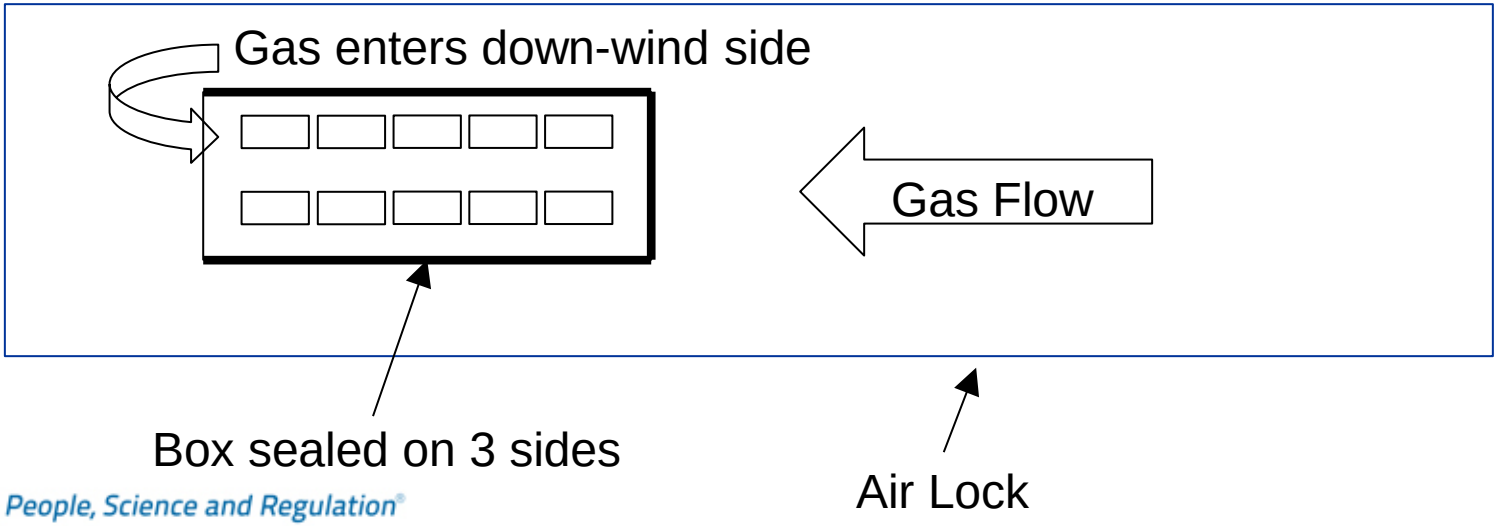




Penetration of Sterilant

- Recent testing:
  - 3 mm gap between two plates, simulating closely positioned components in a filling line
  - Two types of BIs used
  - Short exposure times





H_2O_2 Decontamination Data

N = Sterile	***P*** = Not Sterile

Exposure Time	BI Carrier	BI Position			
		3 cm	8 cm	12.5 cm	18 cm
2 min.	**SS**	***N***	***P***	***P***	***P***
	Q	***N***	***N***	***P***	***P***
4 min.	**SS**	***P***	***P***	***P***	***P***
	Q	***N***	***P***	***P***	***P***
6 min.	**SS**	***P***	***P***	***P***	***P***
	Q	***N***	***P***	***P***	***P***
8 min.	**SS**	***N***	***P***	***P***	***P***
	Q	***N***	***P***	***P***	***P***
16 min.	**SS**	***P***	***P***	***P***	***P***
	Q	***N***	***P***	***P***	***P***
24 min.	**SS**	***P***	***P***	***P***	***P***
	Q	***N***	***P***	***P***	***P***

200 L Transfer Air Lock
(4.5 g/min. injection
1.5 g/min. stabilization)

- All ‘Q’ BIs dead at 3 cm
- ‘SS’ BI results are variable

Note two types of BI carriers are used:

SS = stainless steel; Q = filter media

NO_2 Decontamination Data

N = Sterile		***P***	= Not Sterile

Exposure Data	BI Carrier	BI Position				
		3 cm	8 cm	12.5 cm	18 cm	
4 min.	SS	*N*	*N*	*P*	*P*	200 L Transfer Air Lock
	Q	*N*	*N*	*N*	*P*	
10 min.	SS	*N*	*N*	*P*	*P*	
	Q	*N*	*N*	*P*	*P*	10 mg/L, 75% RH
16 min.	SS	*N*	*N*	*P*	*P*	
	Q	*N*	*N*	*P*	*P*	
24 min.	SS	*N*	*N*	*N*	*P*	
	Q	*N*	*N*	*N*	*P*	
6 min.	SS	*N*	*N*	*P*	*P*	
	Q	*N*	*N*	*P*	*P*	
10 min.	SS	*N*	*N*	*P*	*P*	
	Q	*N*	*N*	*P*	*P*	10 mg/L, 60% RH
16 min.	SS	*N*	*N*	*P*	*P*	
	Q	*N*	*N*	*N*	*P*	
24 min.	SS	*N*	*N*	*N*	*P*	
	Q	*N*	*N*	*N*	*P*	

Gaps and Dead-Leg Summary

- Results with H_2O_2 are consistent with published results
- NO_2 results demonstrate good diffusion 8 cm into 3 mm wide gaps
- At 24 minutes, BIs at 12 cm were negative

- This information can be used when designing filling lines, planning load configurations, etc.

Summary of Challenges

- There are challenges with decontamination processes
- The topics discussed might provide some support for analyses of specific applications
  - Biological Indicators (BIs)
  - Filters – Good lethality requires gas penetration into the media
  - Syringe tubs – Reliable results require …
  - Dead-legs, gaps, etc. – Careful study can support design decisions

Rapid Isolator Biodecontamination

- Key Benefits (Benchmark 1cu.m isolator)
  - Total Process Time (TPT) = 50% Of HPV
  - TPT 45 Minutes To 1ppm, Same Lethality
  - Low Residuals – 0.1ppm* In TPT 1 Hour
    - Multiple Hours for HPV
    - Important for Biologics Manufacturing
  - No Consumables Management
    - On-Demand Generator

* Because ambient air can have 20 ppb to 40 ppb of NO_2, There is no need to aerate lower than 100 ppb (0.1 ppm)

Stand-alone and Integrated Systems

Non-integrated generator can be located up to 50 meters from the isolator

Prefilled Syringes and Vials

Room Temperature Sterilization (and Colder!)

- Room Temperature Process
  - Suitable for Heat Sensitive Products
  - Process has been demonstrated to be effective at 10ºC
- Non-Vacuum Process Available
  - Pressure-sensitive products (eg PFS)

Room Temperature Sterilization

Conclusion

- There are challenges with decontamination
- Challenges require knowledge of the process capabilities
- BIs are a rigorous challenge, but not infallible
- The NO_2 process can provide clear benefits
  - »Low temperature sterilization
  - »Rapid decontamination and sterilization
  - »Fast aeration

Thank you!

David Opie, Ph.D.

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