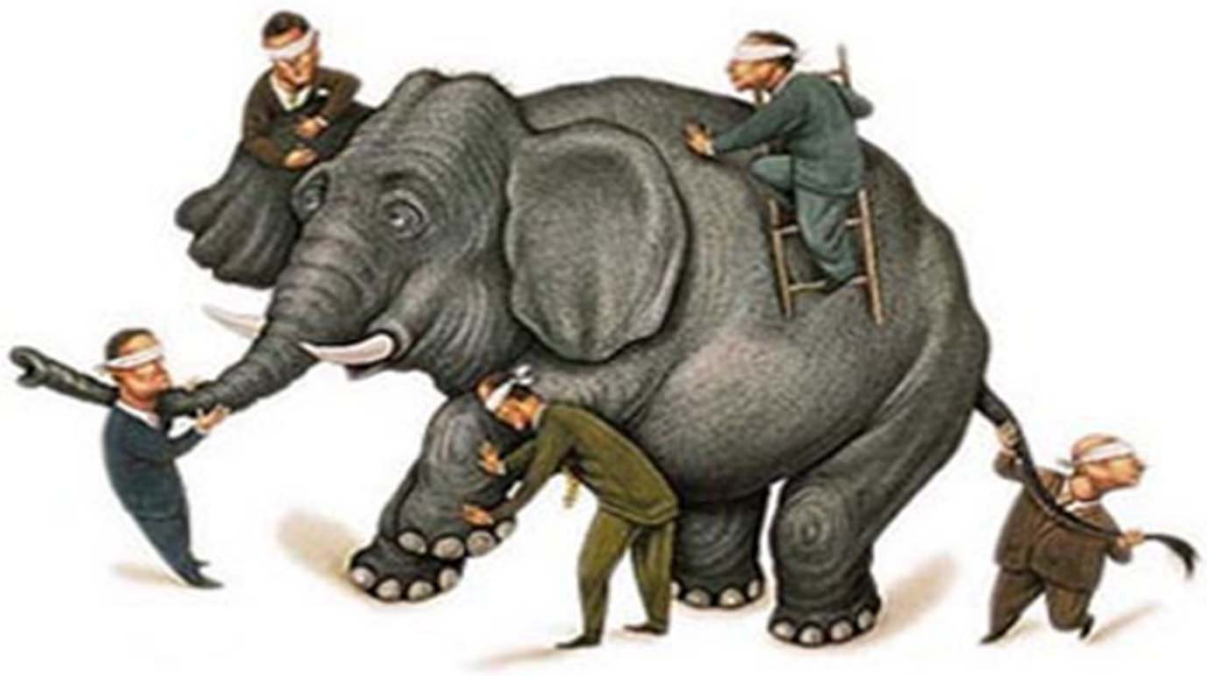
Connecting People, Science and Regulation®

Achieving Meticulous Aseptic Standards & Control in a Filling Isolator – Lessons for Design

Aidan Harrington PhD
Senior Consultant
DPS Engineering, Cork
Ireland

Preface



Agalloco, J.; Akers, J. Aseptic Processing, Elephants, Blind Men, and Sterility: *PDA J Pharm Sci and Tech* ***2002****, 56 231-234*

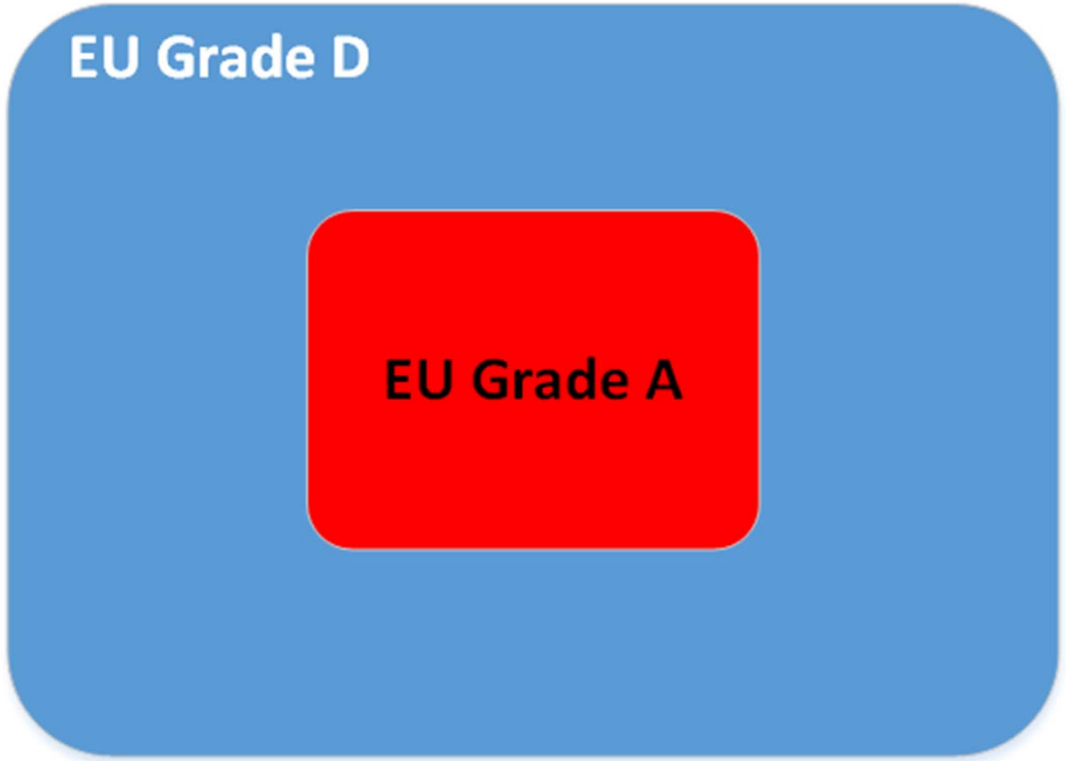
Agenda

Background Classification – Is Grade D Good Enough?

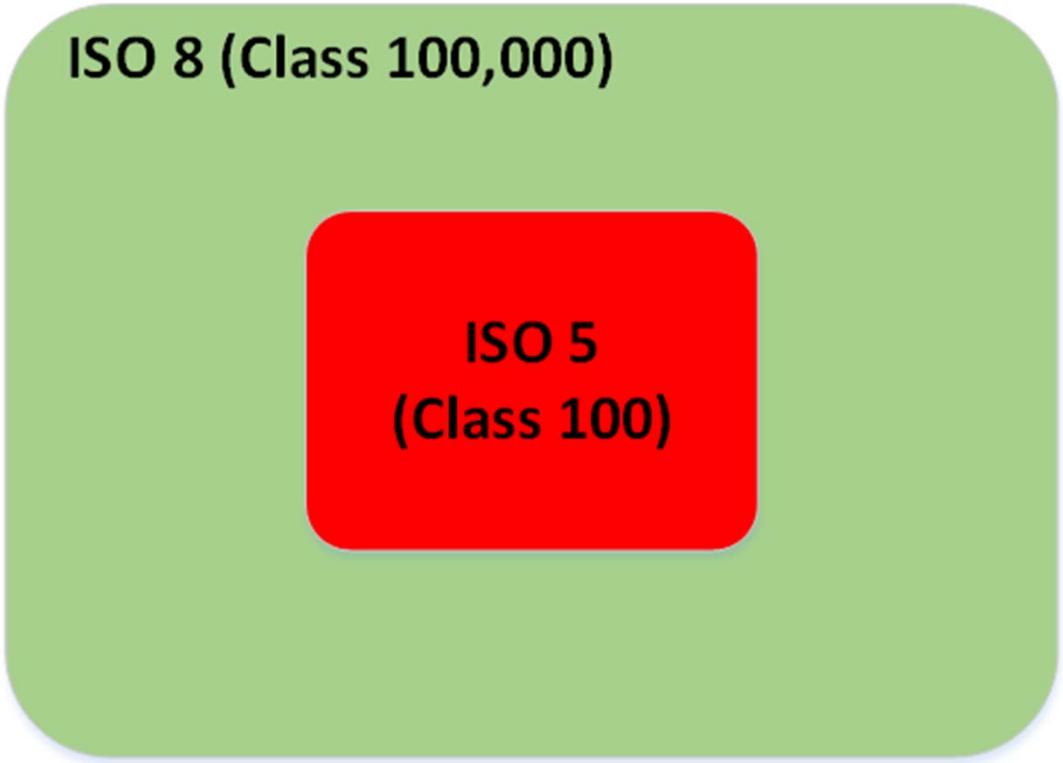
Sterilize Vs Surface Biodecontamination of Indirect Parts

Gloves & Pinholes – a Real Risk?

EU Annex 1: 1997 to Date



FDA - 2004



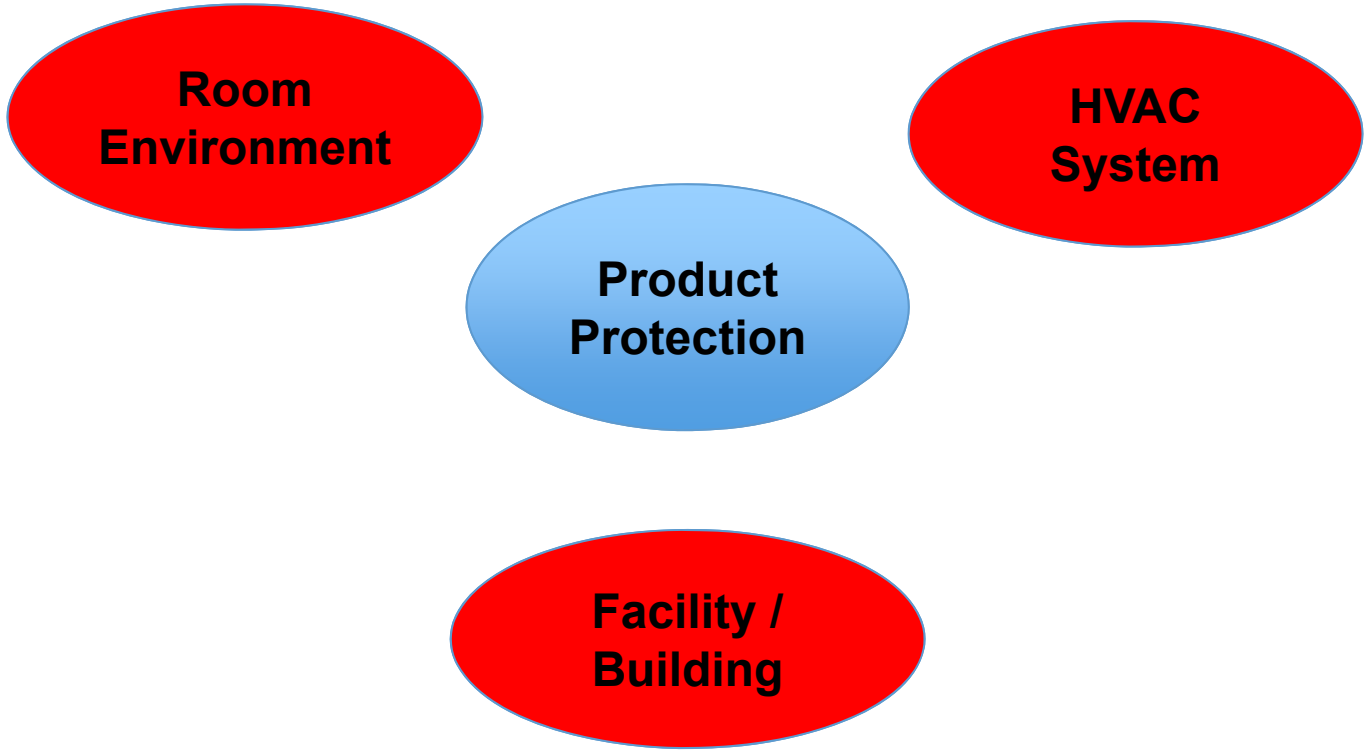
ISPE Baseline Guide 2011

ISPE Classification Grade	FDA, CDER September 2004 Guideline on Sterile Drug Products for Aseptic Processing			European Commission Annex 1, 2008 – Manufacture of Sterile Medicinal Products					
	In Operation		Descriptive	Descriptive /Grade	At Rest		In Operation		
Grade 8	3,520,000 ISO 8 (100,000)	100 (50)	Controlled Areas	Grade C	352,000 ISO 7	2,900 ISO 7	3,520,000 ISO 8	29,000 ISO 8	100

ISPE Baseline Guide: Sterile Manufacturing Facilities 2011

Isolator Background

An Open, Positive Pressure Isolator is a Closed System

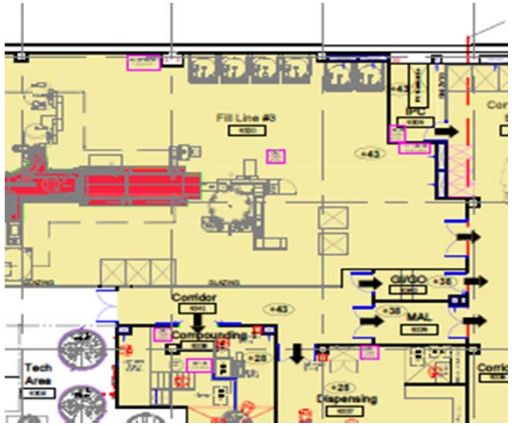


Isolator Background

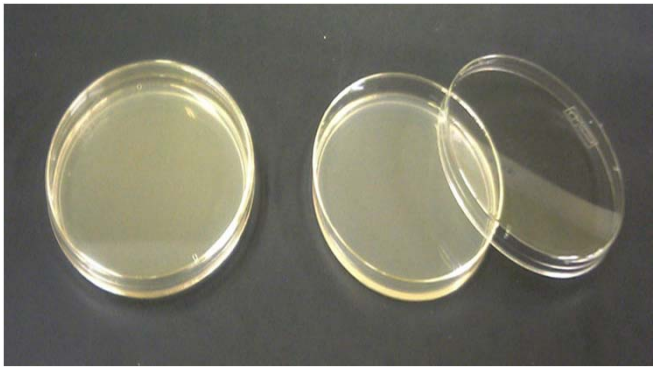
Aseptic Processing Complexity – The Holistic Facility*

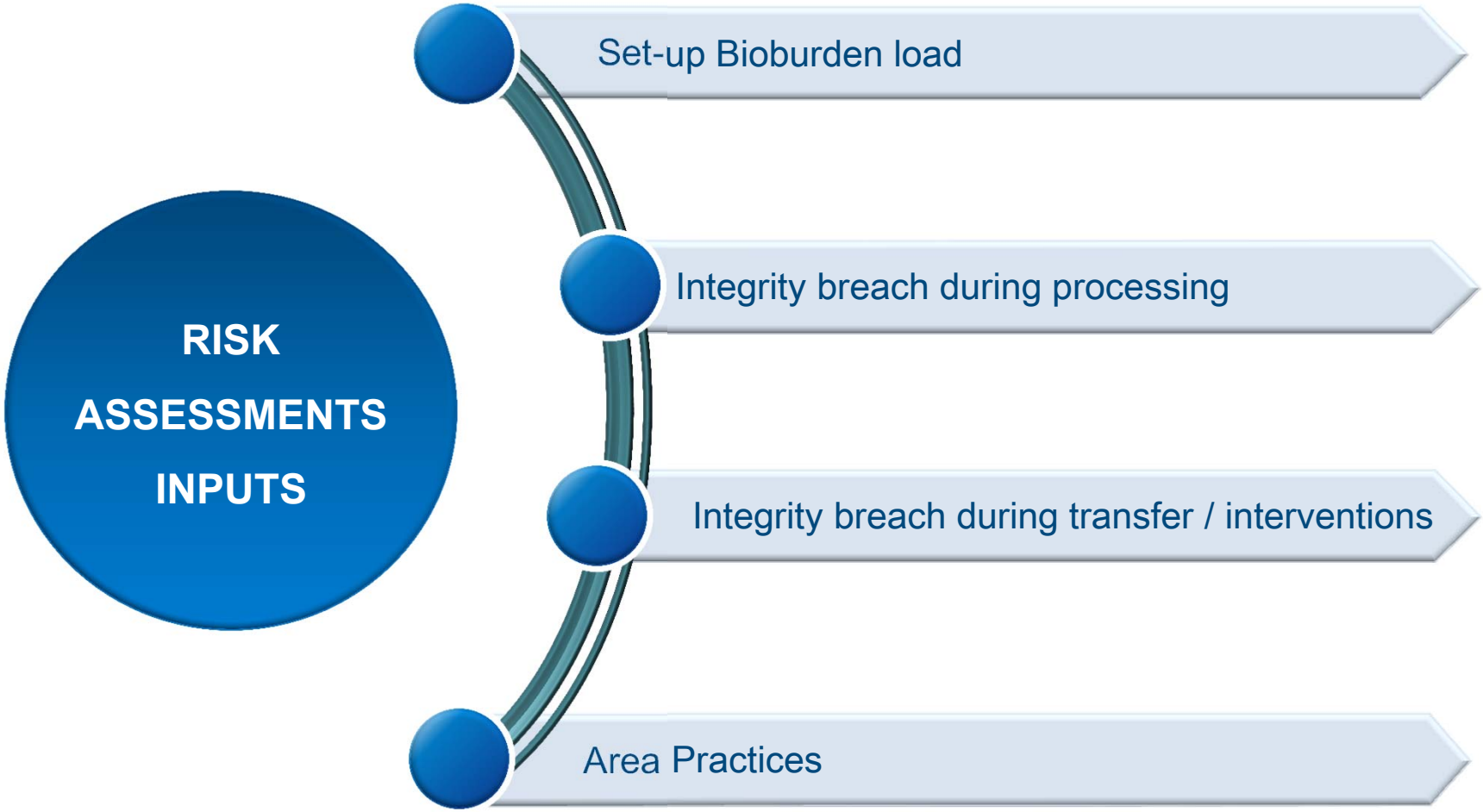
* R. Friedmann- FDA, 2014

Consequences



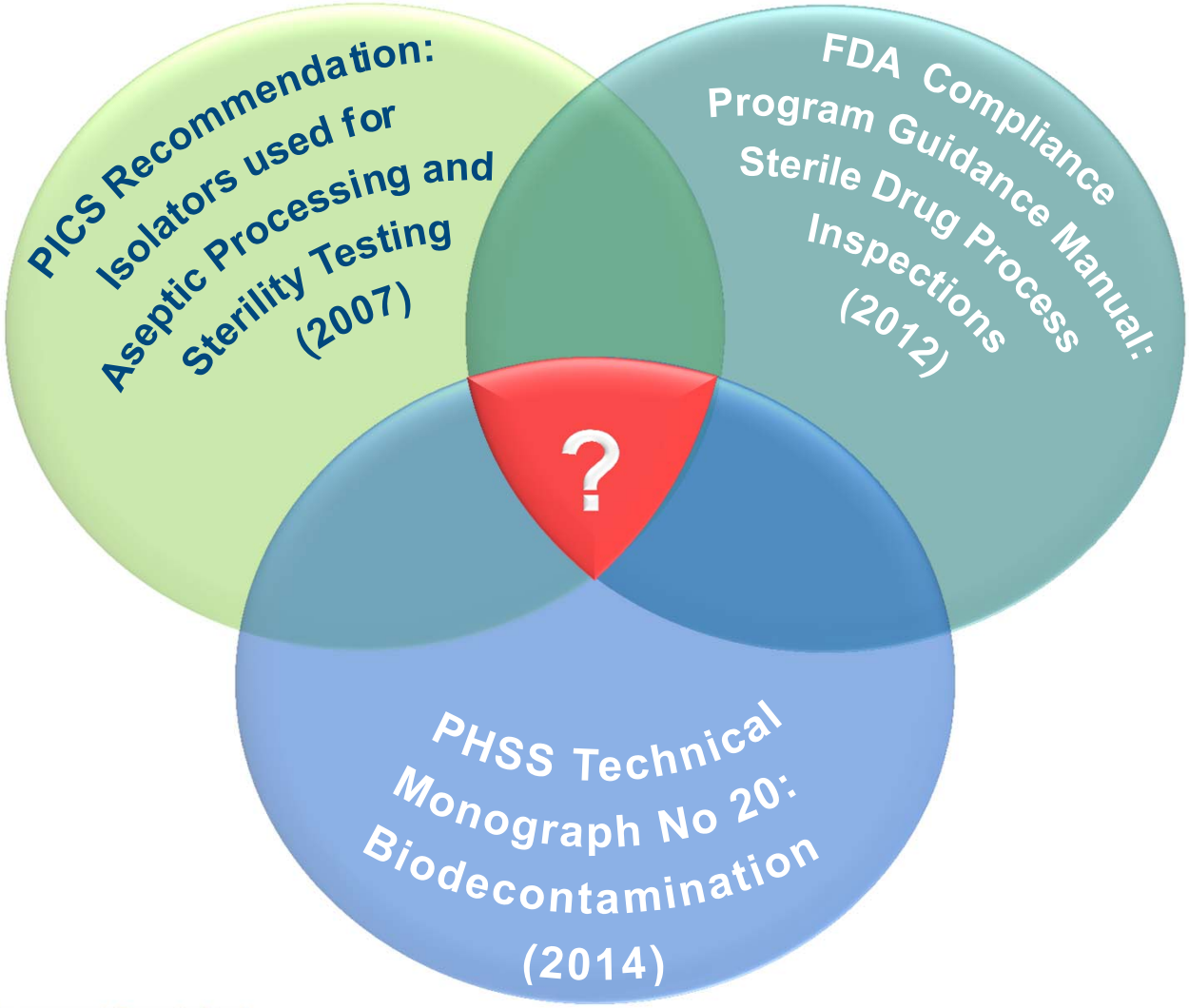
€




RISK
ASSESSMENTS
INPUTS
Set-up Bioburden load
Integrity breach during processing
Integrity breach during transfer / interventions
Area Practices

Autoclave Prior to VHP ?

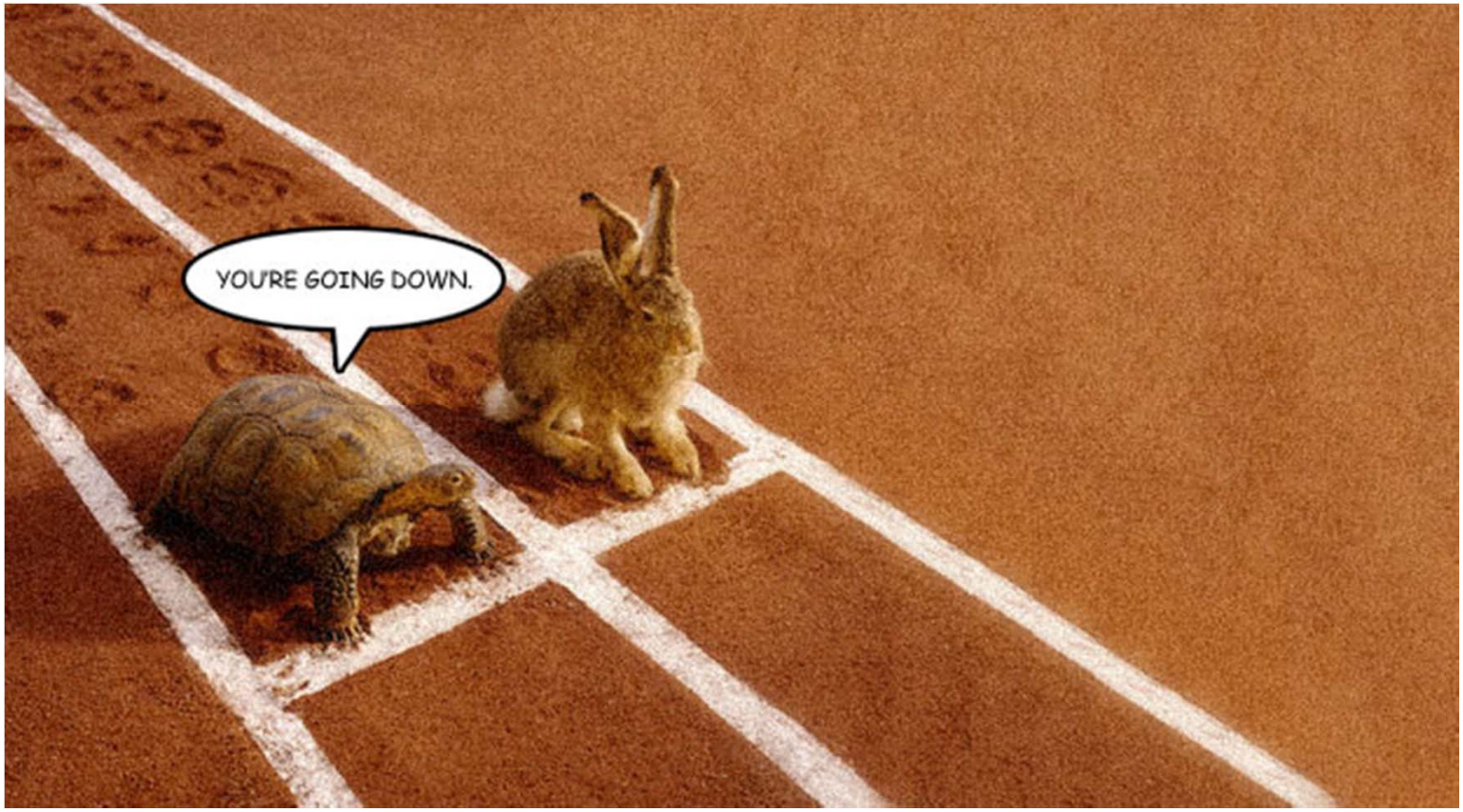
Guidance Documents



Apparent Limitations of VHP ?

- **The application of a sporicidal process is not considered to be a sterilization process**
- **...lacks the penetrating capabilities of steam sterilization**
- **…be mindful of the limitations of surface sterilants**
- **…their inefficiency in penetrating obstructed or protected components**

What Limitations?



VHP Controls

- Airflow
- Temperature & Humidity
- BI's – Mitigation Against Variance
- Slow Motion during VHP to ensure hidden areas are exposed
- Chemical indicators
- System D Value Determination
- Biological Indicators – Establishment of Edge of Failure
- VHP Dosing Rate / Exposure Time

VHP Output

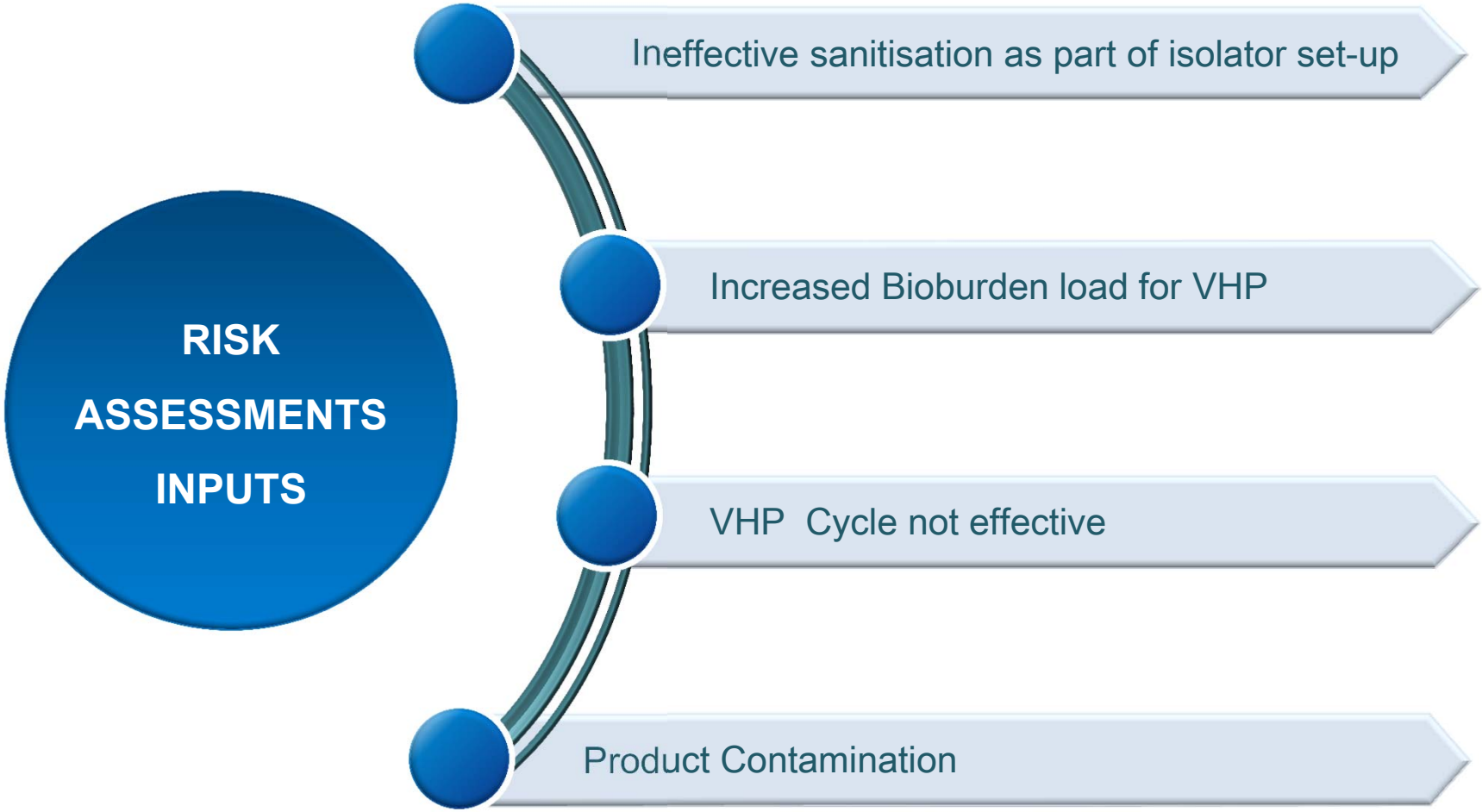
Consistently Delivers at least a 6 log BI Reduction

Is this no longer good enough?

- Autoclave Loads – Cycle Development / PQ / Requalification/ Hold time studies by Media Fill
- Storage Requirements with Control post Autoclaving
- Longer Batch Turnaround Times
- Increased Risk of Damage due to Handling
- Opportunities for Error in all of the above

CONSEQUENCES

- Greater Aseptic Control ?
- Greater Product Quality & Patient Safety ?


RISK
ASSESSMENTS
INPUTS
Ineffective sanitisation as part of isolator set-up
Increased Bioburden load for VHP
VHP Cycle not effective
Product Contamination

Gloves

How Risky are Pinholes in Gloves? A Rational Appeal for the Integrity of Gloves for Isolators

Gessler, A. ; Stark, A.; Sigwarth, S. & Moirandt, C. *PDA J. Pharm Sci and Tech* 2011 65: 227-241

Results

Following 12 batches over two weeks, less than 20% of the gloves (103) showed more than 5 CFU/sample.

Migration of microorganisms through damaged gloves with pinhole was established with high bioload (3.6×10^4 CFU/cm^2)

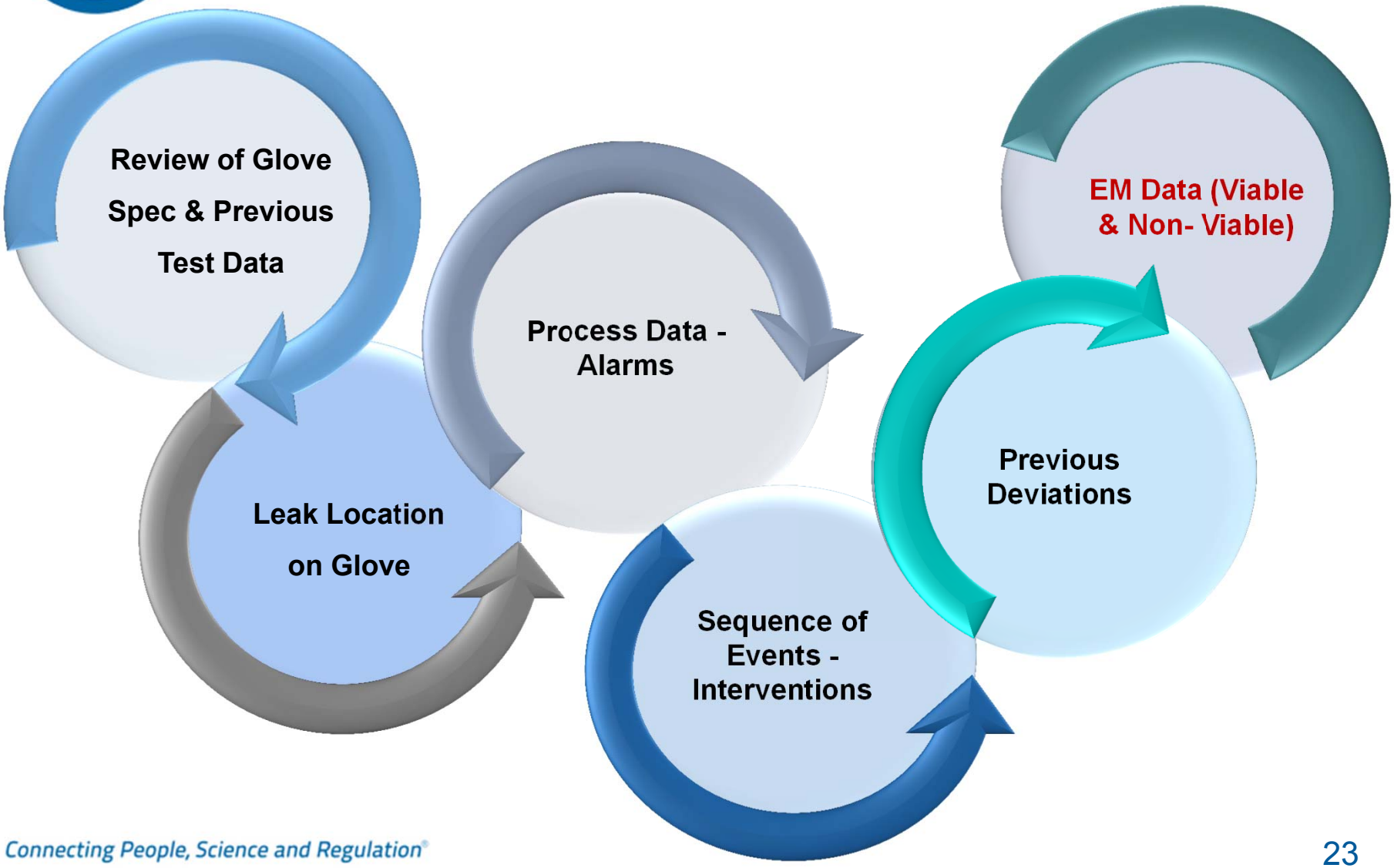
Medium (4.3×10^3 CFU/cm^2) and Realistic (5.0×10^1 CFU/cm^2) bioloads did not result in contamination

Conclusions

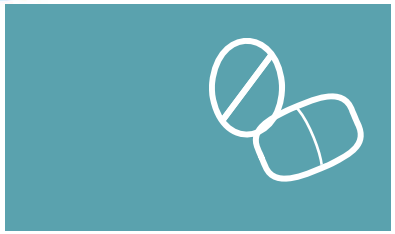
- **Pinholes as a source of contamination does not consider real world situations and may also have enormous economic consequences.**

- **Defective Gloves will not contaminate a product if proper control of the glove inner side and properly evaluated techniques are respected.**

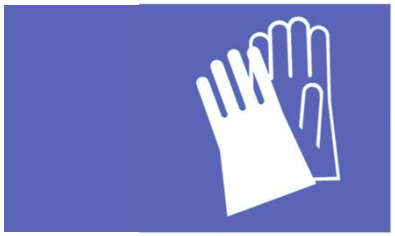
Risks and Opportunities



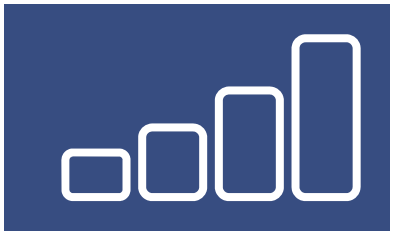
Glove Failure Investigations



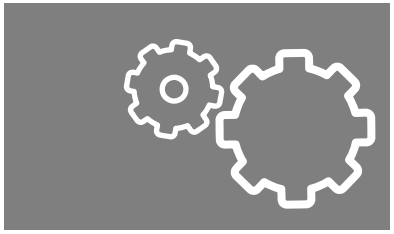
Batch is saved – no microbial contamination



The reason the gloves failed in the first place was not helped by excessive environmental monitoring inside the isolator



Where is the contamination going to come from in the first place?



Is this embracing new technology?

Lessons Learned…or not!

As long as some people erroneously insist on immeasurable perfection, we will have unreasonable expectations

Agalloco, J.; Akers, J. Aseptic Processing, Elephants, Blind Men, and Sterility: *PDA J Pharm Sci and Tech* ***2002****, 56 231-234*