Case Studies in Environmental Excursions

PDA Parenteral Drug Association
Southern California Chapter

PSC

CLIMET INSTRUMENTS COMPANY

Disclosure:

It is an ***informational presentation*** regarding various considerations that should be assessed during environmental excursions.

This presentation may contain certain errors or omissions. Please, consult your organization's Quality Assurance Manager and Risk Assessment Plan if you have any concerns.

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III. Overview: Microbial Contamination
IV. Overview: Physical Particulate Contamination
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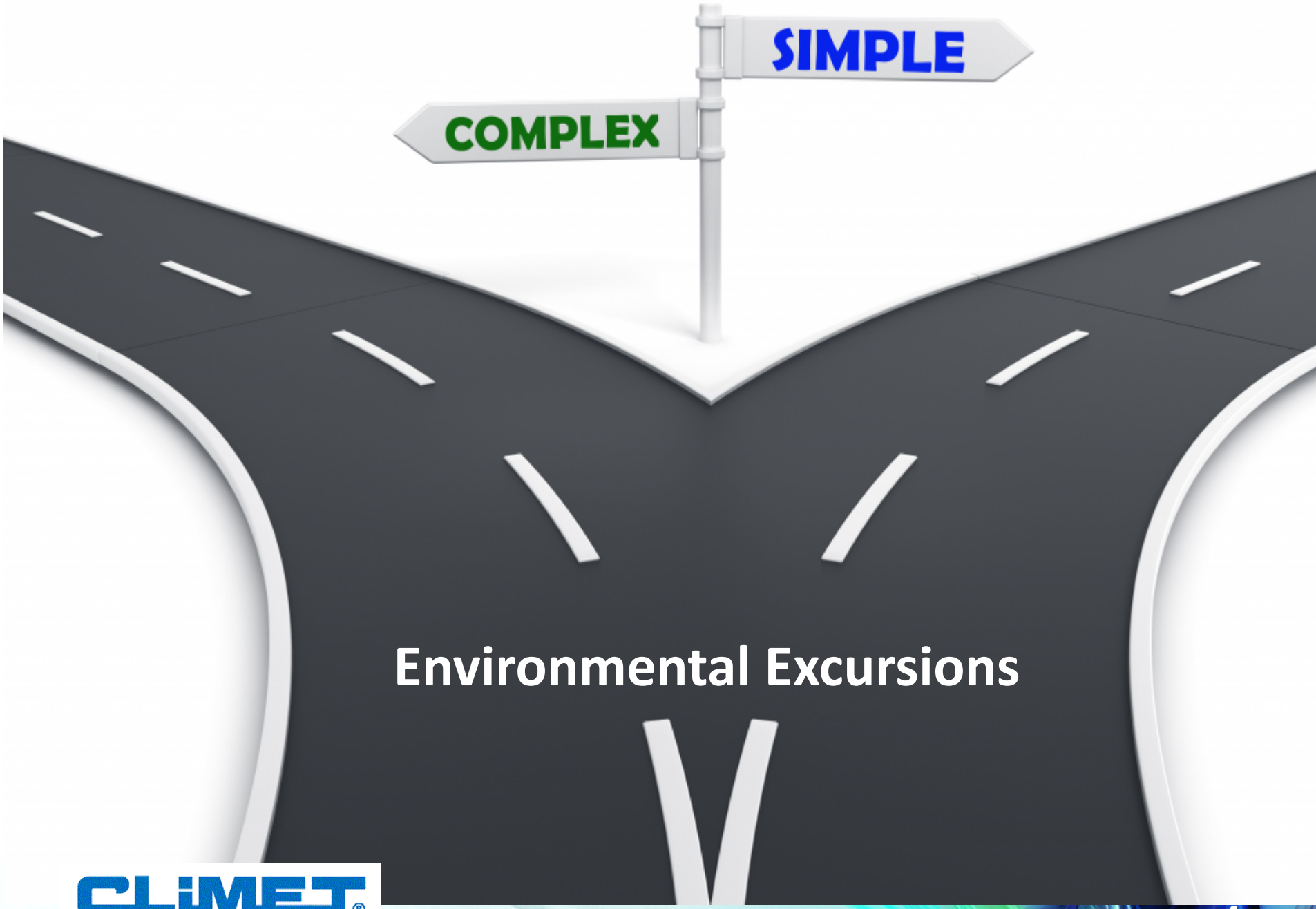
VI. Case Study #2: RABS



Environmental Excursions

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Understanding Environmental Monitoring

3 Purposes of EM (Environmental Monitoring)

EM is the canary in a coal mine:

1. **Measures effectiveness** of contamination control
2. Identifies **negative trends** leading to excursions.
3. Helps to identify the **possible cause** of excursions (i.e., specific threats)

ISO 14644-1: 2015

ISO Class number (*N*)	Maximum allowable concentrati… for particles equal to and greater th… [a]					
	0,1 µm	0,2 µ…				5 µm
1	*10* [b]					e
2	100	24…				e
3	1 000	237				e
4	10 000	2 370	1 02…		83…	e
5	100 000	23 700	10 200	3 520	832	d,e,f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9	c	c	c	35 200 000	8 320 000	293 000

Does not say
0 @ 5µm in ISO Class 5

Notes:

a) All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0.3 µm include all particles equal to and greater than this size.

b) These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

c) Concentration limits are not applicable in this region of the table due to very high particle concentration.

d) Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

e) Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f) In order to undertake classification at this particle size, use of the macro-particle descriptor M should be considered for ≥5.0µm.

ISO 14644-1: 2015

ISO Class number (*N*)	Maximum allowable concentrations (particles/m^3) for particles equal to and greater than the considered sizes, shown below [a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10* [b]	d	d	d	d	e
2	100	*24* [b]	*10* [b]	d	d	e
3	1 000	237	102	*35* [b]	d	e
4	10 000	2 370	1 020	352	*83* [b]	e
5	100 000	23 700	10 200	3 520	832	d,e,f
6	1 000 000	237 000	102 000	35 200	8 320	293
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f) In order to undertake classification at this particle size, use of the macro-particle descriptor M should be considered for ≥5.0µm.

This refers to ISO 14644-1 Annex C

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Macroparticles (>5 µm)

ISO 14644-1: 2015, Annex C :

Defines "Macroparticle" as any particle > 5µm

"In some situations, typically those related to specific process requirements, alternative levels of air cleanliness may be specified on the basis of particle populations that are not within the size range applicable to classification."

This was written specifically for the Life Science Industry.

Macroparticles (>5 µm)

EU GMP, Annex 1

"Grade A and B zones, monitoring of > 5.0 µm particles takes on particular significance as it is an important diagnostic tool."

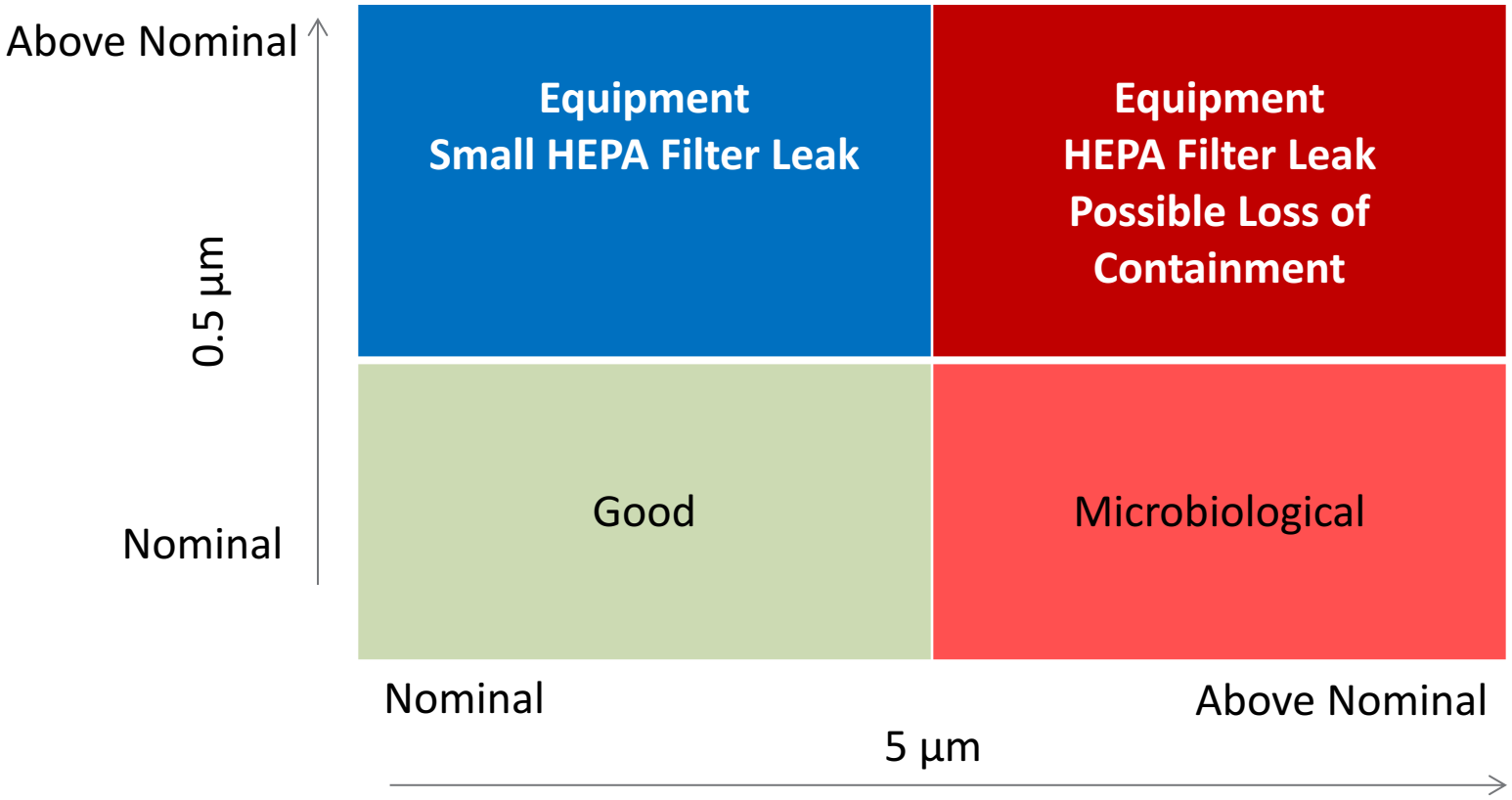
Macroparticles (>5 µm)

USP <1116>

While airborne microorganisms are not free-floating or single cells, they frequently associate with particles of ***10–20 µm***.

The only significant sources of microbial contamination in aseptic environments are cleanroom personnel.

EM – Intuitive Generalities



Importance of Trending EM Data

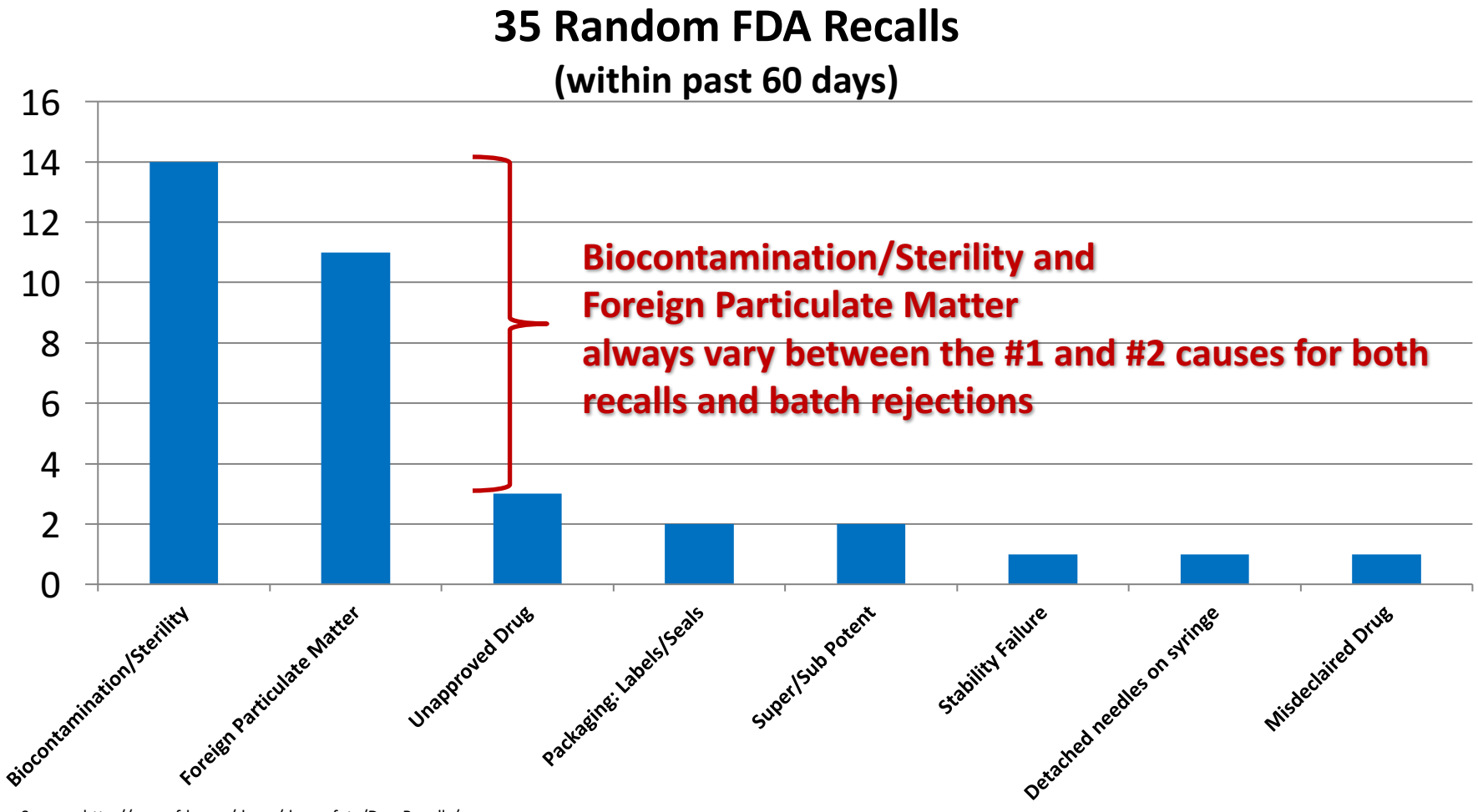
Pharmaceutical Inspection Co-operation Scheme (PIC/S)

- PIC/S: 2014 **GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEXES**

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

Drug Recalls & Batch Rejections

FDA Recalls



Source: http://www.fda.gov/drugs/drugsafety/DrugRecalls/

Microbiological Contamination

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Bioburden Excursion

First step in the investigation:

Species identification? Source? Location?

Species suggests probable cause:

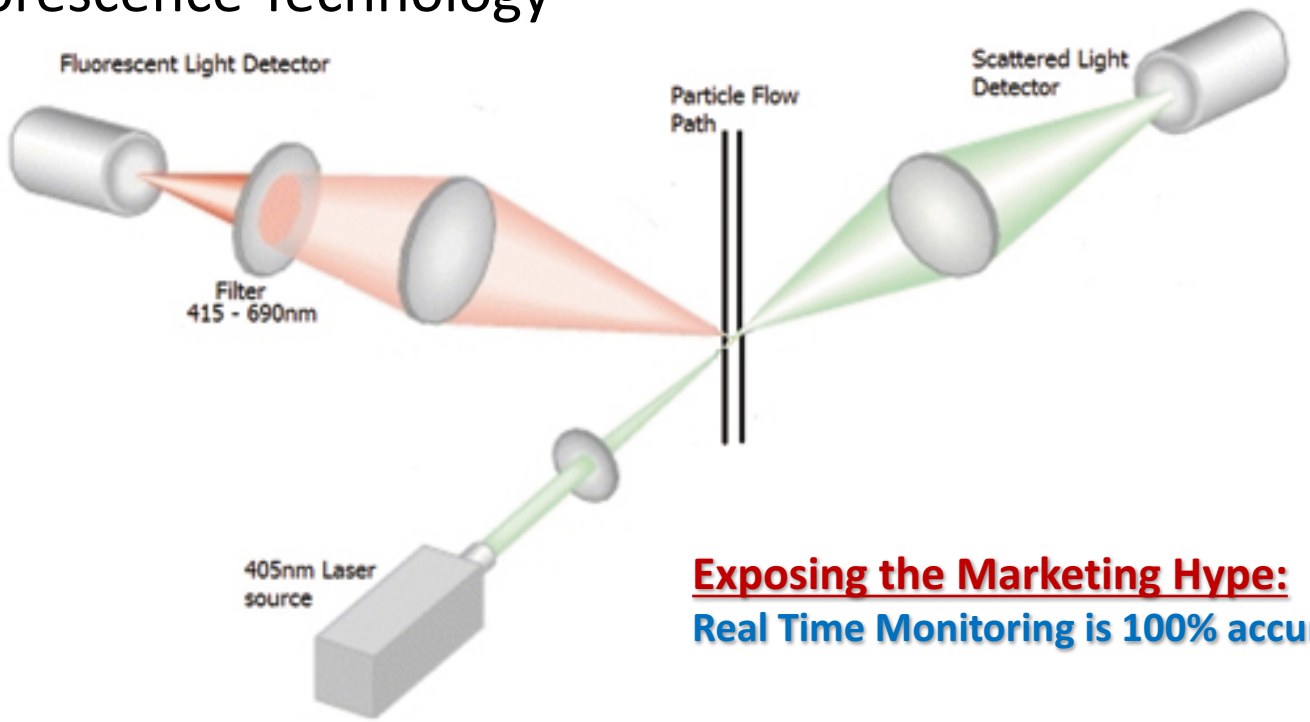
Water, human, etc.

If Unexpected or exotic viable microorganism

Possible contamination of raw materials or personnel recently exposed to a disease not endemic to facility

Real Time Monitoring

Based on Florescence Technology

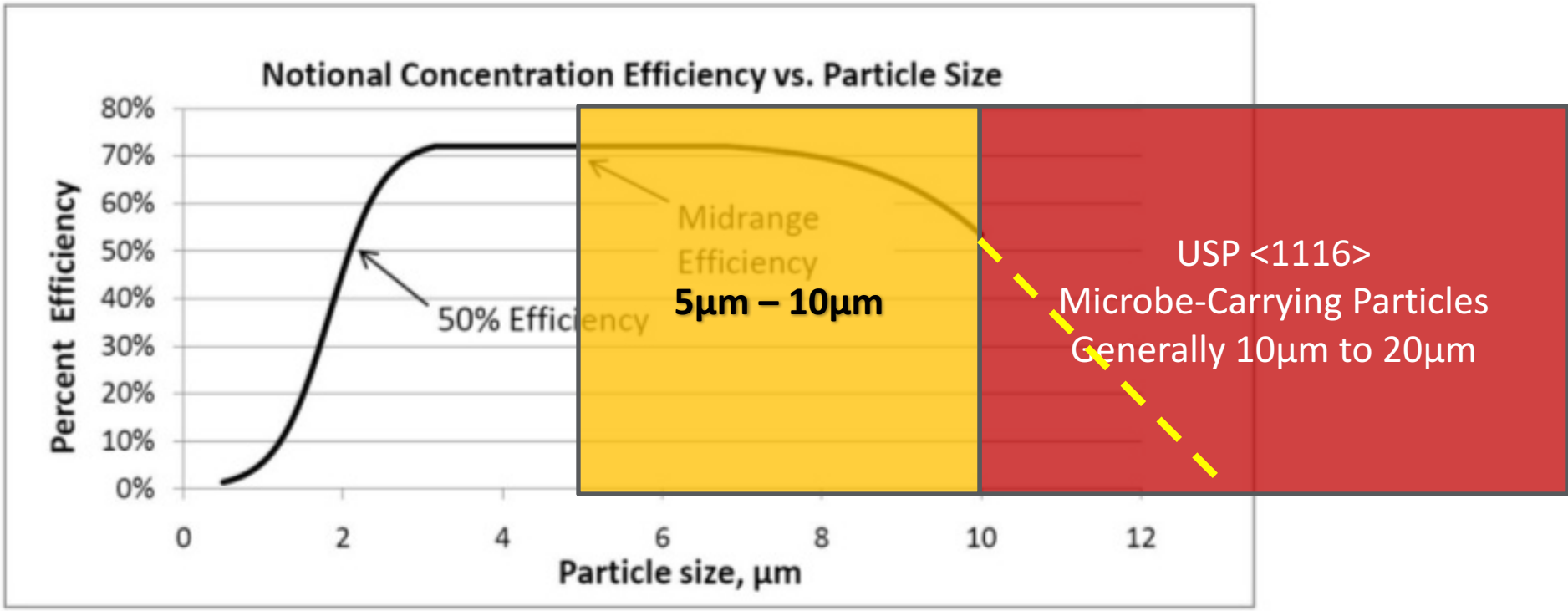


Exposing the Marketing Hype:

Real Time Monitoring is 100% accurate

Short Comings of Real Time Monitoring

Physical Collection Efficiency is generally low: about 70% maximum and drops off after 8 µm. (10µm @ ~56%)



Real Time Monitoring

- Susceptible to false counts – aka False positives
  Pollens, skin flakes, paper dust, some disinfectant sprays, and clothing fibers have fluorescence properties.
- Real Time Technology cannot discern between species
- Real Time Technology uses UV Light (typically at 405nm). Methodology maybe **germicidal** and **destructive**.
  Regardless, **no species identification** with this technology & inability to perform investigation
- Very Low Flow Rate 4-5 LPM (~4 hours for 1m^3 sample)
- **Tubing loss** if using remote ISO Probes and BEV-A tubing (10-20µm):
  BEV-A not recommended, but if you do, keep tubing length < 3 feet.
- **MANIFOLD SYSTEM NOT RECOMMENDED**
- Cost is generally around $70,000

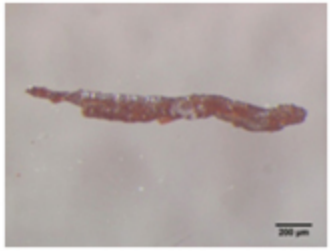
Real Time Monitoring - Conclusions

- Does not replace traditional time-proven methods
- Possibly a good investigational tool to help pinpoint a physical source of biocontamination.
- Possibly might be used in conjunction with traditional sampling methods (particle counter and microbial sampler).
  - Question: What do you do if the RTM readings are not supported by traditional means? Or, visa versa?
- If used, must be along side of traditional time-proven methods
  - Real Time
  - Microbial Air Monitoring
  - Particle Counts

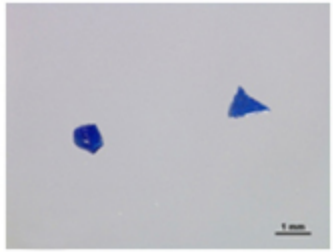
Foreign Particulate Matter Contamination

Foreign Particulate Matter Contamination

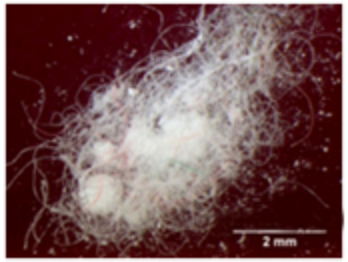
Includes materials such as glass, plastic, silicone, hair, fibers stainless steel, etc.



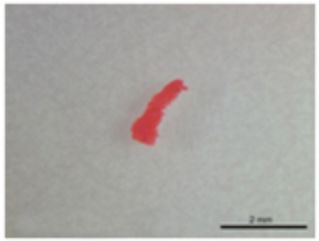
Metals



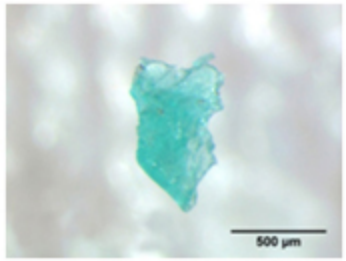
Glass



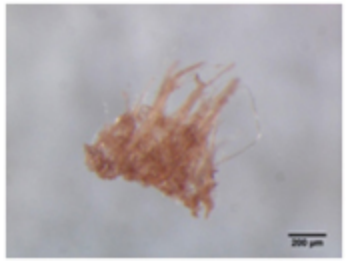
Fibers



Rubber

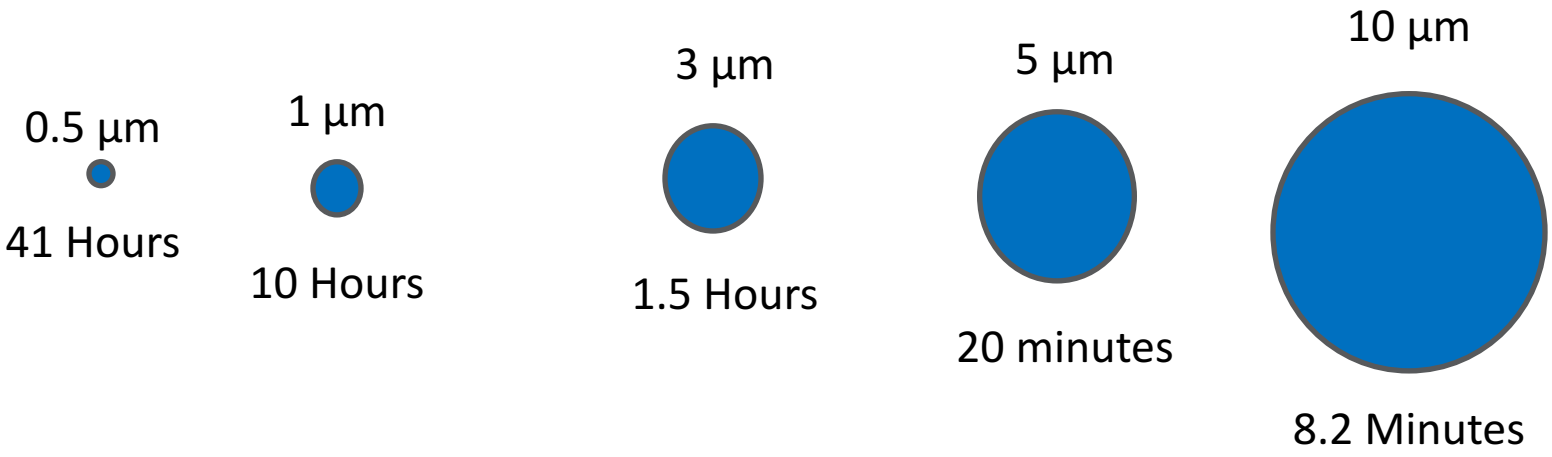


Plastic



Cellulose

Particle Settlement in Turbulent Air: 8 feet



Excursions: False-Positive Excursions

- Dirty or Kinked Tubing:
  - Retention of particles / VHP & harsh chemical degradation
  - Needs to be replaced periodically (4 year intervals minimum)

- Dirty Particle Counter Inlet (always have a supply of dust caps)

- Dirty Isokinetic Probe

- Stray light
  - Particle counter: Always sample **vertically from top to bottom** when using an isokinetic probe so that tubing has slight bend. Or, use a Lightblocker isokinetic probe directly attached to the inlet.

Parenteral Batch Rejection & Recalls

Pharmaceuticals spend ($)Millions on HEPA filter maintenance in cleanrooms, biosafety cabinets, and laminar flow hoods.

Parenteral Batch Rejection & Recalls

>99% of pharmaceutical manufacturers use a particle counter with a HEPA filtered exhaust and stainless steel enclosure.

> 80% (estimated) perform microbial air monitoring with an impaction sampler that does NOT have a HEPA filter, and/or has a plastic enclosure.

Rogue Emissions

Leaky HEPA Filter / Environmental monitoring equipment:

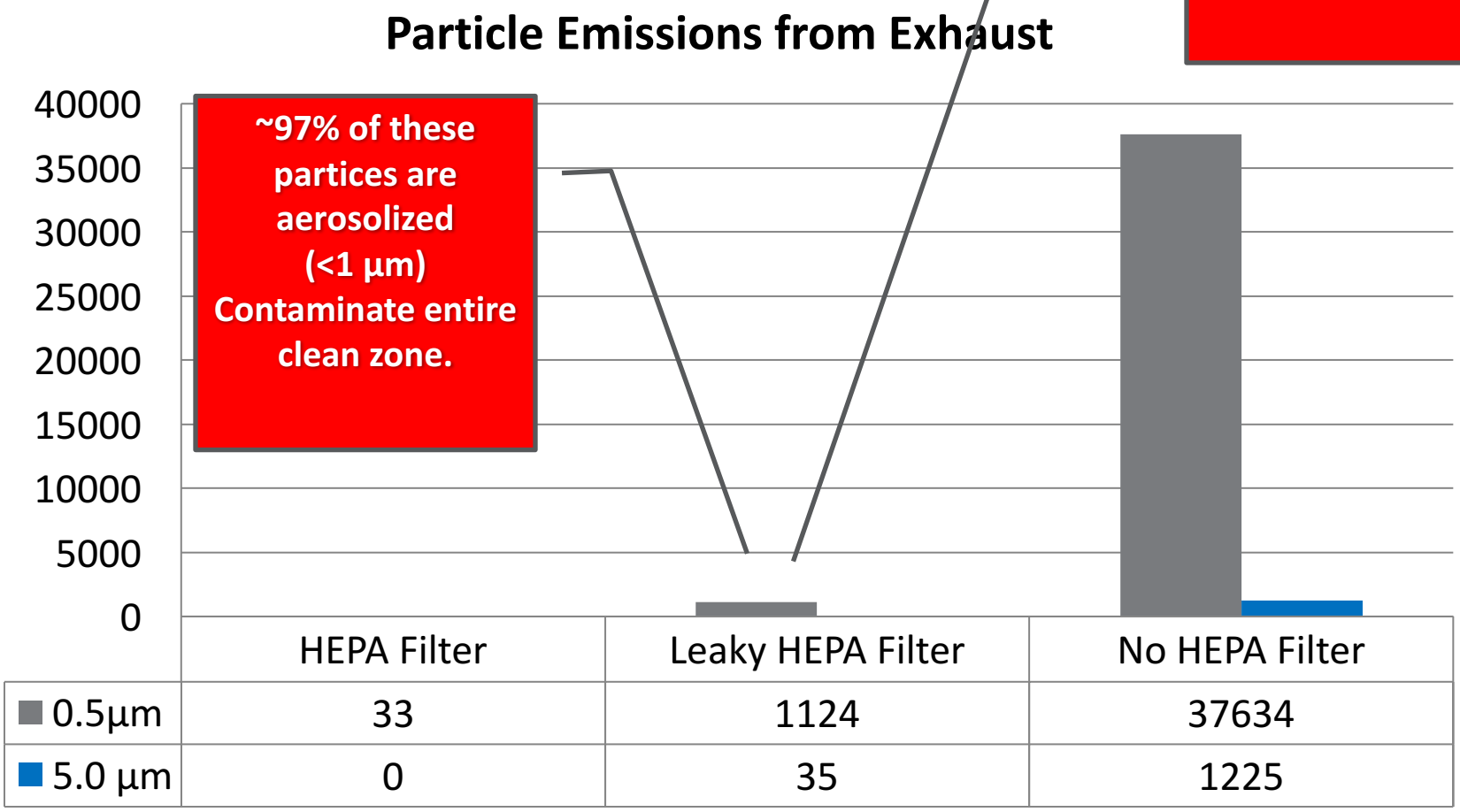
- > 1,100 inert particles released in every m^3 sample
- 97% of these particles are 0.5 µm channel.
- < 1 µm particles are **aerosolized** and will spread widely through an entire cleanroom or clean zone.

No HEPA Filter on environmental monitoring equipment:

- Tens of thousands to hundreds of thousand inert particles released in every m^3 sample.

Rogue Emissions (Cont.)

Fails ISO Class 3,4 & 5 for emissions testing



	HEPA Filter	Leaky HEPA Filter	No HEPA Filter
0.5µm	33	1124	37634
5.0 µm	0	35	1225

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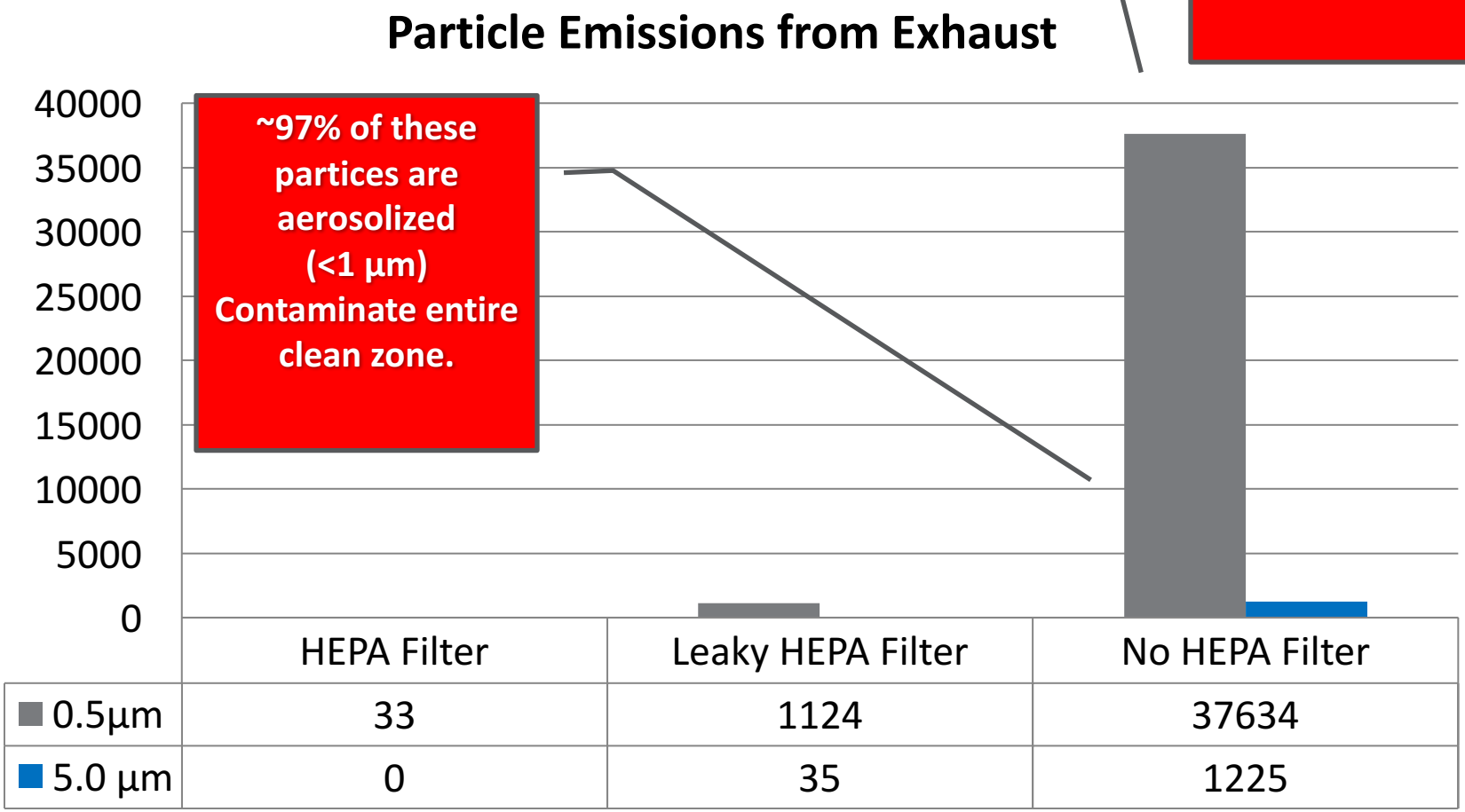
Rogue Emissions (Cont.)

Fails
ISO Class 3, 4, 5 & 6 for emissions, and barely passes ISO Class 7



	HEPA Filter	Leaky HEPA Filter	No HEPA Filter
0.5µm	33	1124	37634
5.0 µm	0	35	1225

Parenteral Batch Rejection & Recalls

USP<1116> : **Contamination should not be introduced into a manufacturing clean room as a result of using contaminated sampling media or equipment.**

Use of a microbial sampler without a HEPA filter may cause substantial foreign particulate matter contamination.

An ounce of prevention is worth a pound of cure!

1. Monitor 5µm channel
2. Trend Monitoring Data
3. GMP and FDA recommend re-evaluation of processes.
   a) When was the last time you evaluated microbial sampler requirements.
   b) Do current requirements make common sense?


CASE STUDY
#1

Biological Safety Cabinet

Class 5 BSC with particulate and biological contamination

Cause: Poor Monitoring Practices

Purge (Zero Count) Test: FALSE SENSE OF SECURITY

- Purpose is *diagnostic*

Current practice does not fully access risk:

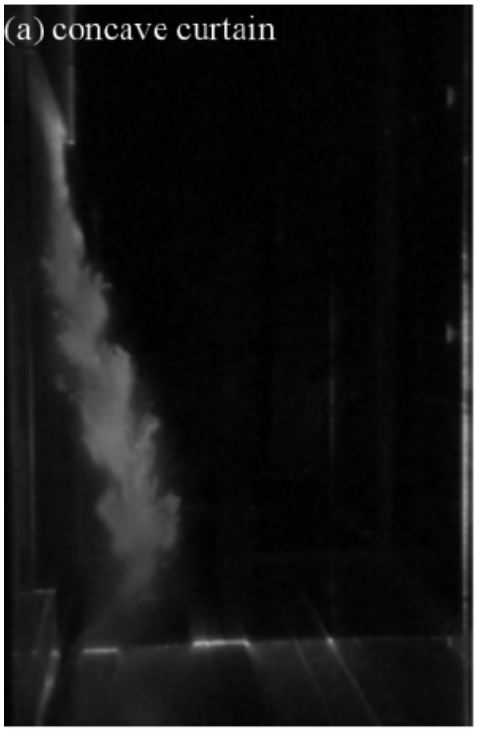
- Zero Count will identify false high counts
- Will not identify gross under-countering, which is more serious

Interval Calibration:

- Over counting poses minimal risk requiring a very simple deviation investigation.
- Under counting is a much more complex failure investigation. Exact variance unknown, and higher risk of batch rejection.

  Pre-test in an areas with stable-known concentrations to allow identification of gross under or over counting. Simultaneously test two or more in area. Variations should be less than 20% difference between counters.
  (Ref. ISO 21501-4, 100% ±10% Count Efficiency)

Per Center for Disease Control (CDC)



Biological Safety Cabinets have a

Fragile Air Curtain that provides containment

Particle counters and microbial samplers should NEVER be brought inside the BSC.

Breach of Containment

Increase risk of biocontamination, particle contamination, and cross contamination

- Disrupts air curtain both during entry and removal from BSC
- Exhaust disrupts laminar flow inside the BSC
- Transfer of viable & inert particles / cross-contamination

Center for Disease Control (CDC)

<u>Solution</u>: Use Remote Isokinetic Probe & Sample Head

Laminar Flow Integrity

Biological Safety Cabinets – Dead Spots

If located in unidirectional flow room, make sure there is adequate space behind, on top, and to the sides of the BSC to avoid pockets of low velocity or dead air.

Be sure all connections are tightly secured.

Center for Disease Control (CDC)

Biological Safety Cabinets – Cleaning

If bleach is used to disinfect a BSC, or particle counter, etc.

A second wiping with ***sterile water*** is needed to remove the residual chlorine, which may eventually corrode stainless steel surfaces.

High amount of bleach will release chlorine in the air, and will attack PCB circuitry.

Non-sterile water may re-contaminate surfaces

Center for Disease Control (CDC)

Biological Safety Cabinets – UV Light not necessary

HOWEVER, if Ultraviolet (UV) lamps are necessary, be sure to clean weekly to remove any dust and dirt that may block the germicidal effectiveness of the UV light.

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Restricted Access Barrier Systems

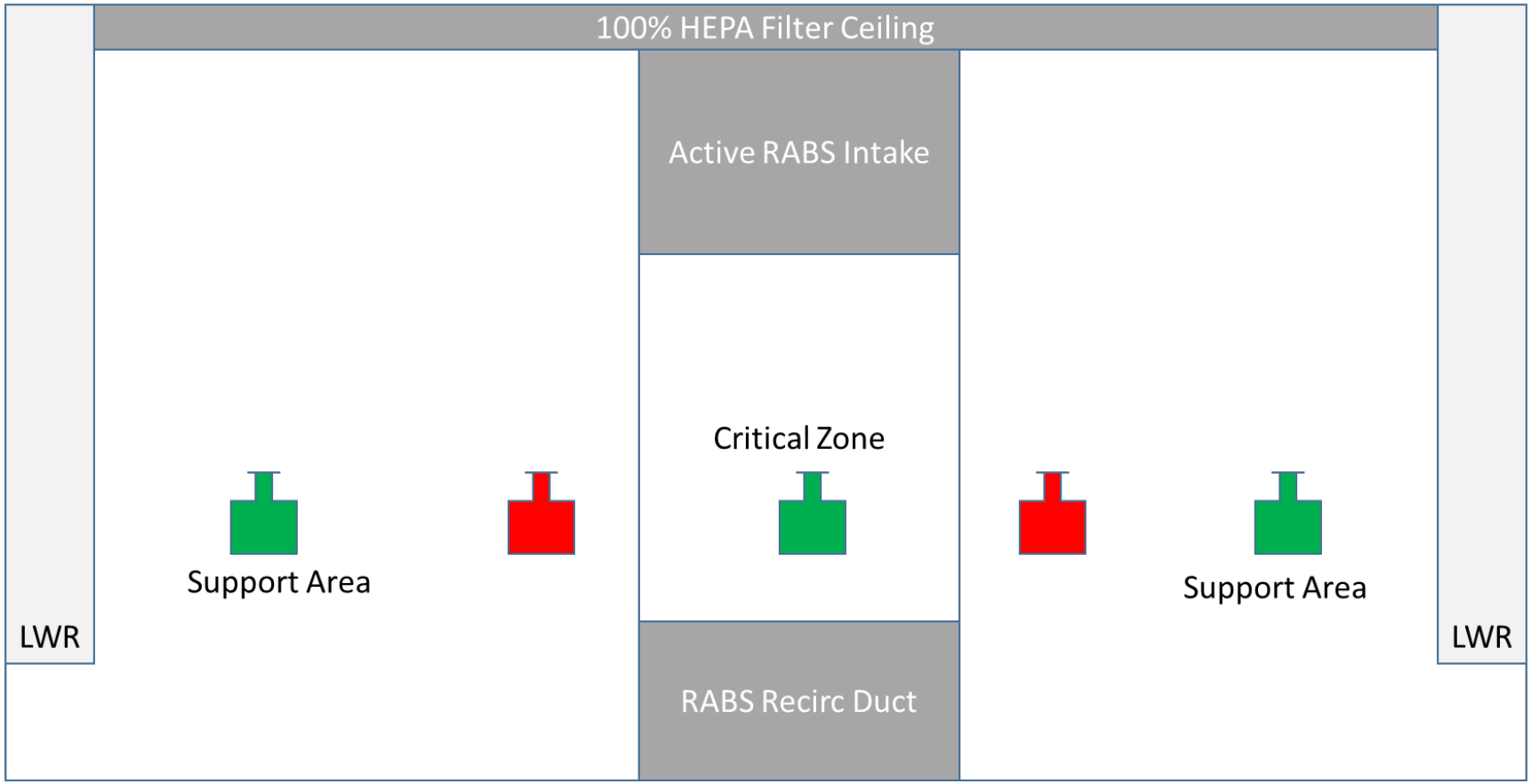
Advanced aseptic processing technology – separates people from product and process.

Active/Passive

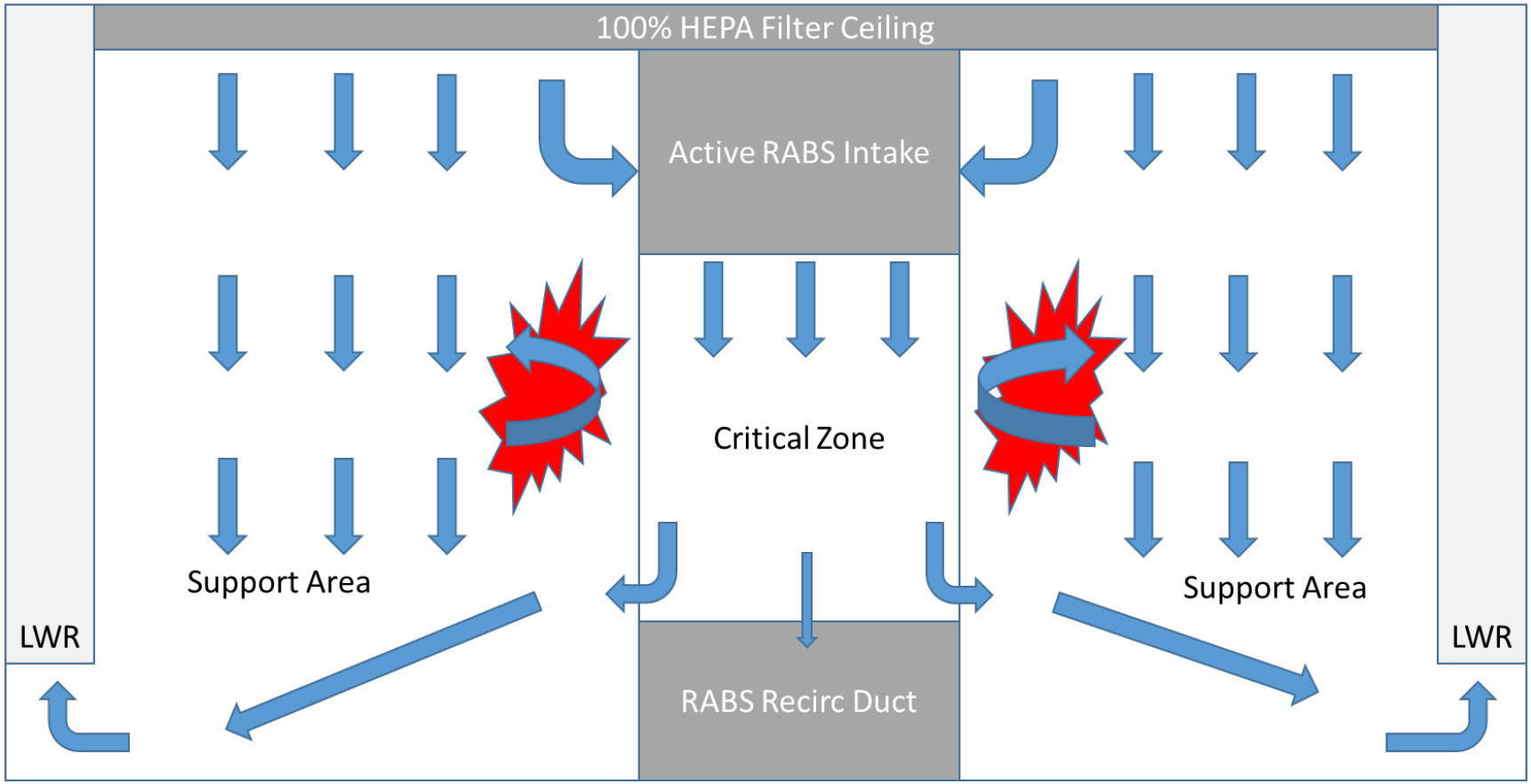
Open/Closed

Critical zone/Support area

Non-Viable Particulate Results – Excursions



Airflow Analysis – Smoke Study and CFD

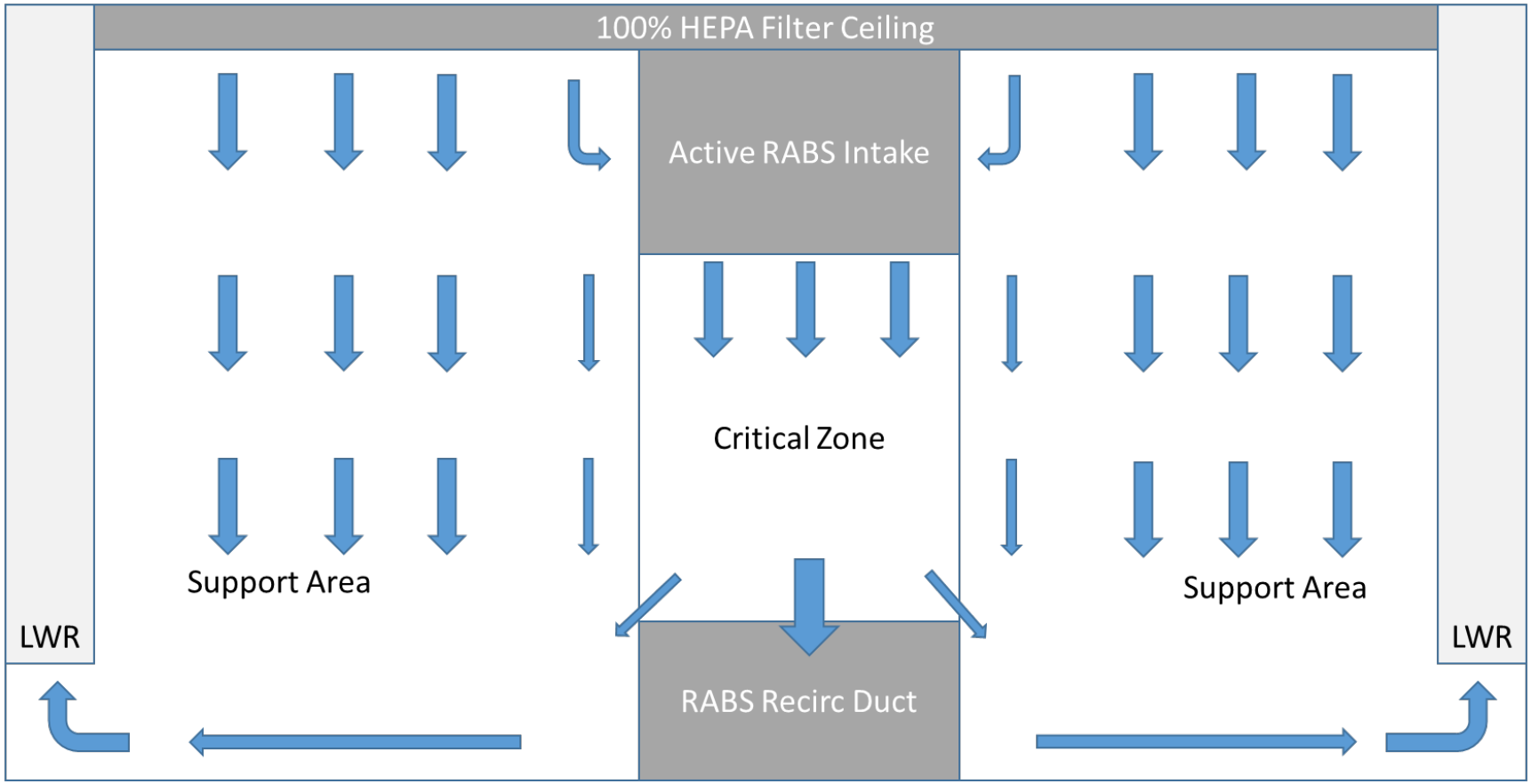


Why is this a problem?

- Only Critical Zone must be ISO 5 with Active RABS
- Support Areas can be ISO 7
- ISO 7 does not require unidirectional airflow

RESULT: No RABS intervention allowed – period.

Optimization – NVP Data, Smoke Study, and CFD

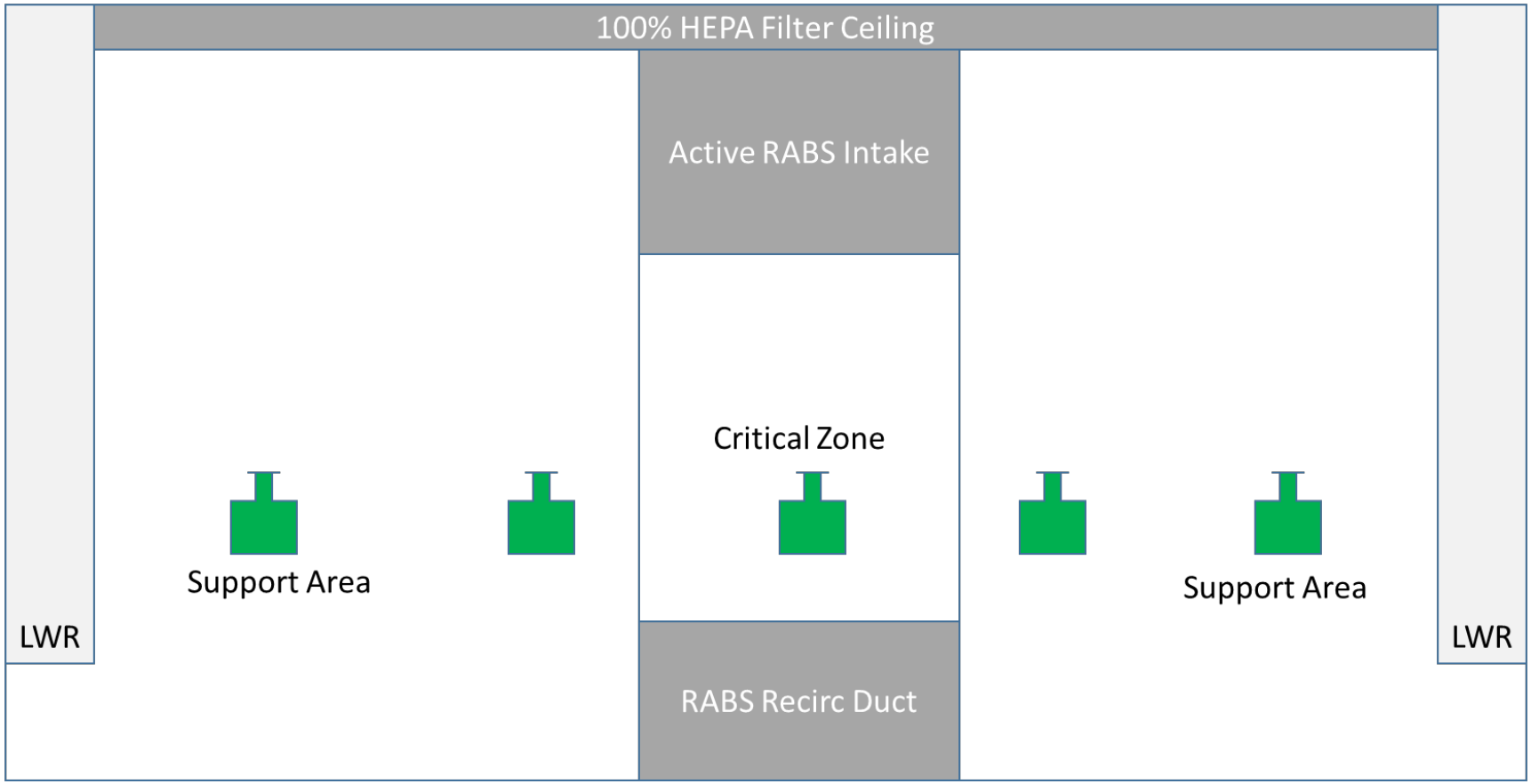


Optimizations Implemented

- Increase RABS recirculation airflow
- Reduce RABS intake airflow
- Reduce RABS outlet airflow
- Install baffles to direct RABS outlet airflow

RESULT: Turbulent zone minimized – ISO 5 support area established – RABS interventions permitted with processes, justification, validation, etc…

Non-Viable Particulate Results - Acceptable



The End

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