Particulates in Sterile Drug Products: Testing, Contributions and Mitigation from Packaging Components

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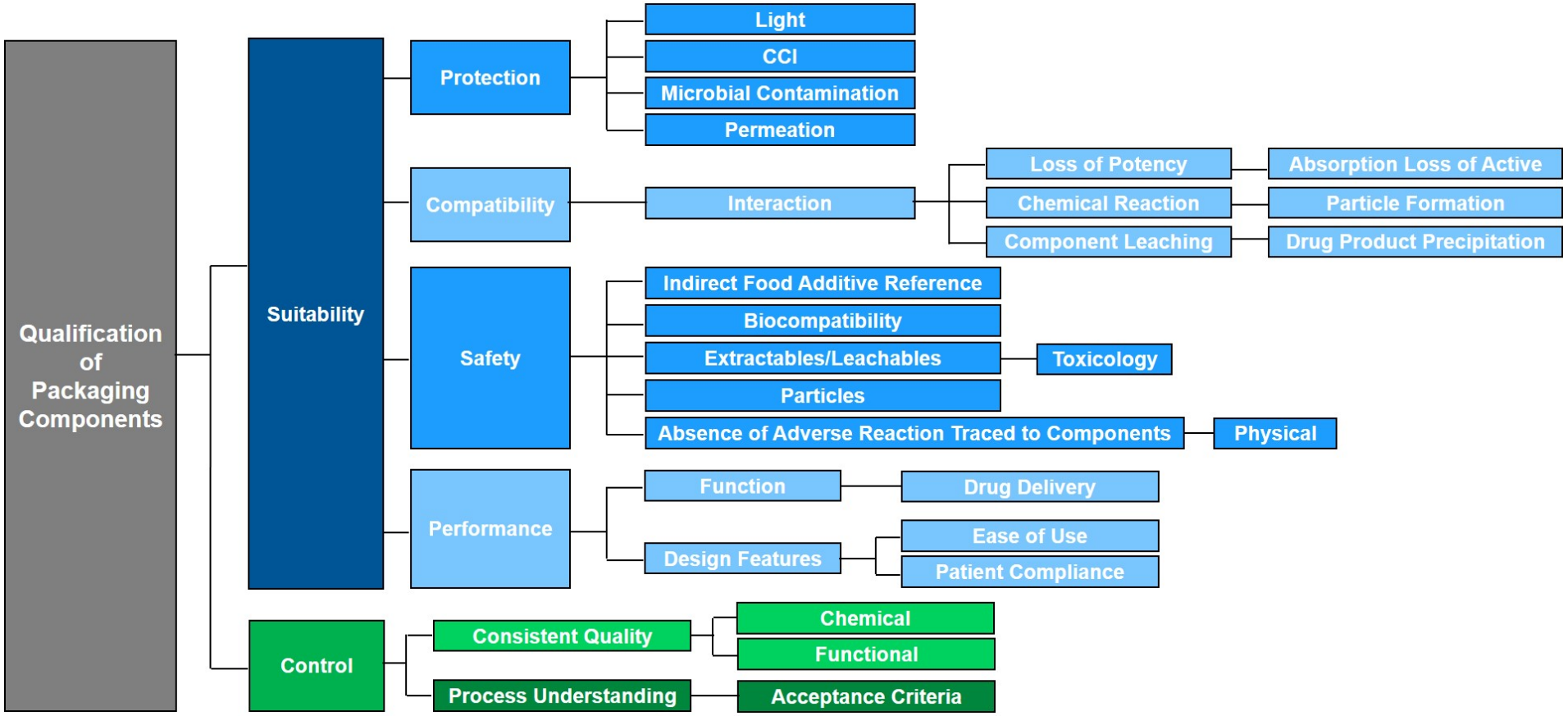
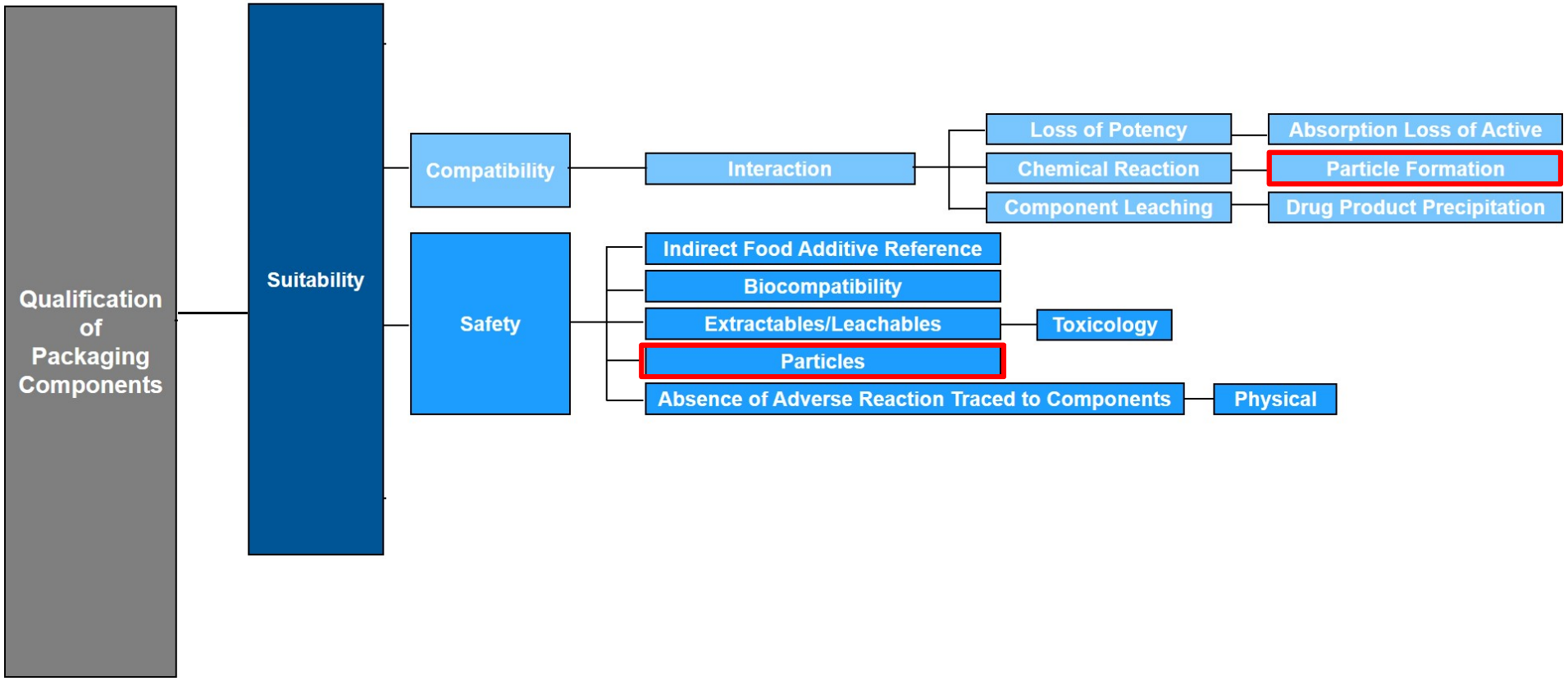
Agenda

- Fit for purpose considerations
  - Understanding a holistic view of particle generation and packaging
    - Incompatibilities
    - Elastomer and it's production process
    - Impact of secondary packaging
    - Sample preparation and testing
- How do you mitigate risk?
- Industry initiatives
  - USP
  - PDA

Packaging Component "Fit for Purpose" Overview



Packaging Component "Fit for Purpose" Overview



Fit for Purpose: Incompatibilities

Freeze Thaw Cycle Mechanical Stress

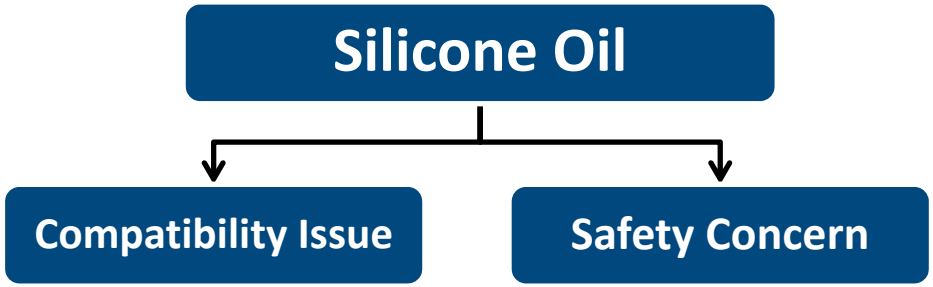
Risk @ -70C for Particles/Lamella, Leachables

Antibody	Lamella	ppb Si	ppb B	ppb Al*
Control	0	11,954	1,085	53
A (-30°C)	0	11,589	1,140	43
B (-30°C)	0	11,949	1,334	52
C (-70°C)	13	11,686	1,123	35
D (-70°C)	30	12,124	1,302	31
E (-70°C)	17	11,082	939	29
F (-70°C)	5	11,531	1,068	31

*Placebo samples and control showed 2-5 ppb leachable Al

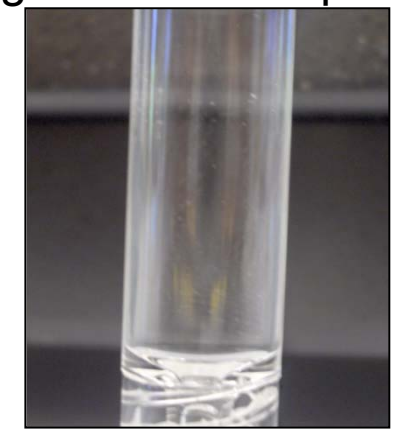
Adapted from G. Jiang, et.al., Novel Mechanisms of Glass Delamination in Type1A Borosilicate Vials Containing Frozen Protein Formulations, PDA J Pharm Sci and Tech 2013

Risk to Protein Aggregation



Particulate formation
of fusion protein 25 mg/mL;
agitation conditions during simulated shipment

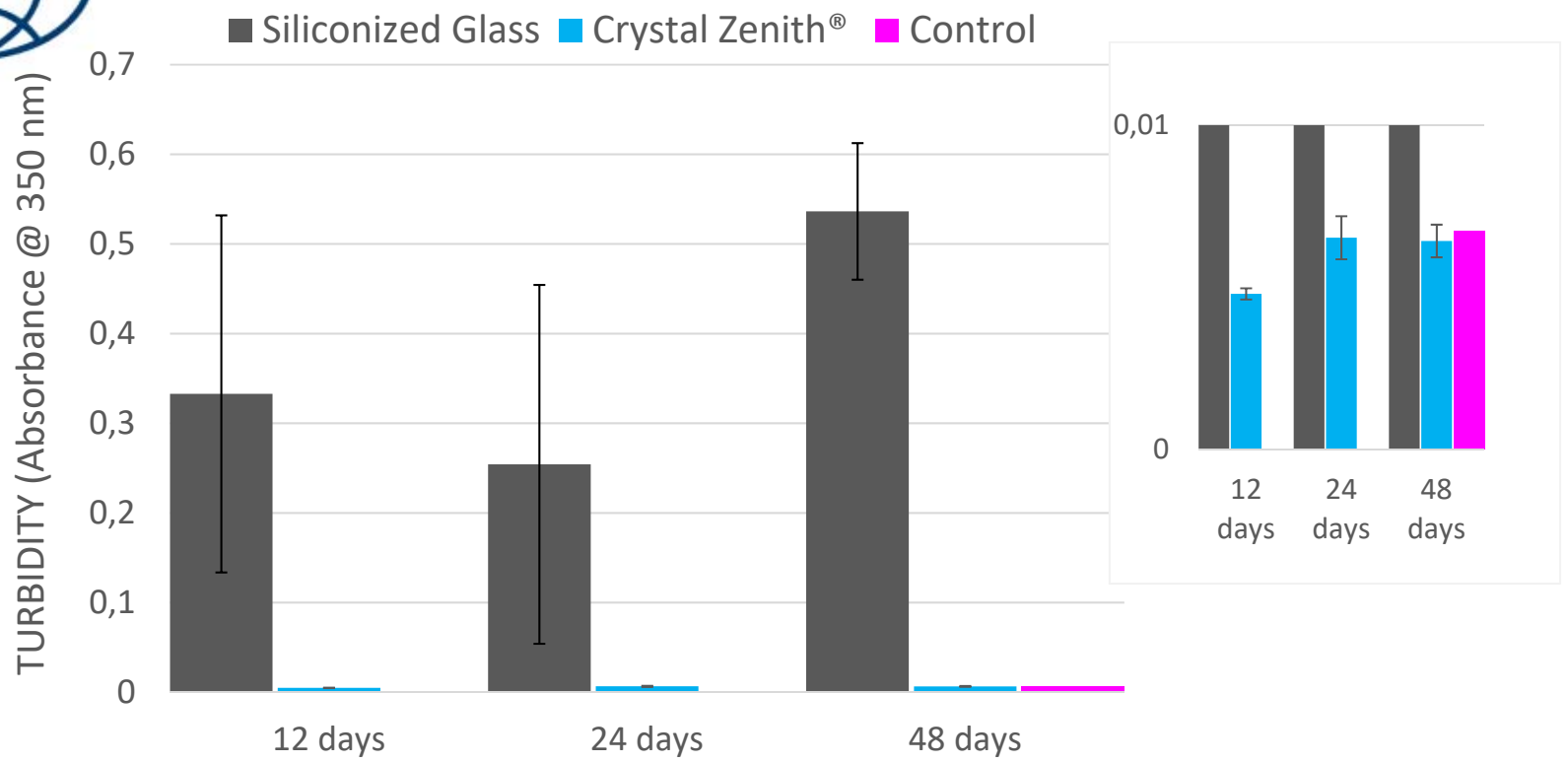
Siliconized



No Silicone Oil

Reference: Characterization of Protein Aggregation & Adsorption on Prefillable Syringe Surfaces; Esfandiary, et al. University of Kansas; and Vinod Vilivalam, West Pharmaceutical Services, Inc.; 2008.

Orencia® Aggregation with Agitation

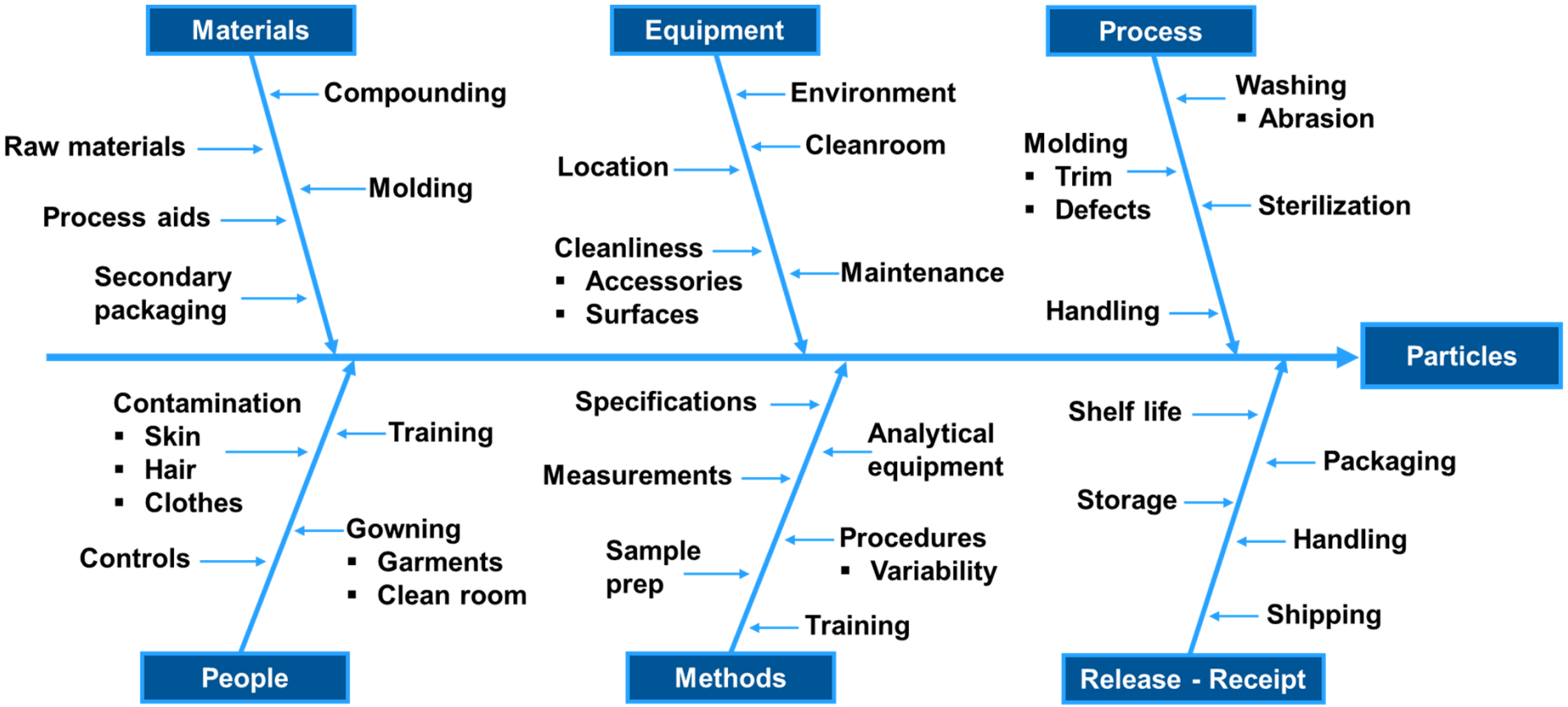


Turbidity (UV absorbance at 350 nm) of a WFI-reconstituted solution of 2.5 mg/mL Orencia® (abatacept) stored in either siliconized glass syringes (grey bars) or Daikyo Crystal Zenith® syringes (blue bars) after continuous end-over-end rotation (extreme agitation), at room temperature for up to 48 days. The pink bar at 48 days shows a control solution, unagitated, stored at 4°C in an unsiliconized glass screw-top container.

Reference: Waxman L., Vilivalam V., West Pharmaceutical Services, Evaluation of End-Over-End Rotation/Agitation of Protein Solutions in Prefilled Syringes Made from Glass or Plastic as a Preliminary Indicator of Protein Aggregation, Poster Presented at Protein Stability Conference, Colorado, 2011

Fit for Purpose: Elastomer and It's Production Process

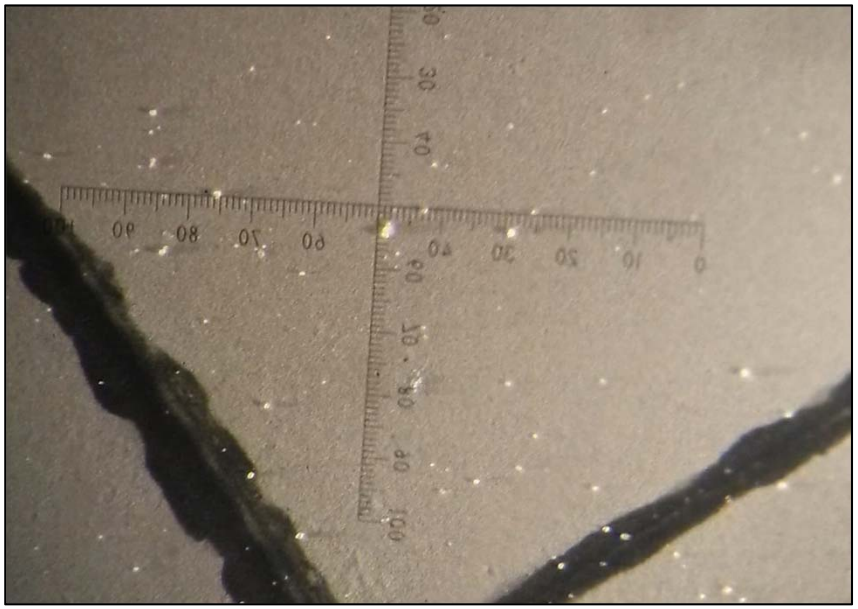
Component Contributing Factors for Particle Generation



Elastomeric Formulation Composition Can Impact Particles

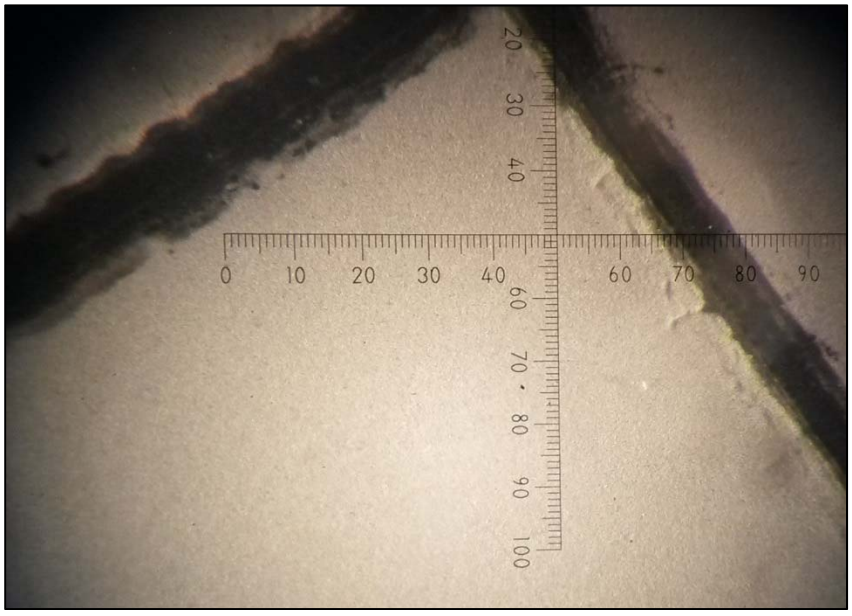
Elastomer A

- High inherent particle load
- Tends to abrade during sample preparation
- High number of sub-visible particles
- High number of borderline particles

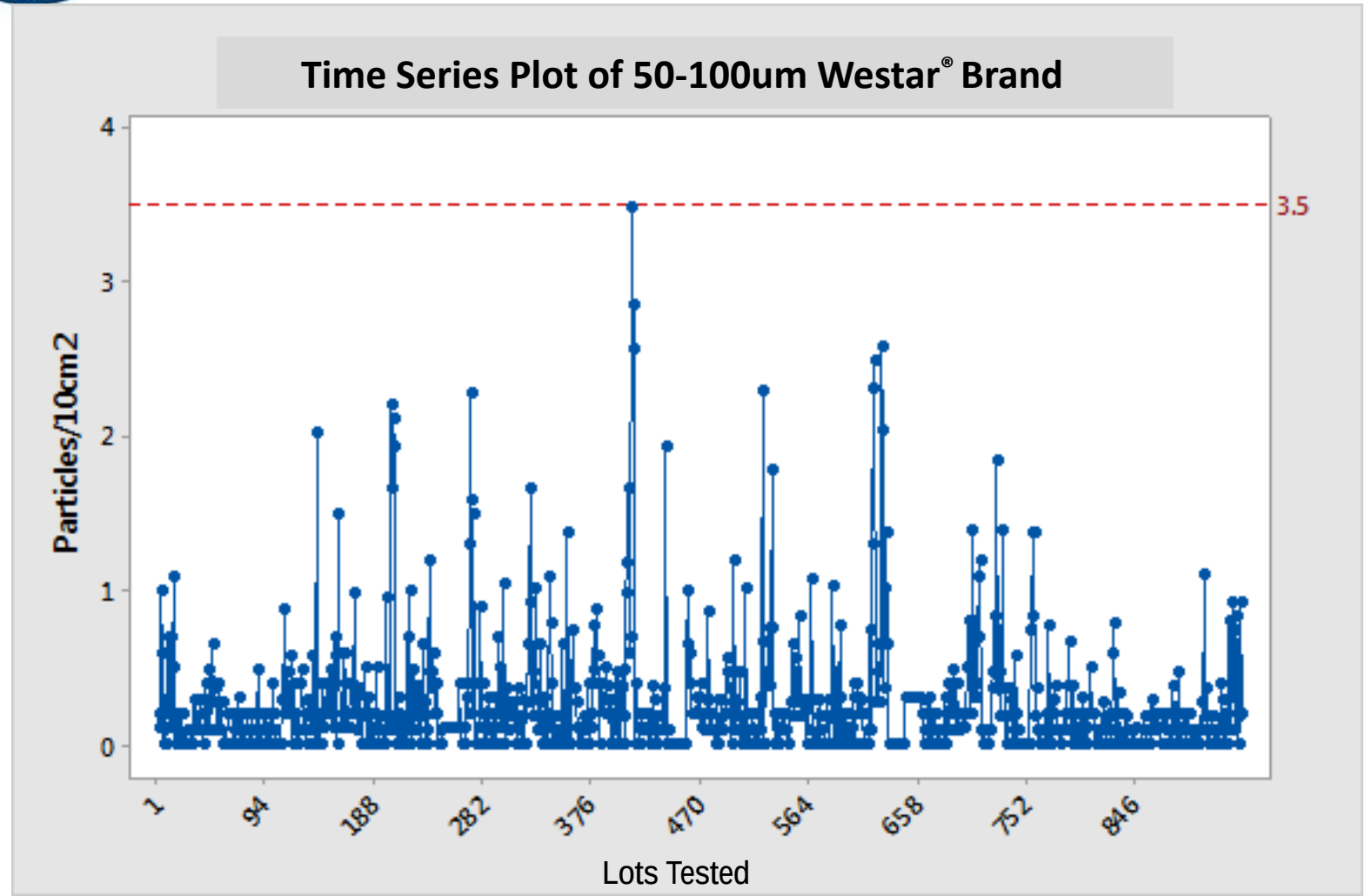


Elastomer B

- Low inherent particle load
- Low abrasion during sample preparation
- Low number of sub-visible particles
- Low number of borderline particles



Component Manufacturing and Post-processing has Direct Impact on Particle Generation



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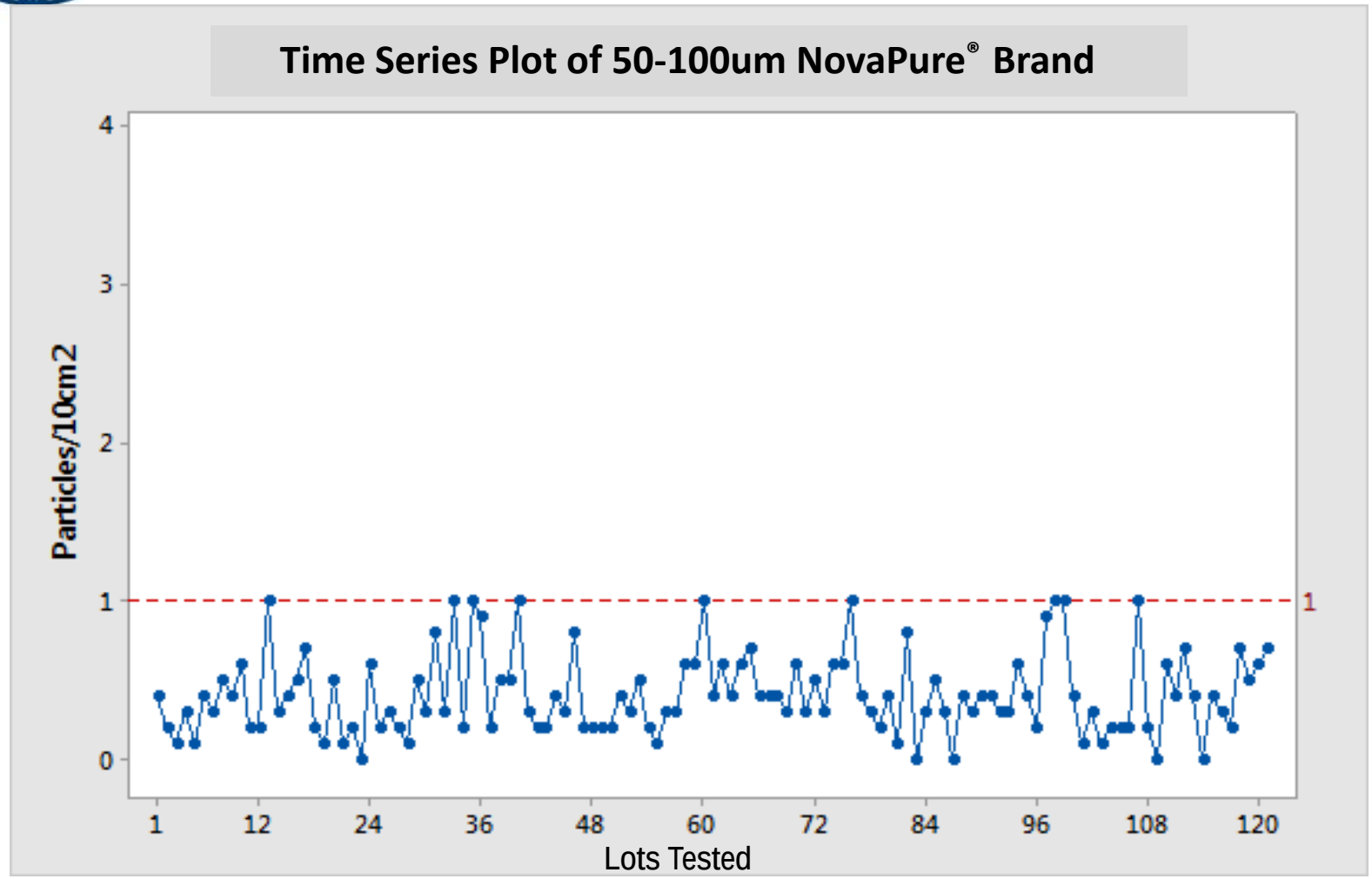


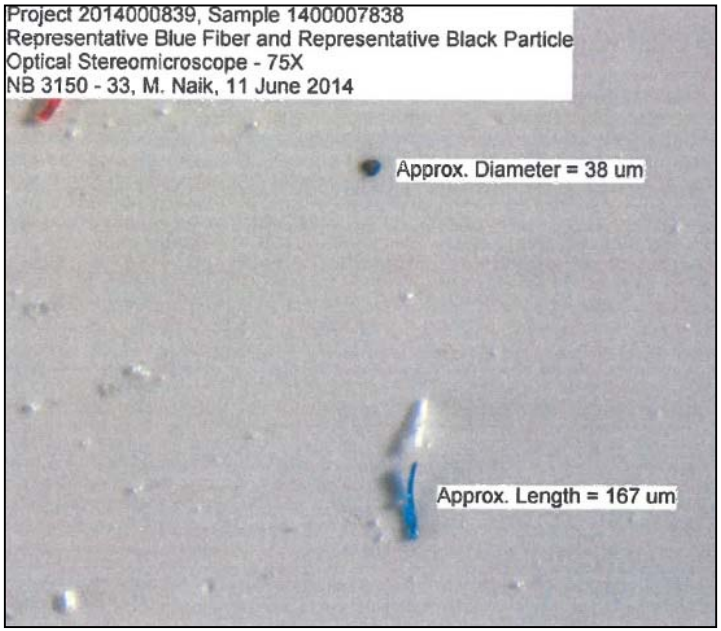
Fit for Purpose: Impact of Secondary Packaging

Background on Secondary Packaging

- Intense focus on particle improvement has resulted in reduction in particle levels on components
- All components need to be shipped in packaging
  - Steribag
  - Port bags for RABS and Barrier Isolators
- Due to complexity of port bag production process particle loads were extremely high
  - Supplier quality initiated programs focused on improvement activities

Impact of Closure Packaging

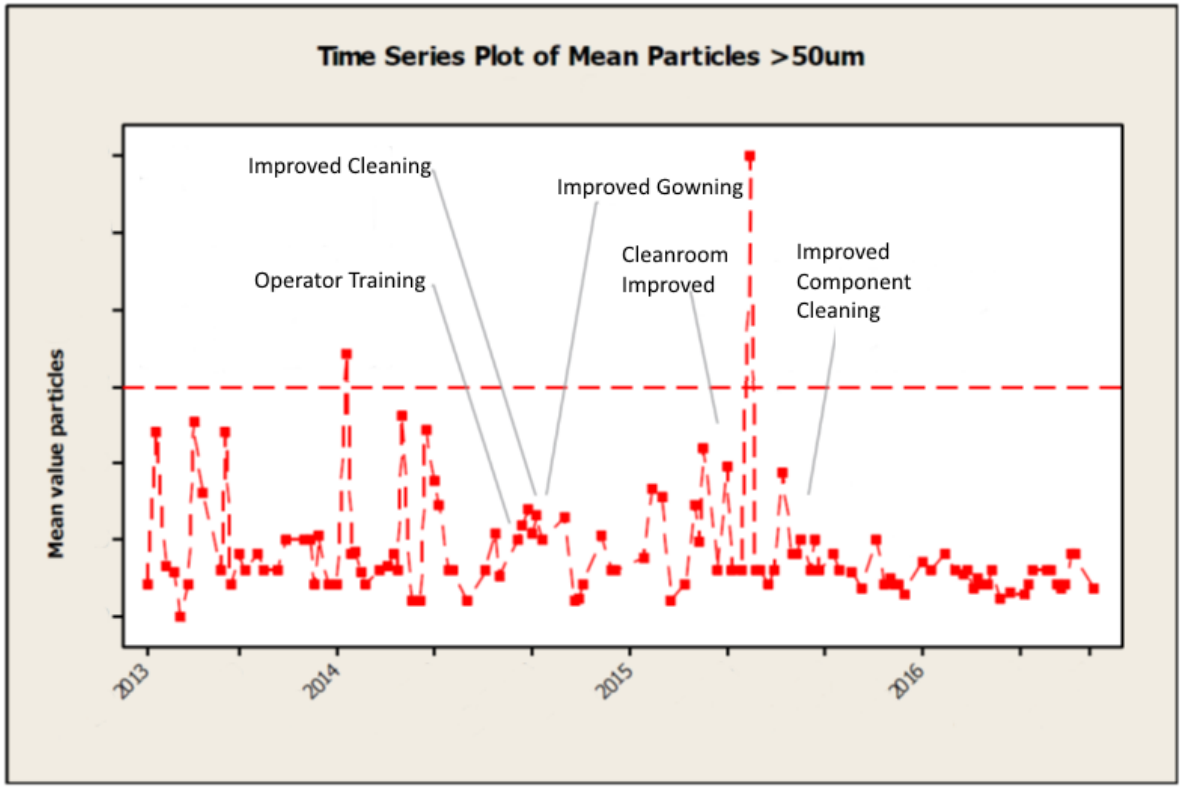
Particles found in original ported bags prior to process improvement



Photos courtesy of West Analytical Laboratories

Particle Trends in Bags Following Focused Continuous Improvement Efforts

Focus on secondary packaging has led to continued tightening of particle levels and specifications



Fit for Purpose: Sample Preparation and Testing

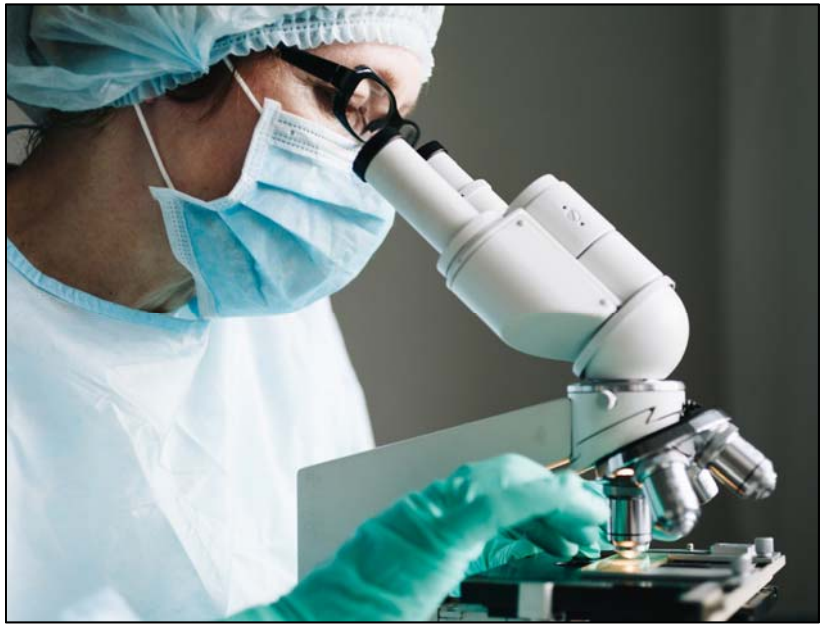
The Expression of Uncertainty in Testing

- Realistic comparison is necessary
- True differences cannot be identified without this understanding
- A consideration of uncertainty indicates aspects to test to improve procedures
- Sources of uncertainty in testing include:
  - Incomplete test definition
  - Imperfect realization of test procedure
  - Sampling may not be fully representative
  - Inadequate knowledge of the effects of test conditions/environment
  - Instrument resolution and calibration
  - Assumptions built into the method
  - Normal variation/fluctuations

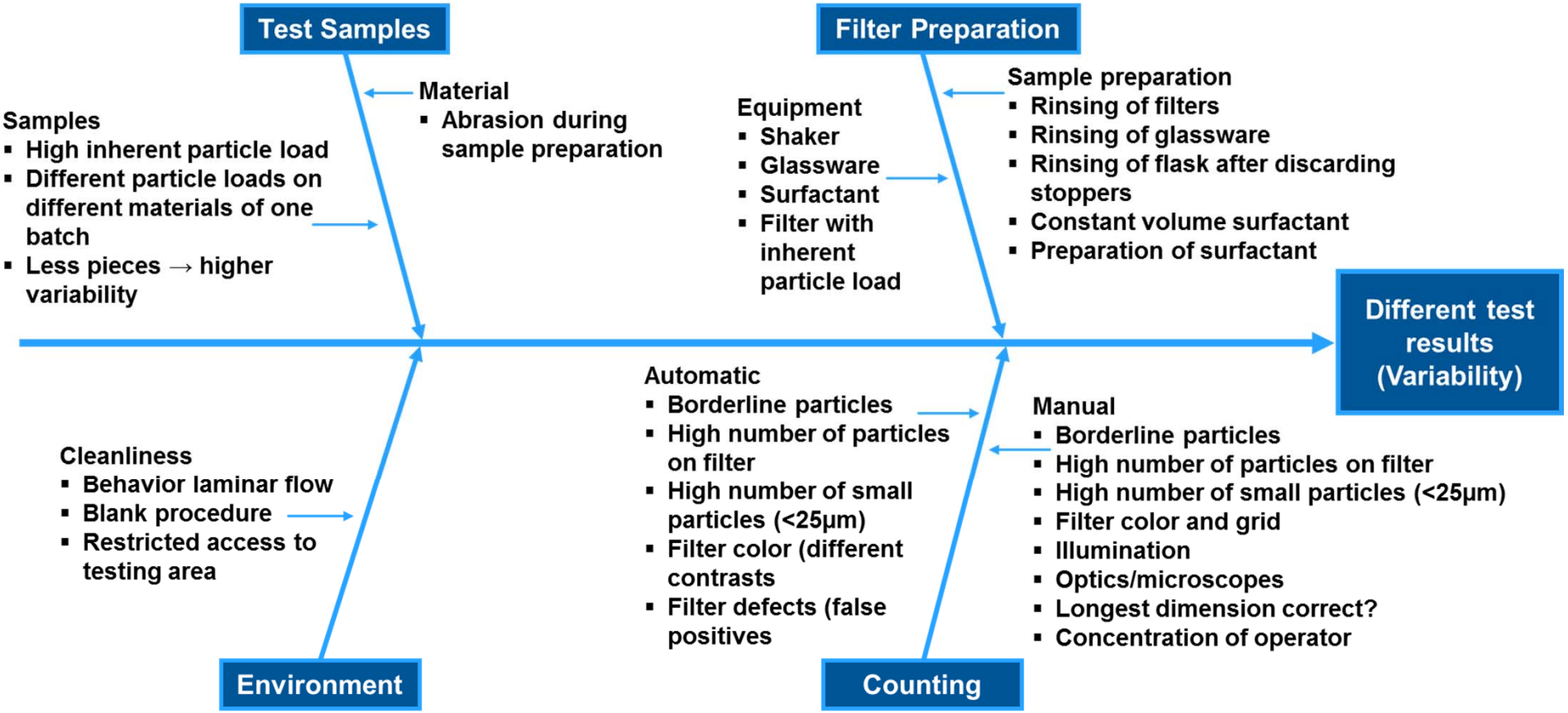
Source: The Expression of Uncertainty in Testing, UKAS Publication Ref: LAB 12

Fit for Purpose – Choosing the Right Test Method

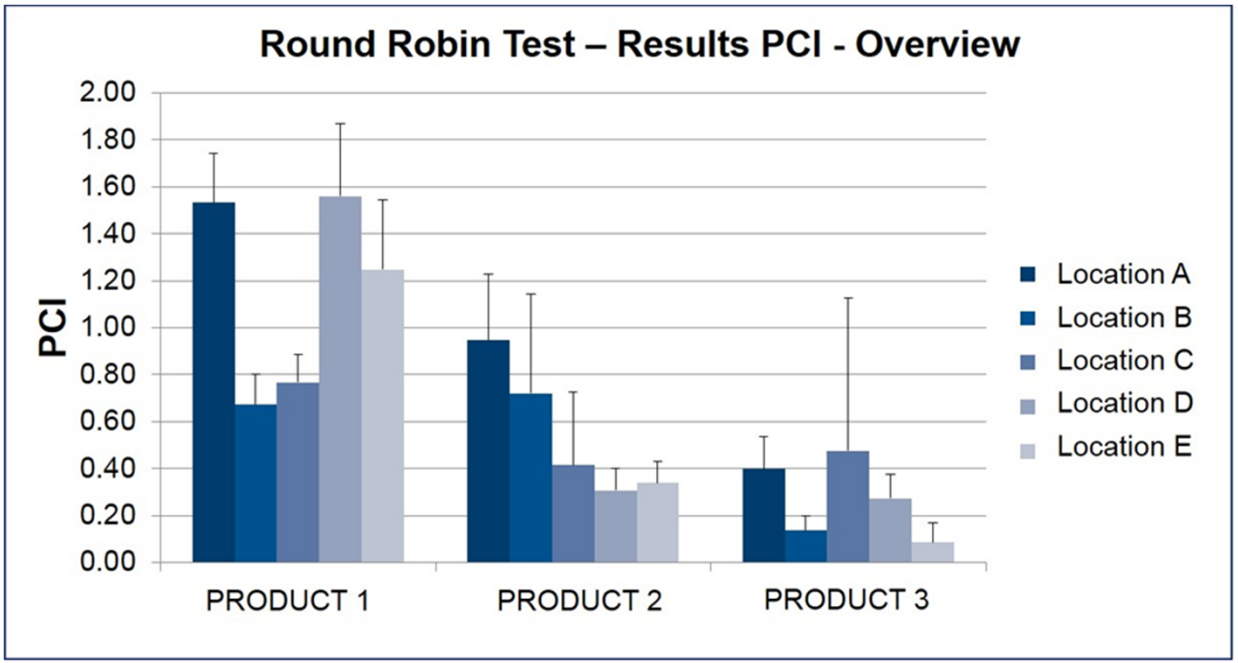
- Is the method appropriate and accurate to answer the **scientific question**?
  - What is the purpose of the method?
  - What are its limitations?
  - Is the method being used for the samples it was validated to analyze?



Particle Test Method Variability



Round Robin Testing Confirms the Level of Variation Across the Testing Sites



Use the following equation to calculate the Proved Clean Index (PCI):

$$PCI = \frac{[(A \cdot 0.1) + (B \cdot 0.2) + C] \cdot 100}{D \cdot E \cdot 10}$$

Note: The 100/10 factor converts data to index per 10cm² of surface area.

A = Total number of counted particles of size class 1

B = Total number of counted particles of size class 2

C = Total number of counted particles (including fibers) of size class 3

D = Number of closures used for testing

E = Surface area of one closure in cm²

PCI = Proved Clean Index (round to number of decimal places according to specification)

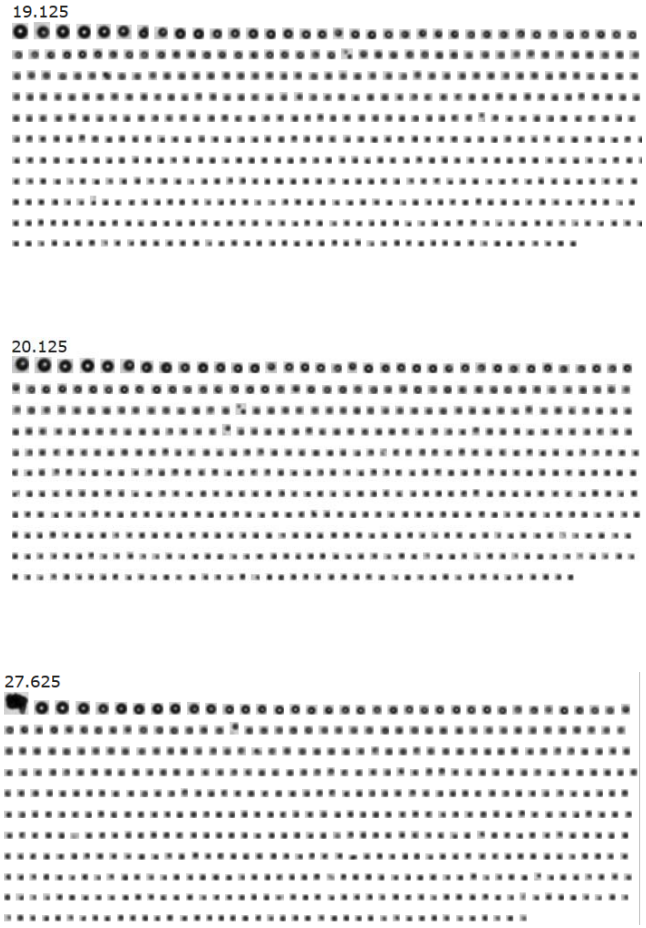
Round robin testing utilized various formulas and configurations

Importance of Sample Preparation Location

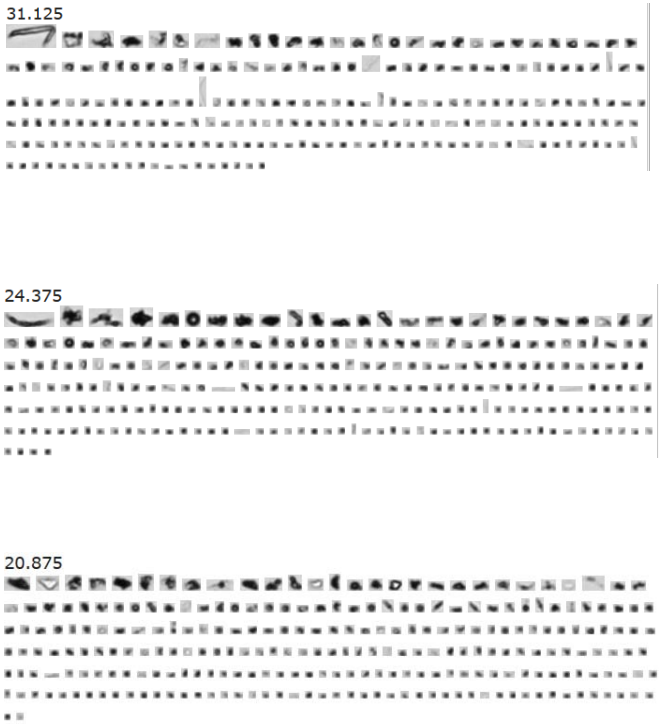
- Proof of concept study
  - Elastomeric closures were from the same batch/sampling
  - Closure samples were prepared at two different lab locations
  - Solutions were tested by the same laboratory
    by the same person
    using the same equipment

Micro Flow Imaging Results – Preparation at Two Different Locations

Prep-Company A



Prep-Company B



Key Conclusions from MFI Dual Prep Location Study

- Prep location A:
  - Vast majority of particles confirmed as silicone oil droplets
- Prep location B:
  - Larger particles identified as environmental contamination (fibers)
- Conclusion: location of sample preparation matters
  - Clean room facilities and procedures vs. non-clean room conditions

Particle Testing Harmonization: Evaluation of Inherent Particle Load of Filters and Rinsing Effectiveness

- Evaluation of filter cleaning capability
  - Inherent particle burden (high inter/intra lot-to-lot variability) from supplier observed
  - Effectiveness evaluation of different rinsing practices
  - Conclusion: rinsing with water not sufficient + implementation of incoming control

	Inherent particle burden			1st rinse: Tween80			2nd rinse: Water		
	25-50 µm	50-100 µm	> 100 µm	25-50 µm	50-100 µm	> 100 µm	25-50 µm	50-100 µm	> 100 µm
Average	35	7	2	5	1	0	4	1	0
sd	12	3	2	3	1	0	3	1	0
Min	21	1	0	2	0	0	1	0	0
Max	59	12	7	10	3	1	10	2	1

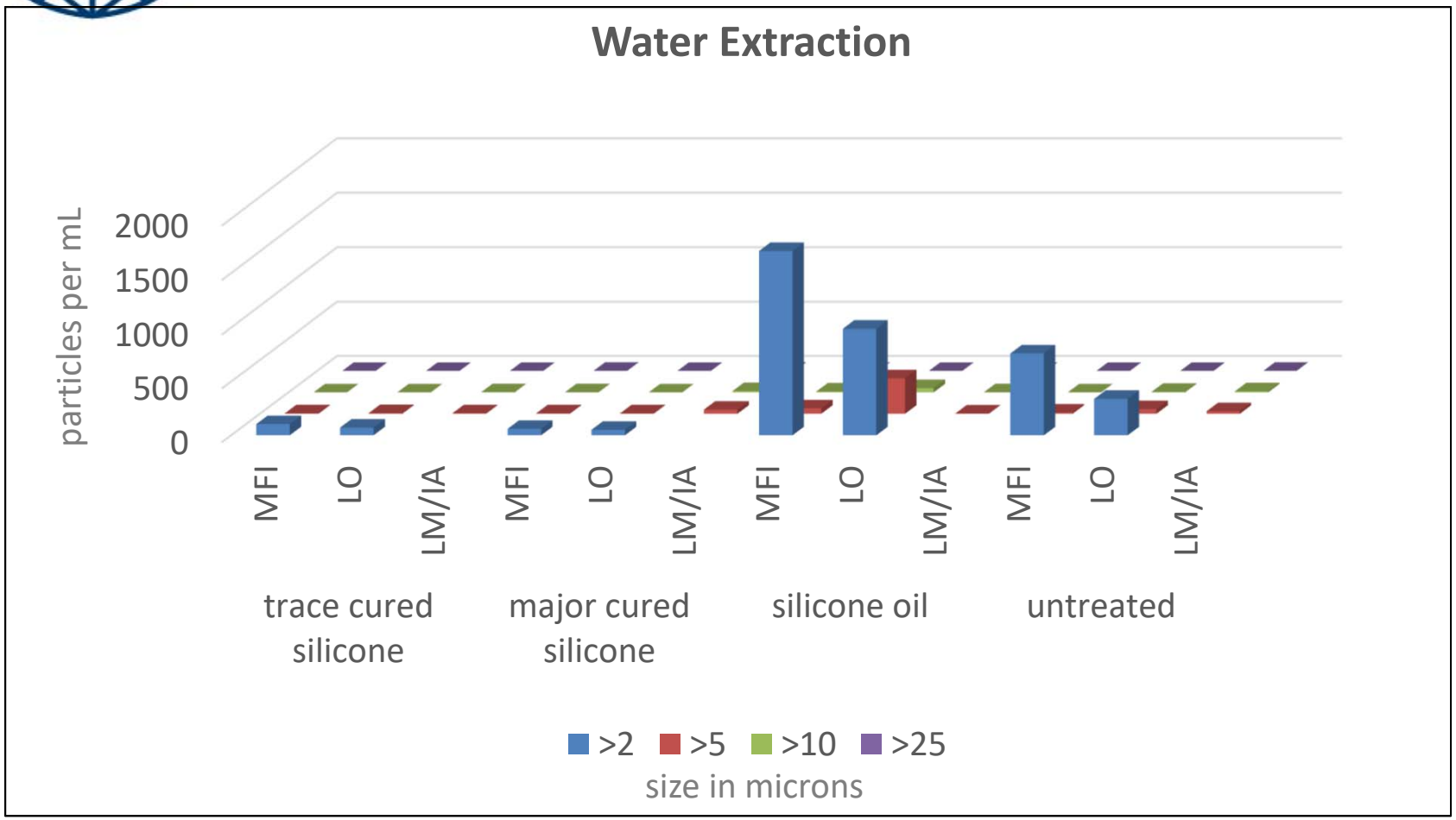
	Inherent particle burden			1st rinse: Water			2nd rinse: Tween80		
	25-50 µm	50-100 µm	> 100 µm	25-50 µm	50-100 µm	> 100 µm	25-50 µm	50-100 µm	> 100 µm
Average	52	8	3	28	4	1	2	0	0
sd	8	5	2	5	1	1	2	0	0
Min	40	3	1	17	2	0	0	0	0
Max	69	19	8	35	5	2	6	1	1

Understanding Appropriate Methodologies for Sub-visible Particles from Elastomeric Components*

- Scope of research conducted:
  - Variations of elastomer post-treatment
  - Variations in analytical methods
  - Variations in method preparation
- Initial findings:
  - Sample preparation and solvent selection are critical
  - Not every method quantifies silicone oil
  - The volume of sample extract analyzed will vary based on instrument

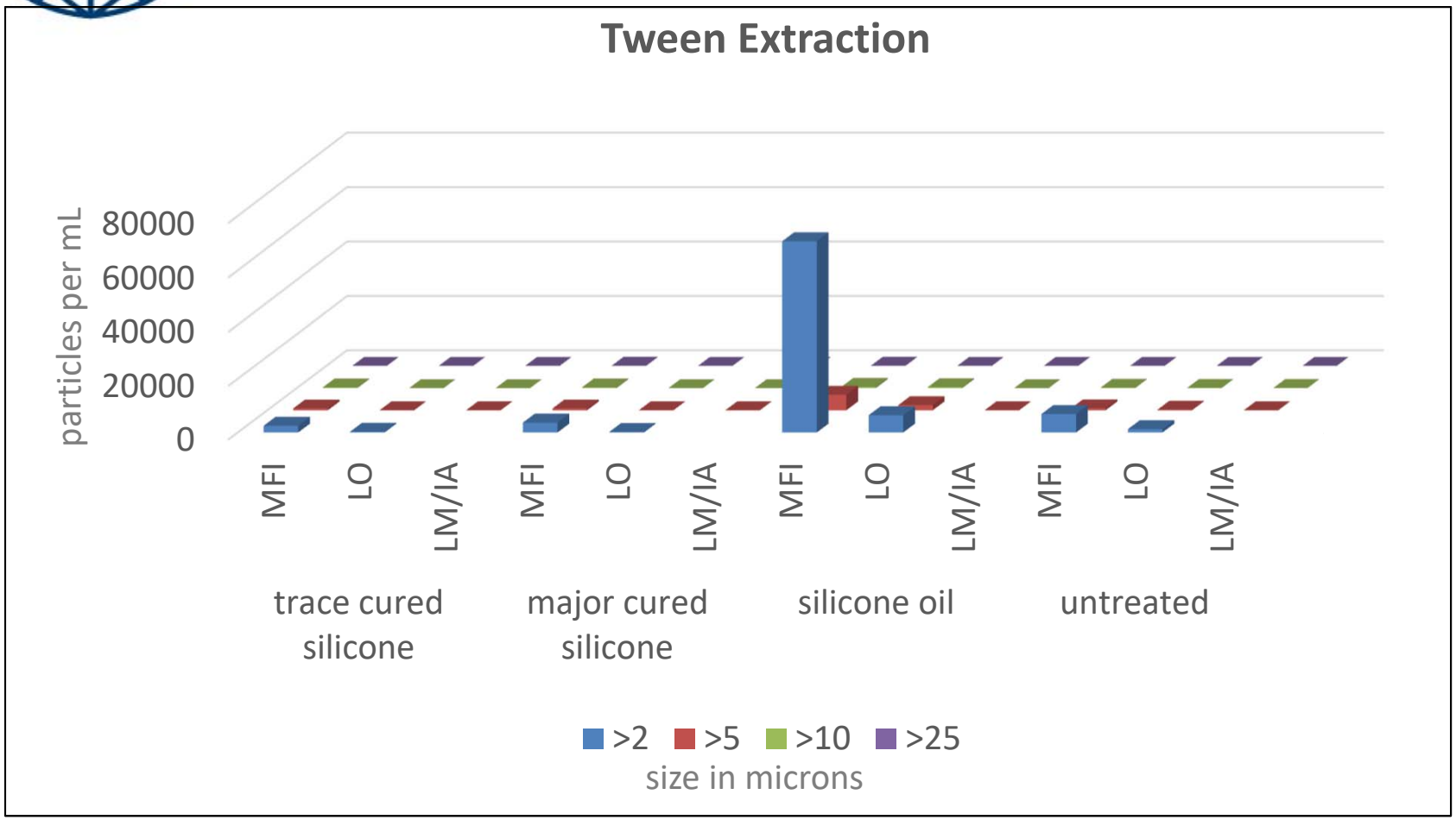
* Research study to be published

Particles Found by Various Analytical Techniques



MFI=Microflow Imaging LO=Light Obscuration LM/IA=Light Microscopy Image Analysis

Particles Found by Various Analytical Techniques



MFI=Microflow Imaging LO=Light Obscuration LM/IA=Light Microscopy Image Analysis

How Do You Mitigate Risk?

Design the Optimal CCS for Your Application While in Development

- Use the appropriate techniques to measure and understand particle sources
- Controlling a product not originally designed to achieve a goal is counterproductive
- Assure future problems are mitigated by choosing the appropriate packaging system that is “fit for purpose” to your drug’s application and today’s rigorous quality and regulatory standards

Understand Closure Alternatives to Fit Your Application

Industry Initiatives

Industry Activities

- USP Workshop
  - Control and determination of visible and sub-visible particulate matter in biologics – June 26 & 27, 2017
    - Particle characterization is critical
    - Use data and science to develop a risked based approach in dealing with particles
    - Analytical methods should be qualified for their ability to detect and quantify particles
    - Compendial particle tests are nothing more than a starting point
- New USP Chapter
  - USP Chapter <667> sub-visible and visible particles in packaging and manufacturing components and systems will be drafted. Team is being formed

PDA
Parenteral Drug Association

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Achieving "Zero" Defects for Visible Particles in Injectables

Packaging Quality Facts

- Trained inspectors can see a 100um particle 50% of the time or less. This size is equivalent to the diameter of a human hair.
- The most common particles seen in injectable drug products are white (cellulosic) fibers.
- Visual inspection has been a requirement for injectable products since 1936.
- Over the past 10 years, the amount of recalls due to packaging components have increased ~10x

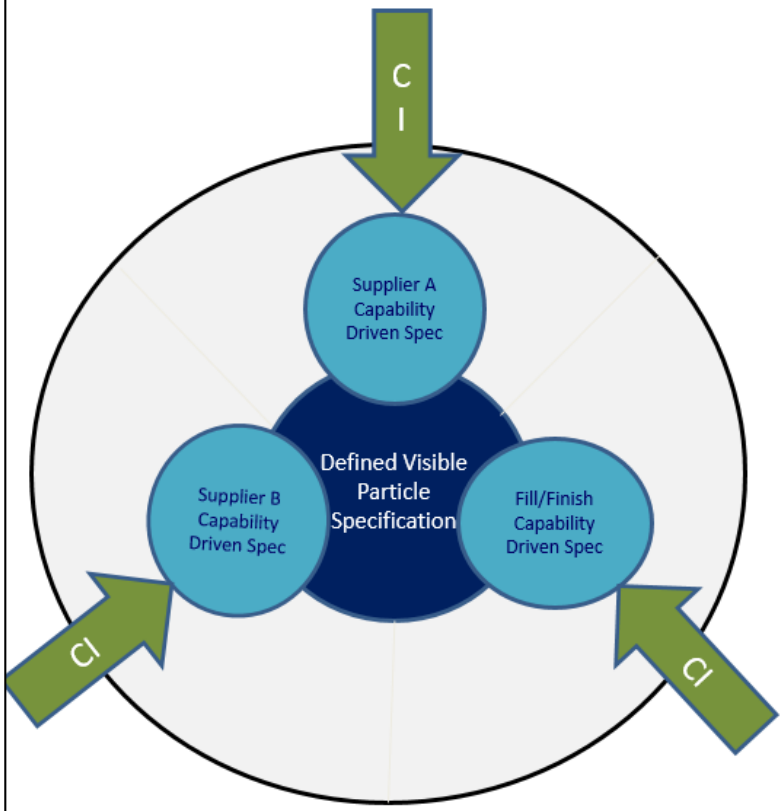
Current State

- Increased Regulatory Scrutiny and lack of Understanding
- Expectations rising faster than suppliers capabilities
- Issues addressed reactively
- Fragmented approaches & Processes
- Limited perspective on cost impact
- Lack of trust and transparency between drug manufacturers and component suppliers
- Industry wide misalignment

Future State

- Influence and Drive Regulatory Understanding
- Harmonized Specifications
- Proactive Focus
- Harmonized View Regarding Technology
- Total Cost of Ownership
- Increased trust and transparency
- Collaborative approach to specification development and problem solving
- Aligned Industry moving forward together

Drive to Target
Through Continuous Improvement Initiatives



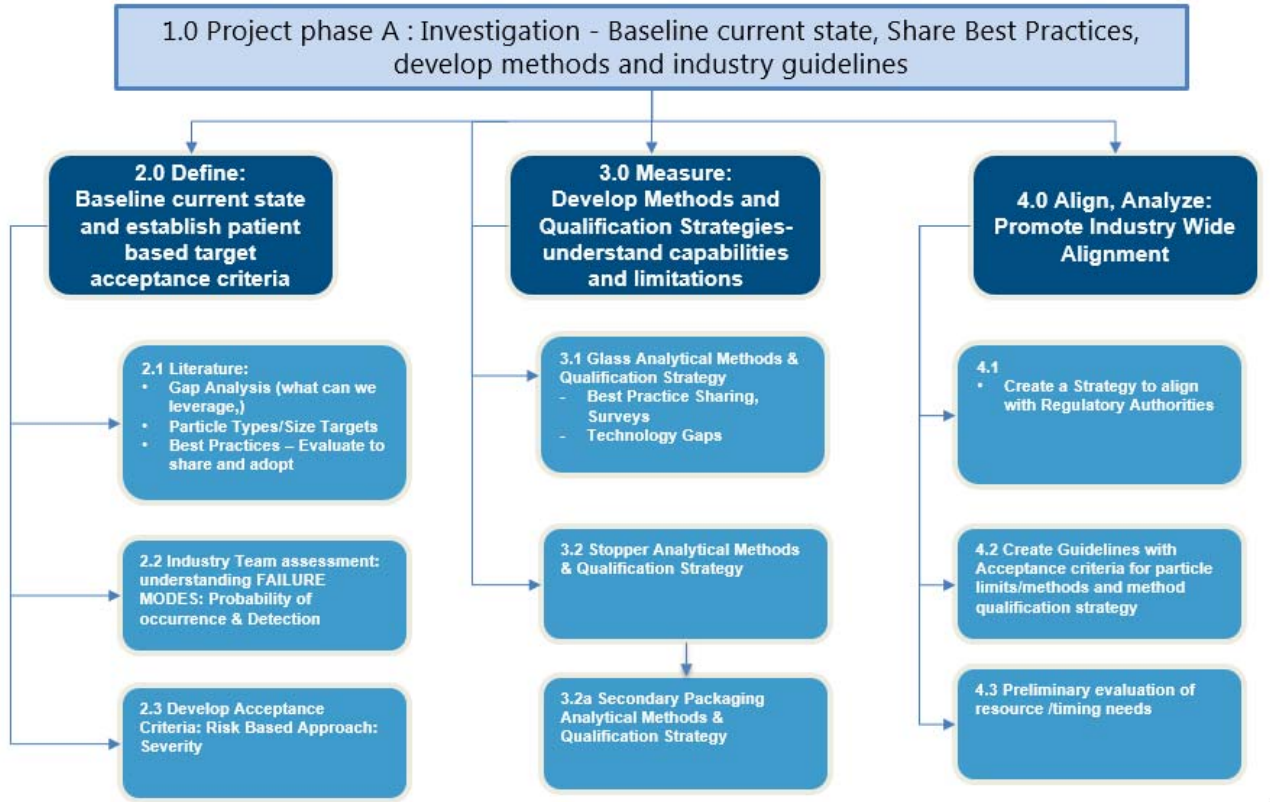
Phase A: **Align** on specifications

- Clear and total alignment on specifications and test methodologies and practices
- Timing: Target end of 2017

Phase B: Achieving "Zero" defects

- Continuous Improvement to drive alignment
- Achieving "Zero" defects for visible particulate matter in injectables that will be in compliance with a new set of proposed particulate requirements.

Project Plan Phase A : Work Breakdown Structure



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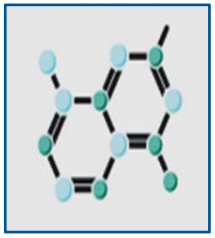
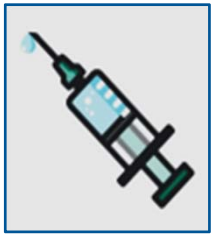
Key Takeaway Points



Understand the risks from a holistic perspective



Utilize a critical thinking approach to assure “Fit for Purpose”

Understand and use appropriate measuring techniques

Design your CCS to mitigate risks vs. “over controlling” a component