Bio-Process Systems Alliance

*Advancing Single-Use Worldwide*

# Addressing risks from particulate matter when applying single-use systems in biopharmaceutical manufacturing

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# Particulates Risk in Biopharmaceutical Manufacturing

## A quality risk management (QRM) approach

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT

Q9

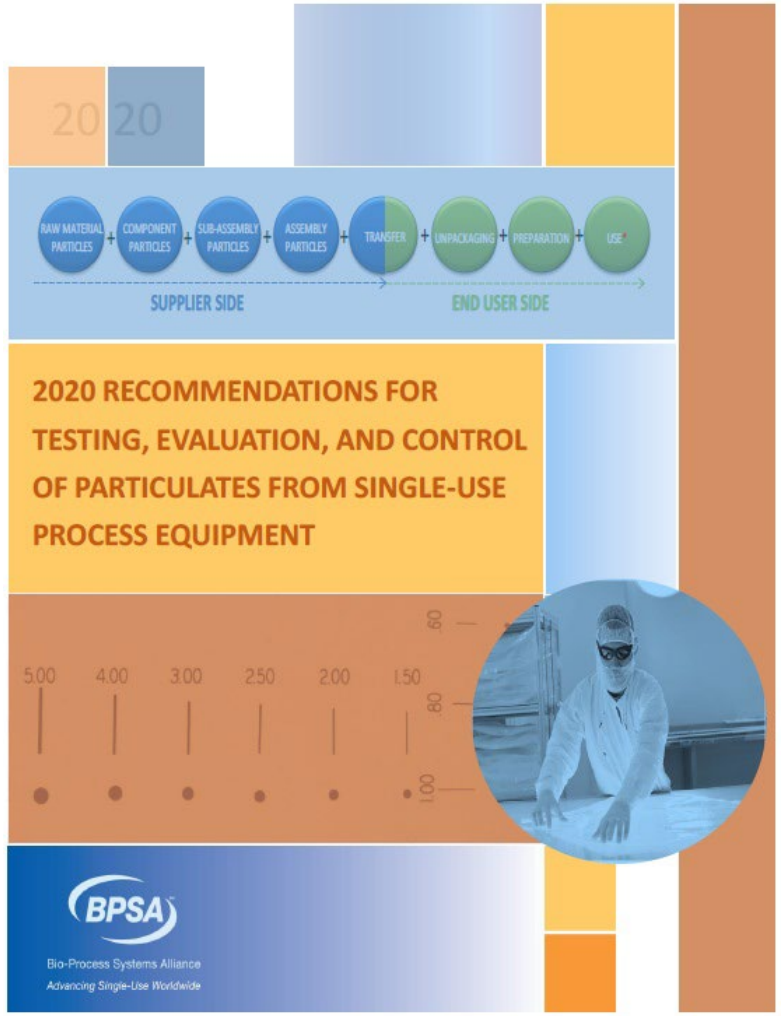

**Harm = Impact of Particulate Matter**

**Particulate Matter = Extraneous particles, foreign particles**

**Risk of Harm = (Probability of Occurrence) x (Detectability) x (Severity of Harm)**

# Particulates Risk in Biopharmaceutical Manufacturing

## Updated BPSA recommendations






***Extensively updated BPSA guidelines published May 2020***

**A quality risk management (QRM) approach to addressing risks from particulate matter in SUS**

# Particulates Risk in Biopharmaceutical Manufacturing

## Single-use systems are not drug products

≠

**Why are risk-scenarios and standards for final drug products applied to single-use systems??**

# Biopharmaceutical Manufacturing:

## Severity of Harm

## Particulate Matter

# Biopharmaceutical Manufacturing: Severity of Harm

## Real versus perceived risk

Each stakeholder has a different perception of risk

- Single-use manufacturers (and their suppliers)
- Biopharmaceutical manufacturers
- Medical device manufacturers (syringes/ampules/IV bags/infusion apparatus)
- Regulatory authorities
- Medical practitioners
- Patient

**A visible particle is visible:**

***Human "gut reaction" to visible particles may not be proportional to actual safety risk***

**End-user perceptions of risks from particulate matter in SUS vary widely**

# Biopharmaceutical Manufacturing: Severity of Harm

## Types of potential foreign particulate matter

Intrinsic

- Sources: *materials, ingredients, processing equipment, packaging*
  - Materials and sources are generally known

Extrinsic

- Sources: "outside" process
  - Human generated (clothing fibers, skin flakes, hair, ....)
  - Insect/animal/microbiological
  - Nature (dirt, dust, plant material....)

"Visible"

- Visible by eye upon inspection (approximately ≥ 100 μm)

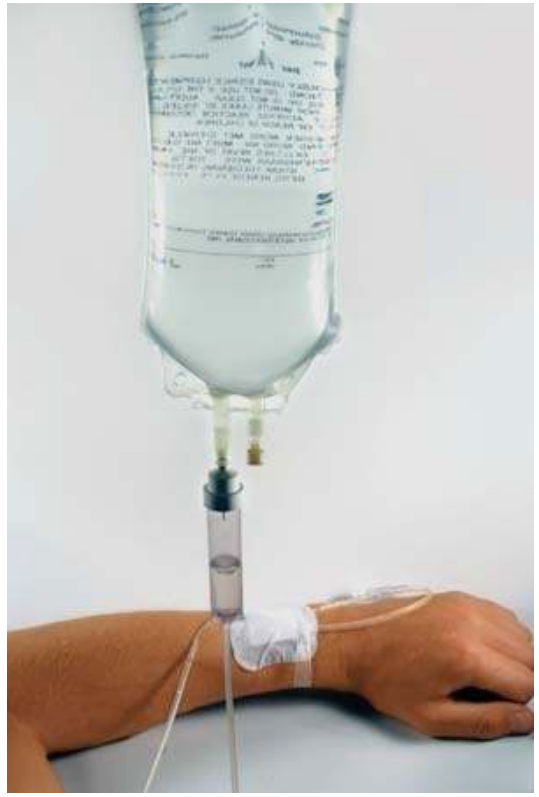
"Sub-visible"

- Generally: 10 to 100 μm

# Biopharmaceutical Manufacturing: Severity of Harm

## Potential patient safety risks due to particulate matter

**Good Manufacturing Practice (cGMP) and 100% Visual Inspection of drug product assures a low number of particles are received by the patient via injection or infusion**



*Risks depend upon dosage amount, frequency, and injection location*

Toxic limits unclear, but large amounts of particles can be lethal:

- Trauma/Embolization/Thrombosis/Inflammation
- Larger particles (> 10 mm) considered most problematic
- Injection location
- Patient condition

***Millions of injections and infusions per day:***

***Usually unproblematic, due to controls in the manufacturing of pharmaceuticals***

# Biopharmaceutical Manufacturing: Severity of Harm

## An example of a worst-case situation

Fierce Pharma: August 2021

Contamination in vials of its COVID-19 vaccine were discovered in Japan

Contaminant is believed to be a metallic particle

Use suspended of 1.63 million doses that had been distributed to 863 vaccination centers

The suspension of the doses comes as 80% of Japan's population is under coronavirus restrictions

Moderna has traced the issue to a production line in Spain

The particulate matter was discovered in roughly 40 unused vials across eight vaccination sites

**Product recalls due to particulate matter are rare….**

**But when they occur, potential impact on patient safety and drug supply**

# Biopharmaceutical Manufacturing:

## Probability of Occurrence

## Particulate Matter

# Biopharmaceuticals Manufacturing: Probability of Occurrence

## Many contributions to particle levels, in addition to SUS

**Potential contributions to particles levels in final drug product:**

**Formulation ingredients: excipients, buffers, etc…**

**Final filters: particles shed due to insufficient rinsing, etc…**

**Final filling: local environment, needles, filling open vials, etc…**

**Final containers: vials, syringes, infusion bags, etc…**

***in addition to the contribution from other single-use processing equipment***

**Biopharmaceutical manufacturers need to control multiple potential sources of particulate matter**

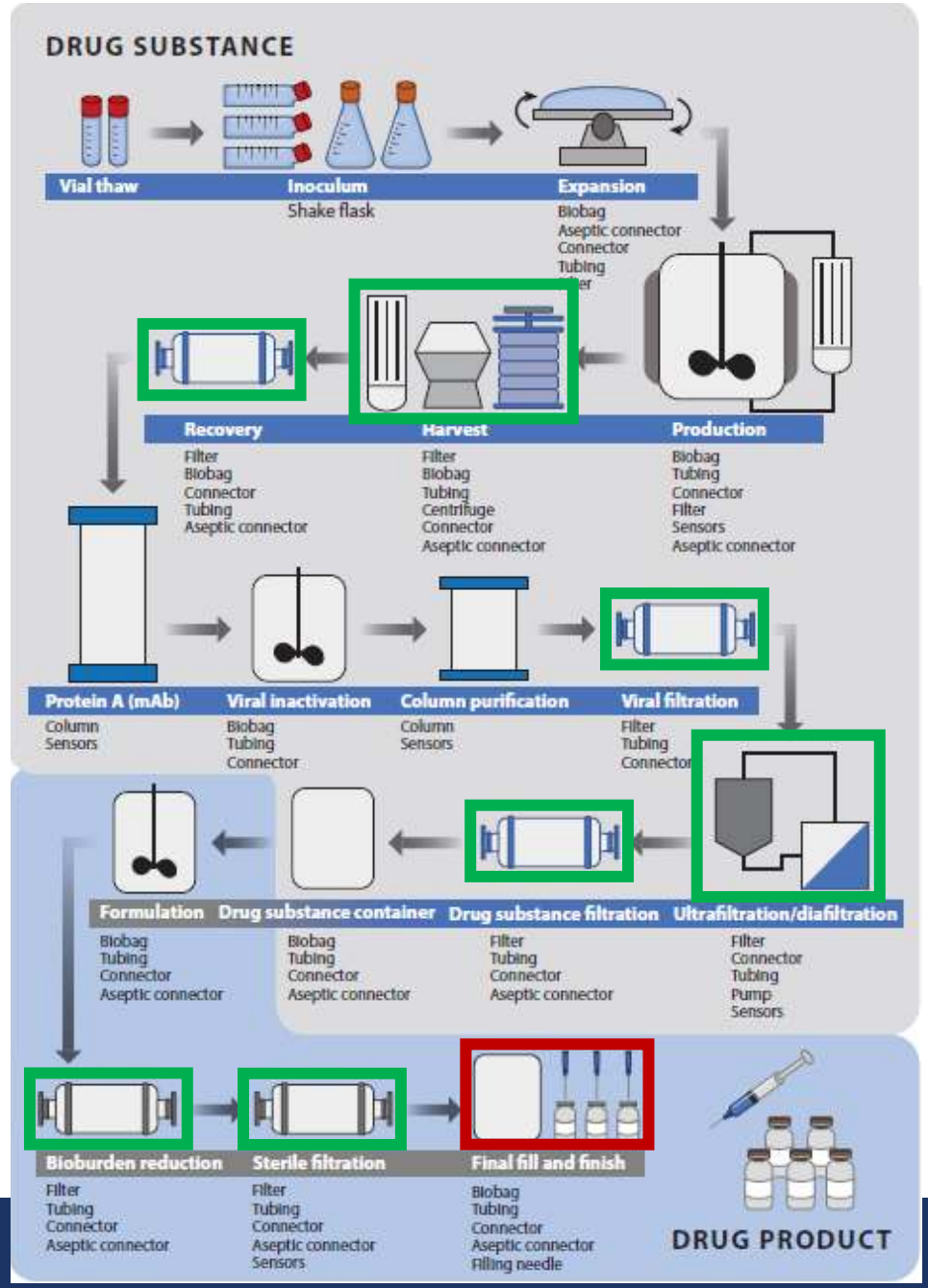
# Biopharmaceutical Manufacturing: Probability of Occurrence

## Purification/filtration reduce risk from particulate matter significantly

**Schematic of single-use process for mAb production**

**Particles on inside surfaces of SUS (STR, mixing, centrifuge, bags) contribute to particle burden**

***Green: filtration/purification steps remove particles***
***Red: potentially higher risk due to direct drug substance/product contact***




J.J. Samaras et al.
Ann Rev Chem Biomol Eng
13, 73, 2022

# Biopharmaceuticals Manufacturing: Probability of Occurrence

## Binary risk scenario

**Upstream** → **Downstream** → **Final Sterile Filtration** → **After Final Filtration**

Severity of Harm:
*Reduced process yield or purity*
*(cell-particle interactions, particle leachables, protein denaturation)*

Severity of Harm:
*Particle in drug product causes patient injury*

**Sterilizing grade filters remove particles > 0.2 µm**
**Risk scenario is <u>binary</u>:**
**Low upstream of final filters**
**Much higher downstream of final filters**

# Cell Therapies Manufacturing: Probability of Occurrence

## Active ingredient is in particle form

**Cell therapy products are a suspension of living cells**
- **Cell size typically between 10 and 30 µm**

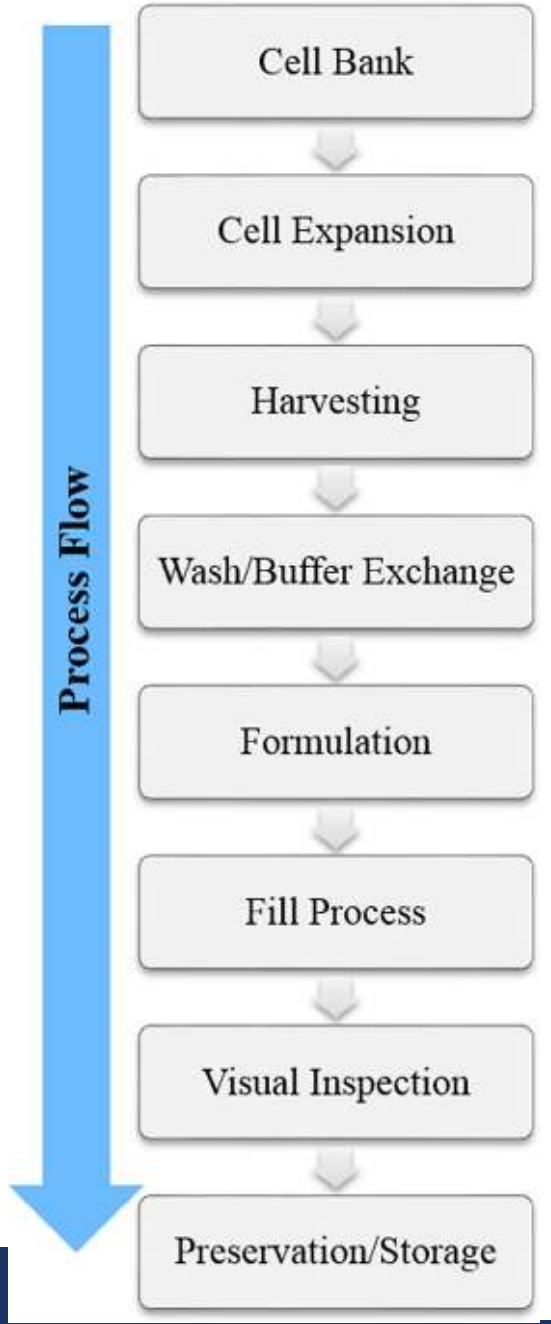
**Complex, multistep manufacturing process**
- **Contact with many materials and reagents/media**

**Aseptic processing required**
- **No final clearance/filtration step**
- **0.2 µm sterile filters will remove active ingredient (cells)**

**Cell therapy products may be highly opalescent and viscous**
- **due to high concentration of cells**

**Final drug product:**
- **single-dose, low volume**
- **sterile suspension in vial or IV bag**

**Complex process…Many potential sources for particulate matter…No filtration**




ISCT Guidance Paper 2016

# Biopharmaceutical Manufacturing:

## Detectability

## Particulate Matter

# Biopharmaceutical Manufacturing: Detectability

## Pharmacopoeia requirements for final drug product

100% Visual Inspection of Final Drug Product (USP <1>, <790>)

www.cxvglobal.com

www.syntegon.com

**Risk to patient safety usually low since visual inspection is highly regulated**

**Sophisticated automated visual inspection systems find particles**

# Biopharmaceutical Manufacturing: Detectability

## Particulate matter is a visible quality indicator

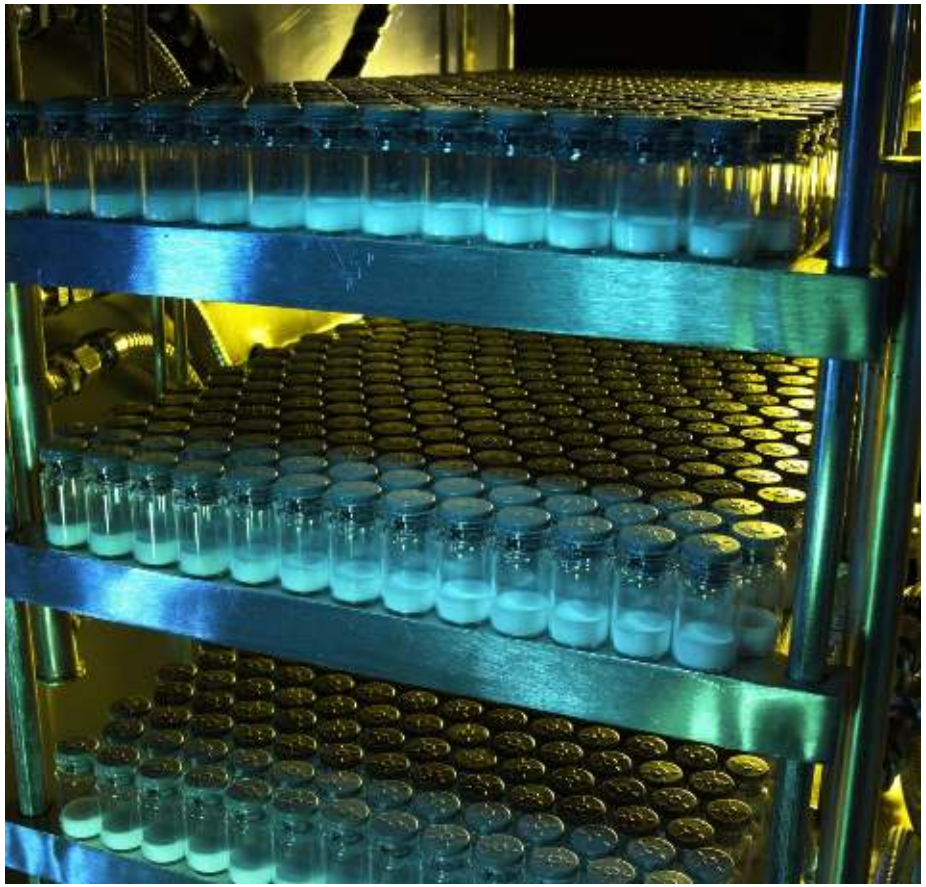


Image: West Pharmaceuticals

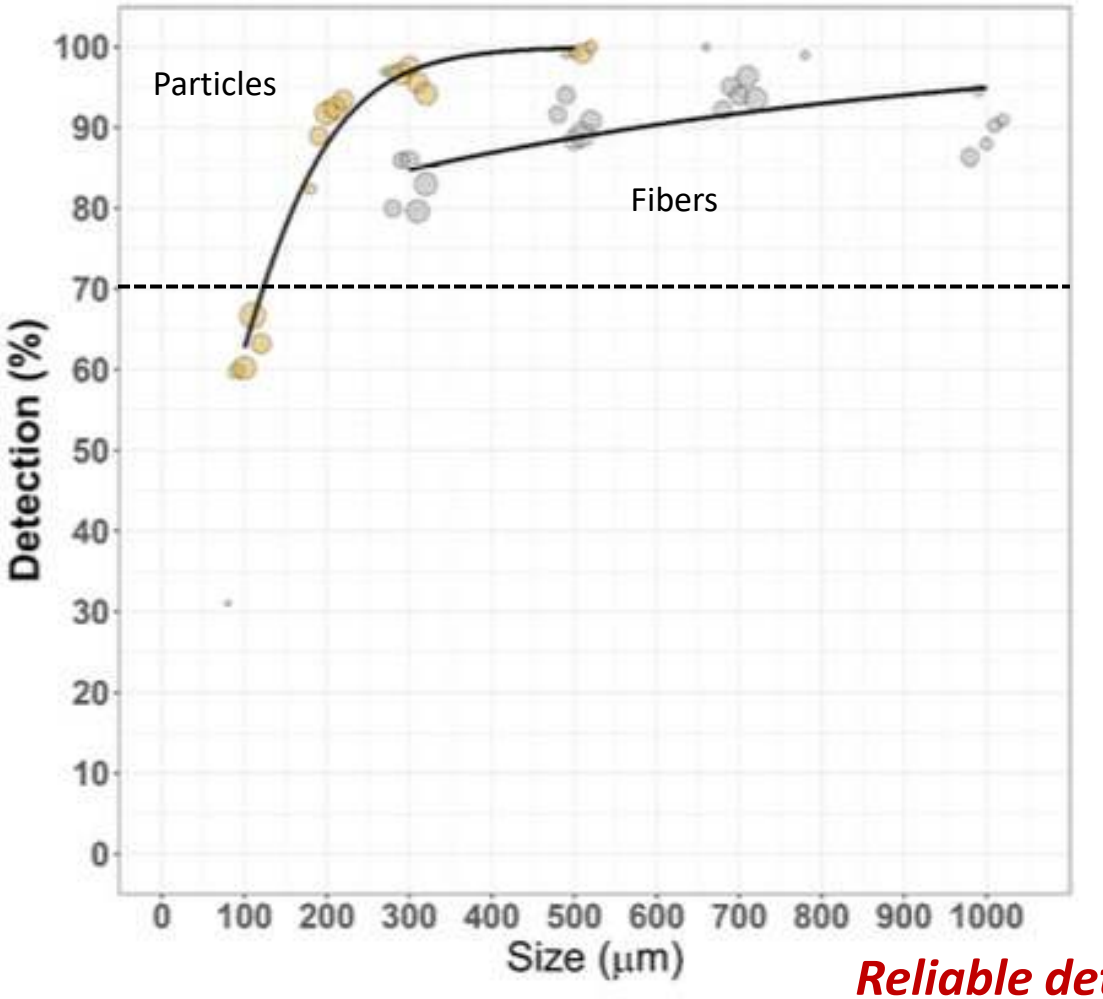
***Detection of particulate matter requires investigation and risk analysis: costly!***

***Entire lot may need to be discarded: costly!***

**Risk to end-user is cost associated with drug product rejects**

# Biopharmaceutical Manufacturing: Detectability

## Particulate matter in 10 mL glass vials




***Manual visual inspection results for particles and fibers in empty glass containers (59000+ measurements!)***

PDA TR 85 (2021)
Enhanced test methods for visual particle detection and enumeration on elastomeric components and glass containers

***Reliable detection in glass vials: Particle ≥ 125 µm, Fiber ≥ 300 µm***

# Biopharmaceutical Manufacturing: Detectability

## USP <790> and <1790> are standards for injections

USP <790> Visible Particles in Injections

- Inspection without magnification
- Inspect against a black and a white background
- Inspection time 5 seconds for each background
- Minimum intensity of illumination between 2000 and 3750 lux
- Following 100% visual inspection, a statistically valid sampling re-inspection with AQL = 0.65%

USP <1790> Visual Inspection of Injections

Guidance on development of visual inspection processes for all types of parenteral drug product defects:
particles, container integrity, cracks, misplaced stoppers, incomplete seals, fill level, discoloration, clarity….

**Standards written for the visual inspection of injectable drug products**

**Some end-users are asking if SUS visual inspection conforms to USP <790>**

**USP <790> is not a standard written for single-use systems**

**Some of the guidance in USP <1790> is useful for developing visual inspection methods for SUS**

# Single-Use System Manufacturing:

## Detectability: Visual Inspection

## Particulate Matter

# Single-Use System Manufacturing: Detectability

## Visual inspection of single-use bags and assemblies

Optimize inspection conditions

- Guidance from USP <1790>
- Lighting conditions and background:
  transmitted/reflected, angle, intensity
- Scanning methodology
- Timing of inspection
- Particle defect kits
- Inspector training (regular eye exams)
- Visible defect inspection (including particles)

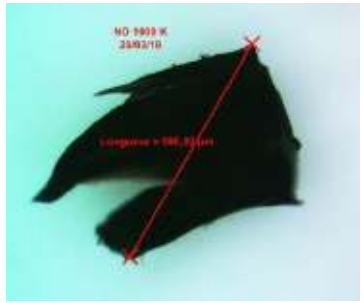
**Visual defect inspection of single-use systems:**

**Complexity and size reduces probability of detection of small particles**

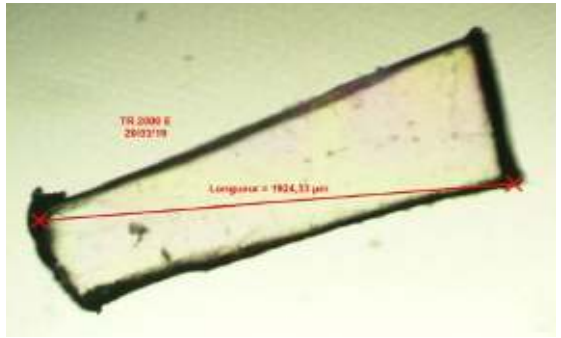
**Inspection of inside surfaces only possible through transparent components**

# Single-Use System Manufacturing: Detectability

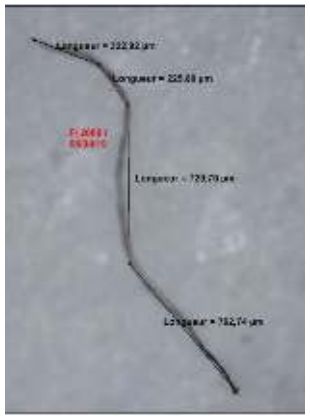
## Scientific study of particle detectability in single-use systems



Cable Tie Shaving
(Polyamide)



Bag Film or Tubing Shaving
(EVA or Silicone)



Various Textile Materials

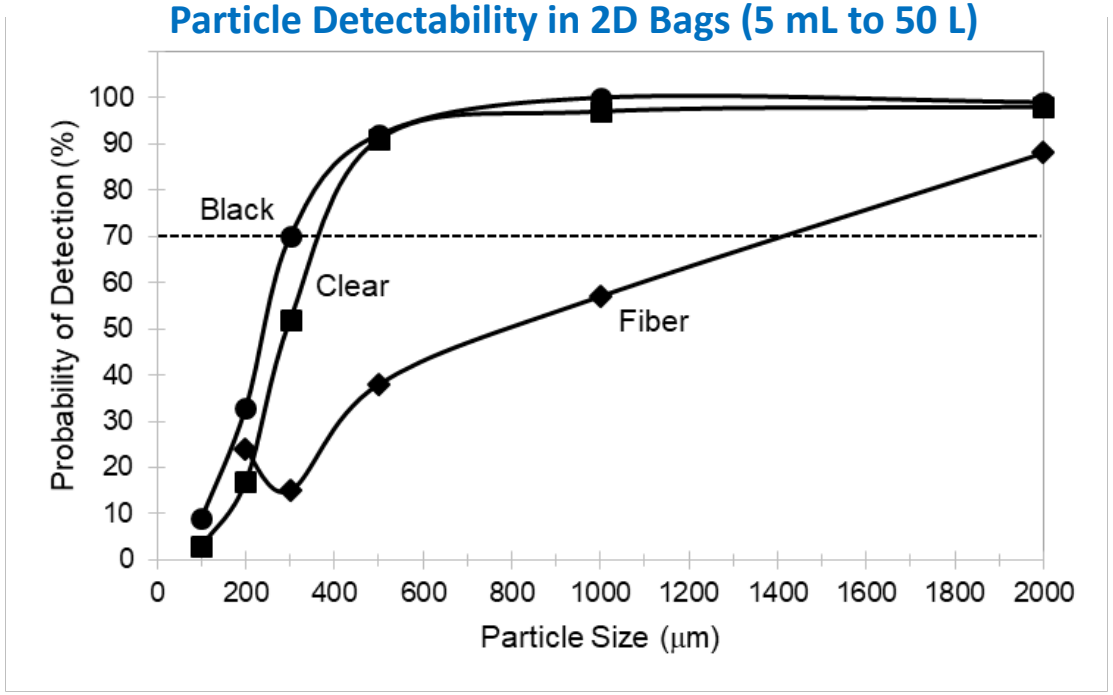
**Particles carefully placed inside 2D bags, tubing lines, and bag+tubing assemblies**

**<u>Particle size categories</u>**
**100, 200, 300, 500, 1000, 2000 µm**

# Single-Use System Manufacturing: Detectability

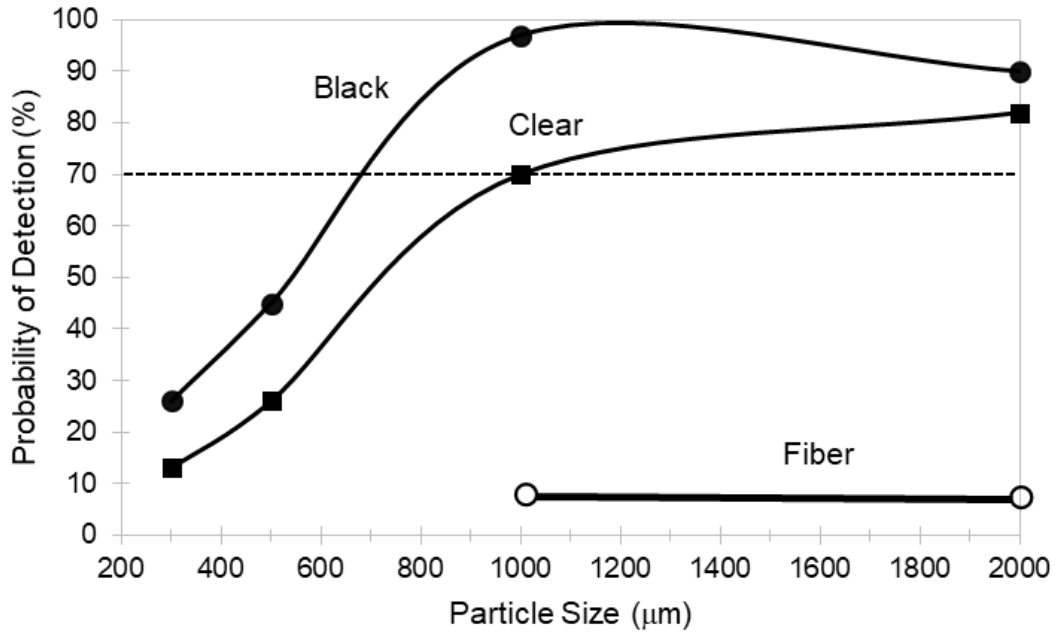
## Scientific study of particle detectability in single-use systems

### Particle Detectability in 2D Bags (5 mL to 50 L)




**Black, Clear and Fiber particles:**
**100, 200, 300, 500, 1000, 2000 µm in size**
**Placed in bags, tubing lines and assemblies**

### Particle Detectability in 2D Bag + Tubing Line Assemblies




**2D bags alone:**
**Black and clear particles reliably detected ≥ 500 µm**
**Fibers reliably detected ≥ 2000 µm**
**2D bag+tubing assemblies**
**Black and clear particles reliably detected ≥ 1000 µm**
***Fibers not reliably detected @ 2000 µm***

Wormuth, et al., PDA J Pharma Sci Technol, 75(4), 332-340, 2021

# Single-Use System Manufacturing: Detectability

## Capability of manual visual inspection process

| Samples | Particle size @ POD ≥ 70% | Reference |
|---|---|---|
| Spherical particles in clear liquid<br>10 mL glass vial | ≥ 150 µm | USP <1790> |
| Fibers in clear liquid<br>10 mL glass vial | ≥ 500 µm | USP <1790> |
| Particles<br>Empty glass containers | ≥ 125 µm | PDA TR85 |
| Fibers<br>Empty glass containers | ≥ 300 µm | PDA TR85 |
| **Black particles**<br>**2D bag assemblies** | **≥ 500 µm** | **PDA Journal*** |
| **Fibers**<br>**2D bag assemblies** | **>> 2000 µm** | **PDA Journal*** |

***Wormuth, et al.,**
**PDA J Pharma Sci Technol**
**75(4), 332-340, 2021**

**Particle detectability in glass vials (≥ 150 µm) much better than for 2D Bag Assemblies (≥ 500 µm)**

# Single-Use System Manufacturing:

## Detectability: Liquid Extraction

## Particulate Matter

# Single-Use System Manufacturing: Detectability

## Measurement of particles in SUS using liquid extraction

**Liquid Extraction** → **Particle Count/Size**

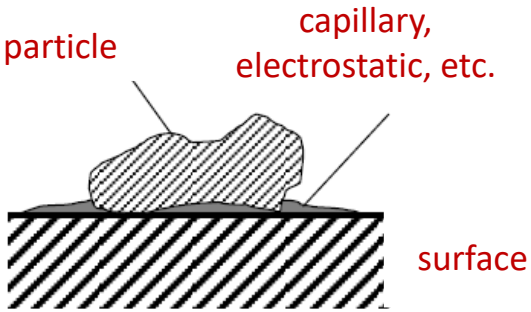
# Single-Use System Manufacturing: Detectability

## Liquid extraction of particulate matter from SUS surfaces

Liquid extraction (clean/rinse/flush) required to make particles available for analysis

Liquid extraction variables:

- Liquid (solvent, water, water plus surfactant...)
- Volume of liquid
- Time/Temperature
- Agitation (rinse, pressure rinse, shake...)




**Effectiveness of particle extraction depends upon many variables**

# Single-Use System Manufacturing: Detectability

## New standard for extraction of particulates from SUS

Designation: E3230 – 20

### Standard Practice for Extraction of Particulate Matter from the Surfaces of Single-Use Components and Assemblies Designed for Use in Biopharmaceutical Manufacturing[1]

#### 1. Scope

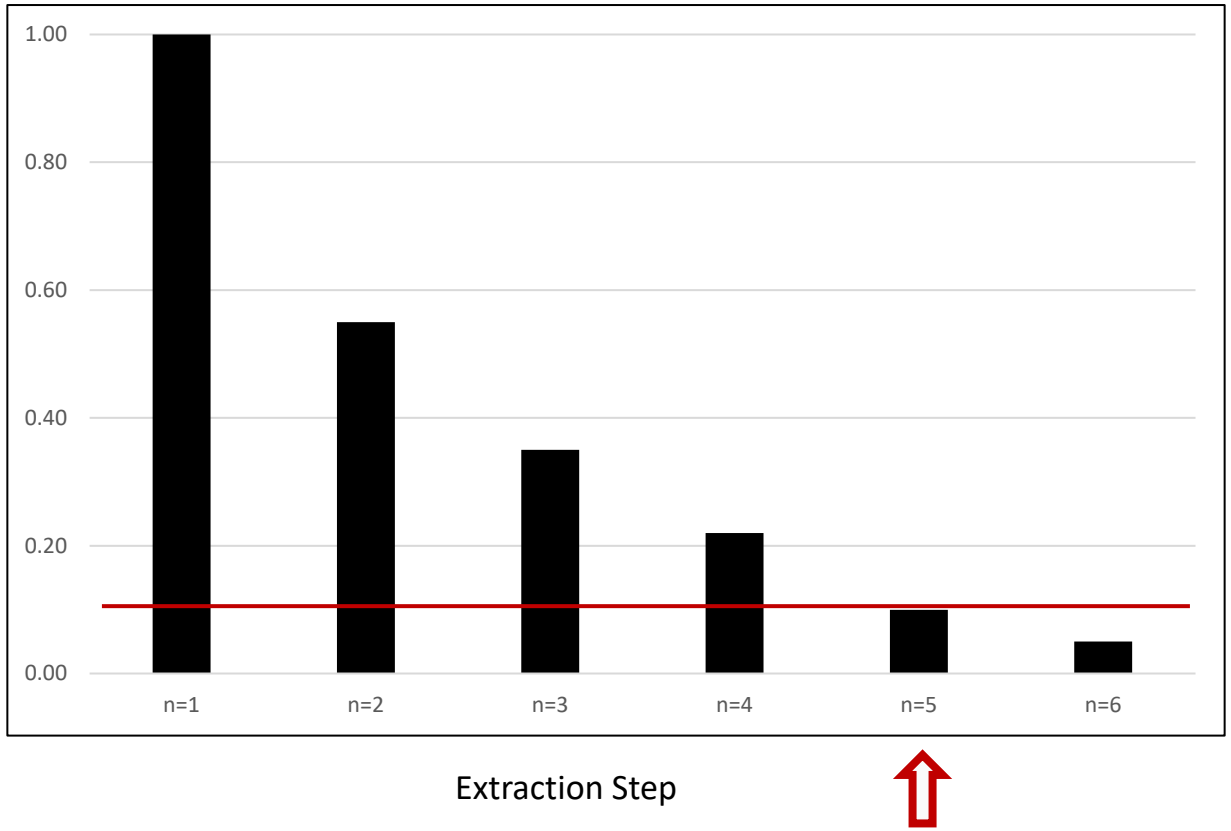
1.1 This practice describes the requirements for development, qualification, and routine application of a procedure for the effective liquid extraction of particulate matter from the surfaces of single-use components and assemblies designed for use in biopharmaceutical manufacturing processes. The extraction generates a suspension of particulate matter in liquid which makes the particulate matter readily available for analytical characterization.

**Standard approved and published as ASTM E3230-20**

# Single-Use System Manufacturing: Detectability

## Maximizing effectiveness of particulate extraction from single-use assemblies

Extraction Effectiveness Index



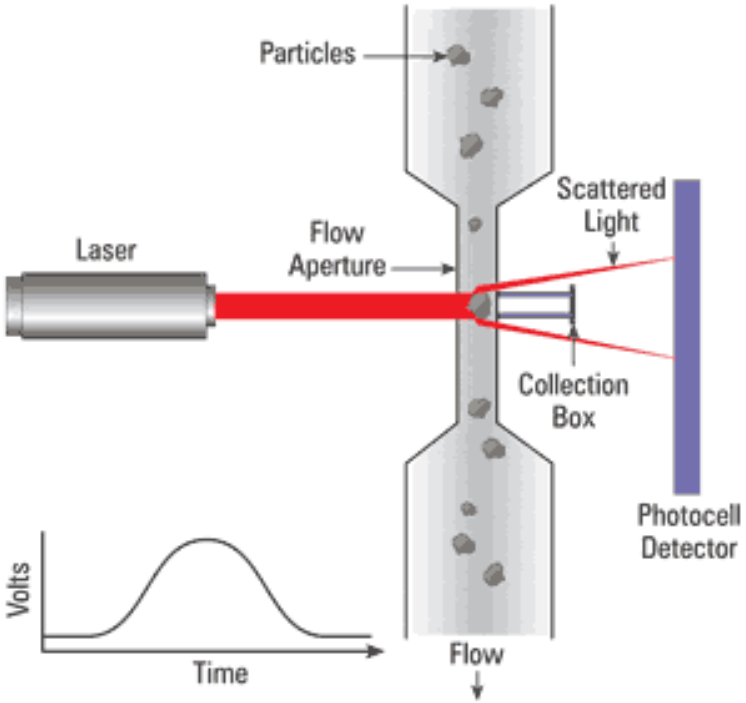

**Challenges:**
**Complex geometries**
**Uneven fluid flow**
**Imperfect extraction**

***After 5 extraction steps: > 90% of particles extracted indicates an effective particle extraction method***

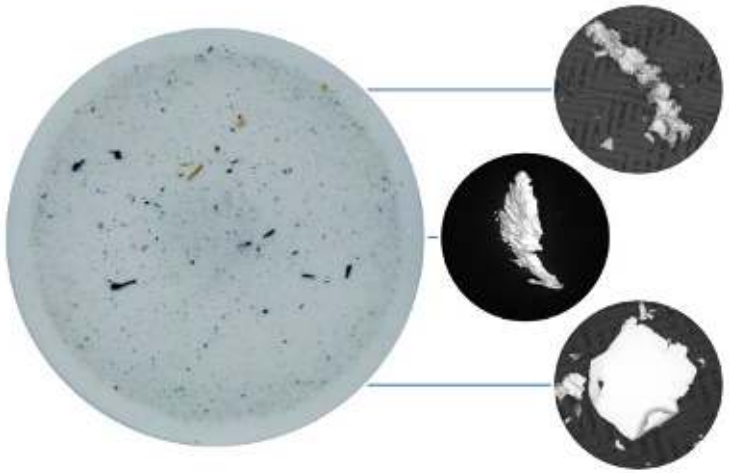
# Single-Use System Manufacturing: Detectability

## Common methods for particle counting and sizing

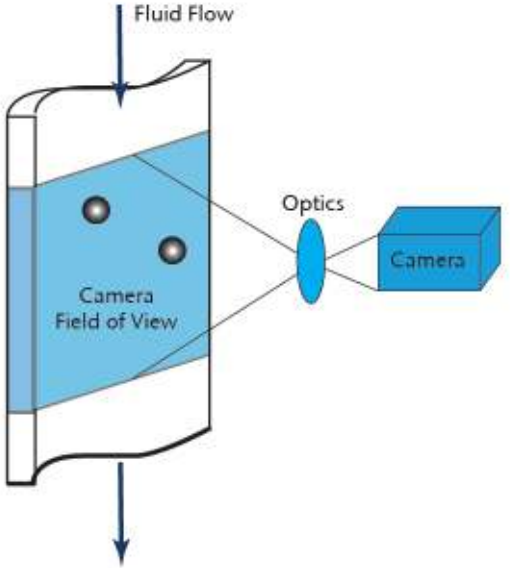
### Light obscuration

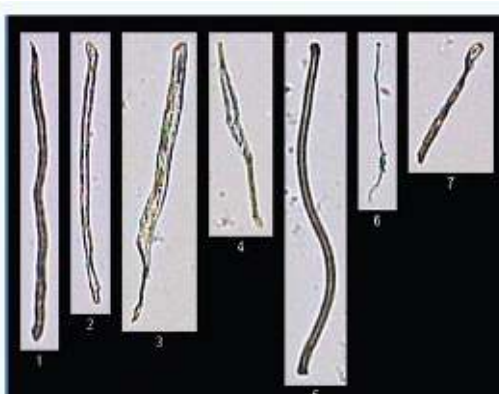



### Membrane microscopy



### Flow imaging



**Typical methods used for counting and sizing of particulate matter in pharmaceuticals**

# Single-Use System Manufacturing: Detectability

## Issues with applying USP <788> to single-use systems

**USP <788> Particulate Matter in Injections**

*Only describes:*

- Test method for counting and sizing particles in **parenteral drug products**
- Two categories of drug products: Small volume and large volume parenterals
- Two methods for particle count and sizing:
  - Method 1 Light Obscuration
  - Method 2 Membrane Microscopy

USP <788> is not a test method written for single-use systems

- No description of liquid extraction method
- Single-use systems are not the same as “large volume parenterals” (LVP)
- Specifications of allowed particle levels in USP <788> apply to drug products may or may not be relevant for single-use systems

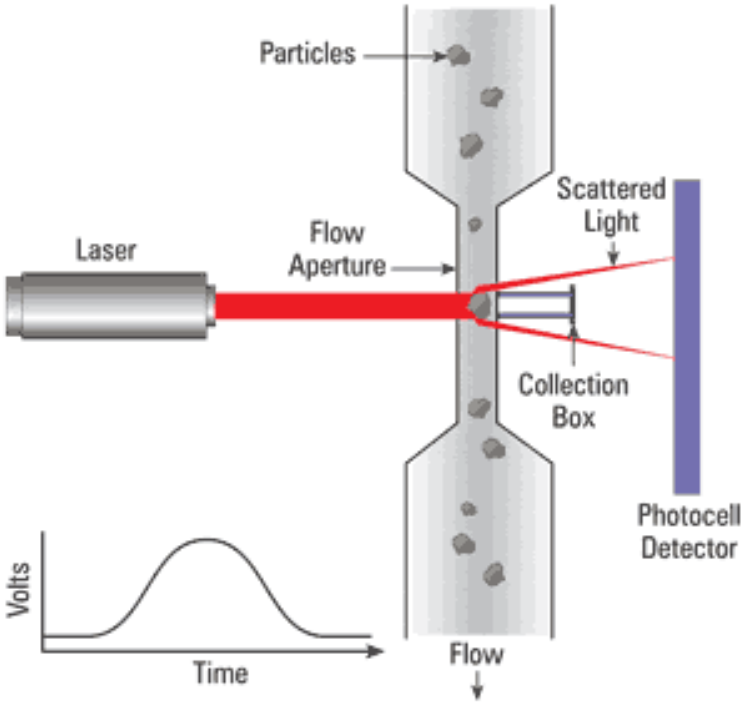
Key variable undefined: In LVP specification, particles reported per milliliter drug product

**For SUS, particles per which volume???**

# Single-Use System Manufacturing: Detectability

## Advantages and limitations of light obscuration

### Light obscuration




Advantages

- Automated
- Rapid
- No filtration required
- USP/EP/JP Harmonized and standardized method
- In use since 1985

Limitations

- Indirect measurement of particle size:
  - Light blockage depends strongly on particle morphological and optical properties (shape, transparency), which may be very different than calibration standard
- No information on particle morphology or color (shape)
- Detects air bubbles and liquid droplets
- Will not reliably detect particles > 50-100 µm
  - Particle shape and density may limit ability to aspirate particle into detection cell

# Single-Use System Manufacturing: Detectability

## Advantages and limitations of light obscuration

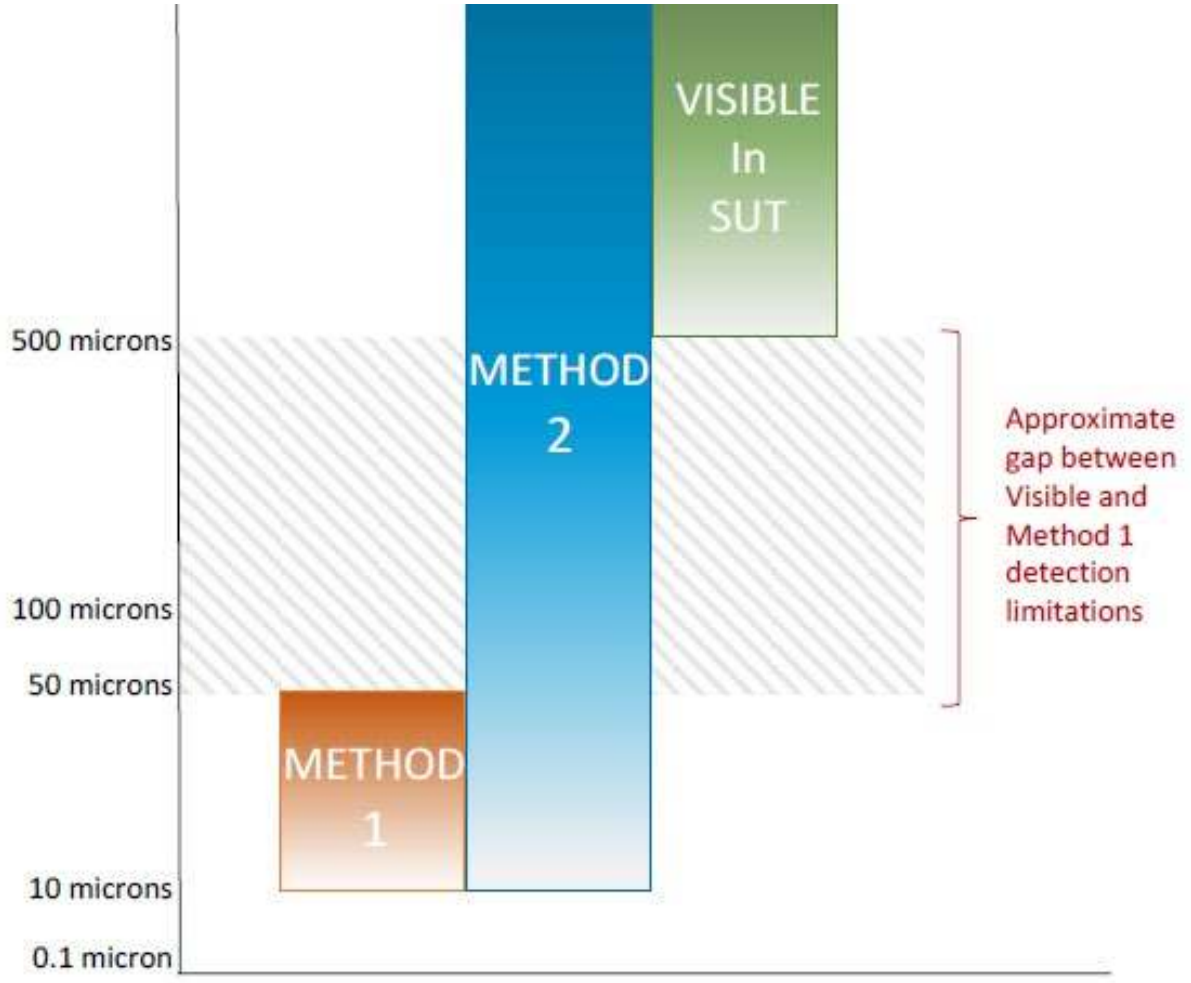
Method 1: Light obscuration

Method 2: Membrane microscopy

Visual inspection

If only use light obscuration (typical USP <788> method) and visual inspection:

Grey-zone of poor detectability approx. 50 µm to 500+ µm



# Single-Use System Manufacturing: Detectability

## Guidance from the newly revised USP <1788>

USP <788> Particulate Matter in Injections

Test method for particulate matter to be developed with the guidance given in:

USP <1788> Methods for the Determination of Subvisible Particulate Matter

New subchapters:

USP <1788.1> Light Obscuration Method for the Determination of Subvisible Particulate Matter

USP <1788.2> Membrane Microscope Method for the Determination of Subvisible Particulate Matter

USP <1788.2> Flow Imaging Method for the Determination of Subvisible Particulate Matter

**Important new information for development of test methods for measurement of particulate matter in injectable drug products**

**New emphasis: test methods for "subvisible particulate matter"**

**Not specific methods for visible particulate matter**

# Single-Use System Manufacturing: Detectability

## Standards for Validation of Test Methods for Particles in SUS

**Liquid Extraction**

**ASTM E3230-20**
Standard Practice for the
**Extraction of particulate matter from the surfaces of single-use components and assemblies**

**Particle Count/Size**

**ASTM WK74514**
Working Title: Standard Practice for
**Development and validation of automated membrane microscopy test methods for the counting and sizing of particulate matter in parenteral pharmaceutical manufacturing processes and final drug products**

**Data Reporting**

**ASTM WK80957**
Working Title: Standard Practice for
**Reporting and classifying cleanliness with respect to particulate matter in pharmaceutical processes**

**ASTM WK81610**
Working Title: Standard Practice for
**Development and validation of test methods to quantify particulate matter on the surfaces of single-use systems**

# Addressing risks from particulate matter when applying single-use systems in biopharmaceutical manufacturing

**Single-use systems are not final drug products:**

***Need to stop "force fitting" risk-scenarios and standards for final drug products to single-use systems***

**USP <790> and USP <788> are standards for <u>injections</u> (parenteral drug products) not single-use systems**

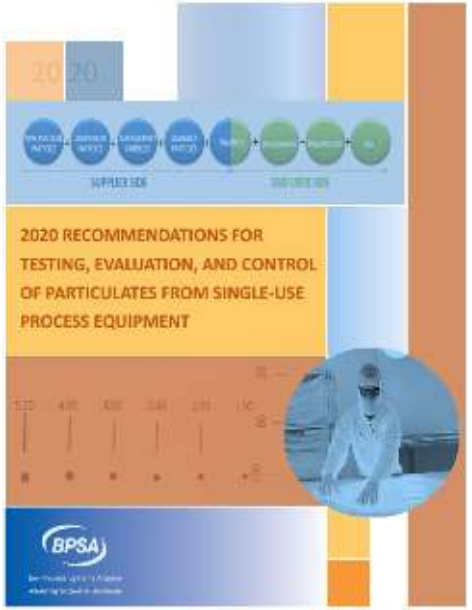
***New ASTM standardization efforts underway on test methods specific to single-use systems***

**Risk-scenario binary:**

- **Single-use system applied upstream of final filters: Lower risk**
- **Single-use system applied downstream of final filters: Higher risk**
  - **Cell therapy manufacturing: usually no filtration**

**Detectability of particulate matter in single-use systems:**

- **Limited in a visual inspection (especially for non-transparent components)**
- **Liquid extraction plus light obscuration: grey-zone of poor detectability**




**Risk of Harm = (Probability of Occurrence) x (Detectability) x (Severity of Harm)**