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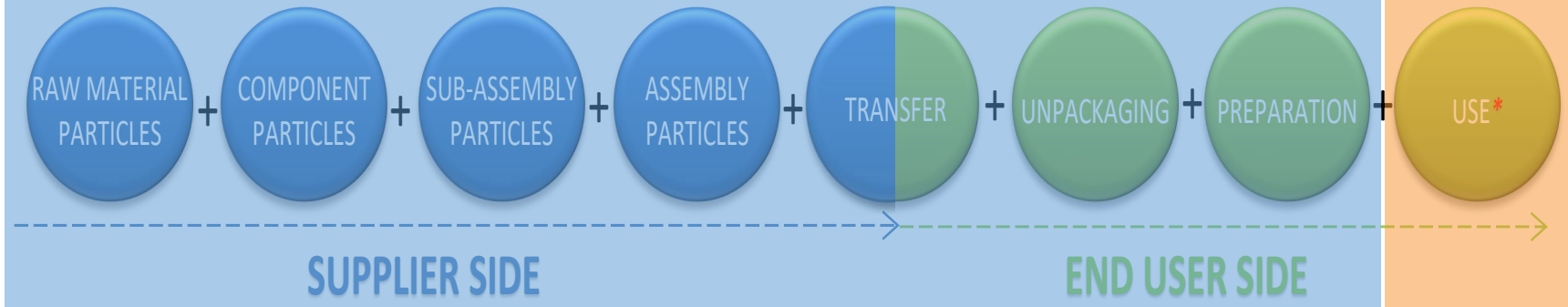

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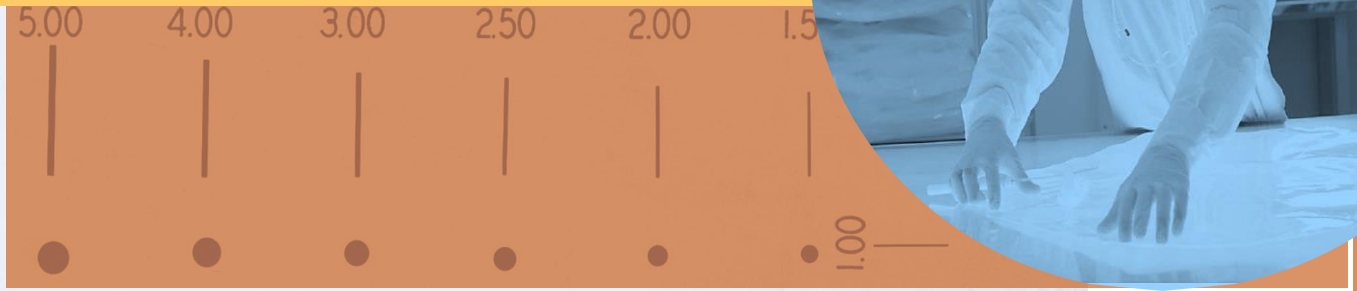

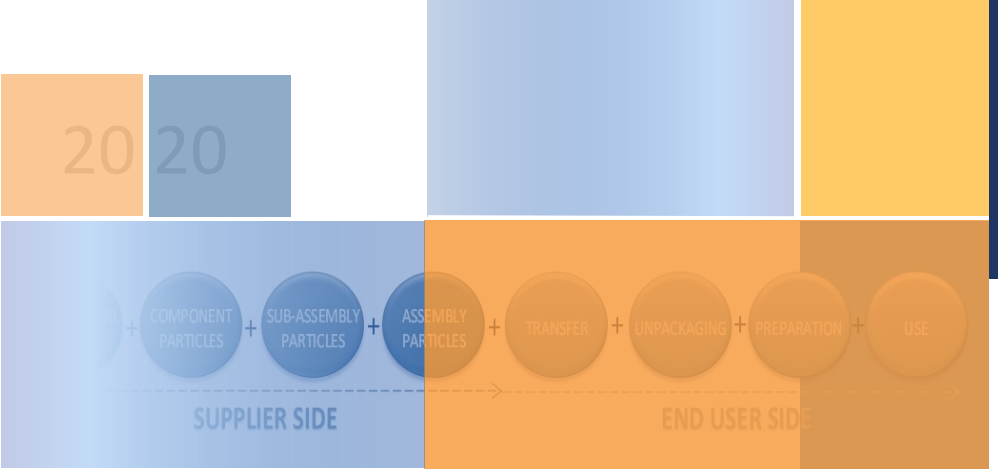

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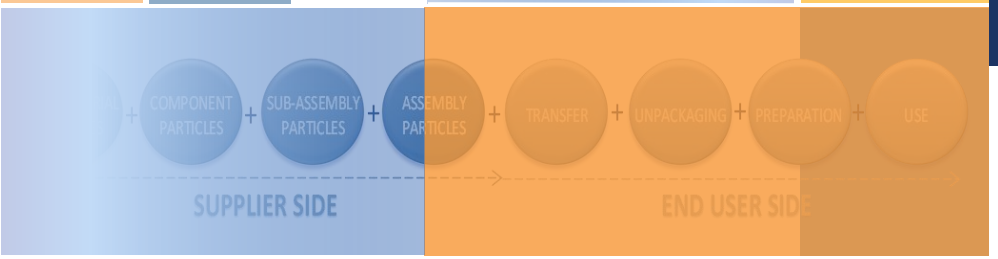
James Dean Vogel, The BioProcess Institute
Maureen Eustis, The BioProcess Institute

Agenda

- Review paper
- Changes since 2014
- Current Best Practices
- Q&A

Today's Author Panel



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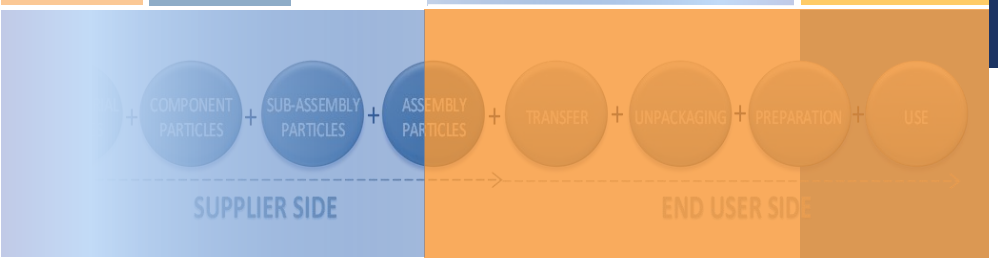

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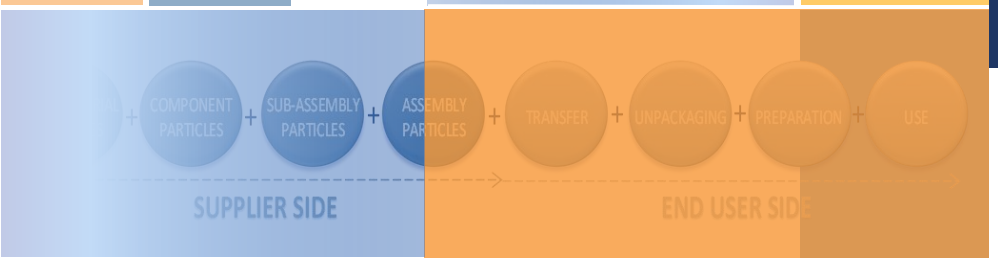
Topics



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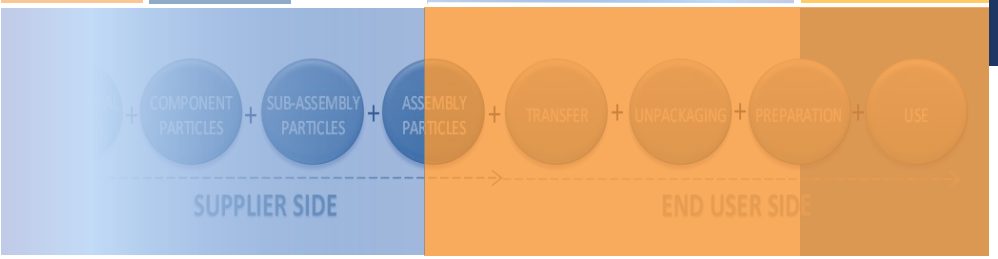
Part I: Introduction

2020 Update



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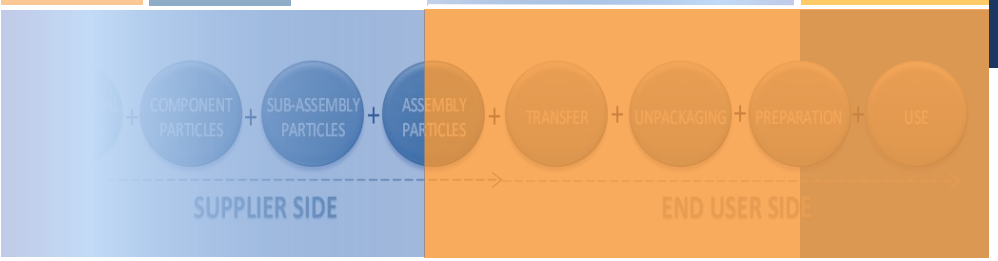
- 2014 Particulate paper captured the state of the industry at that time.
- Influenced discussions in the standards organizations (ASME BPE, ASTM, etc.)
- New Documents were published since: PDA Technical Report 79, USP<790> and <1790>
- Cell and Gene Therapies

The Goal

"The goal of end users, regulators, and standards-setting organizations should be to minimize particulates in drug products, without placing unnecessary expectations on suppliers for minimal safety gains. Improving the manufacturing quality will reduce the risk of harm to patients from particle contamination."

This Document Helps Clarify

- ***Why are particles a concern when using SUT?***
- ***Why are particulates in SUT a risk to the drug product?***
- ***What factors are key to assessing particulate risks from SUT?***
- ***How can you improve the detectability of particulates in SUT?***
- ***How do you distinguish levels of particle risk based on location in the biopharmaceutical manufacturing process?***
- ***How do you control and minimize particulates during the manufacture of SUT?***



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Part II: Particle Definition & Classification

Particle Definition

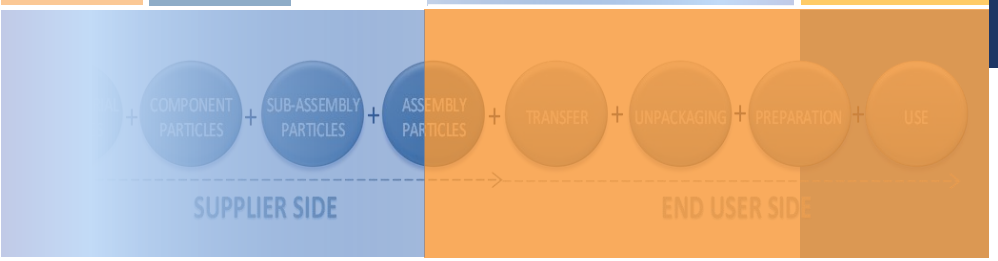
"Extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in solutions."

- USP

Particle Definition

"A particle is loose mobile or embedded matter that is unintentionally present in/on the single-use component/assembly and potentially may contact or may end up in the process/product fluid."

- BPSA



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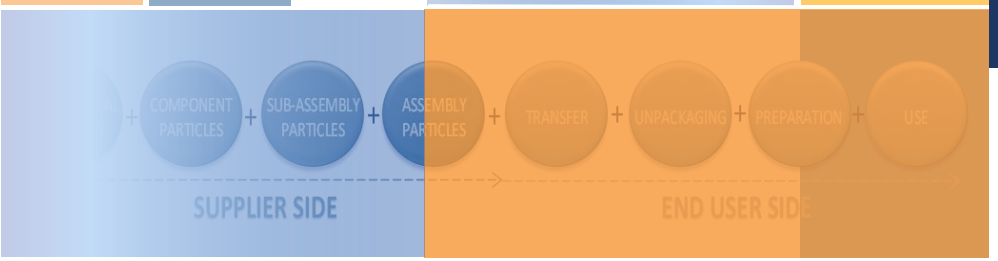
Part III: Risk

ICH Q9

“the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.”

But it is important to understand that all stakeholders may not necessarily agree on the degree of risk from particulates.



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BPSA RECOMMENDATION

When it comes to particulates in biopharmaceutical processing, fewer is better! Both SUT suppliers and end users are taking many steps to decrease the levels of particulates in their products. This is in order to minimize the risk of contamination of drug products and, consequently, decrease the risk of harm to patients from particulate contamination.

Figure 1

Classification of particulate matter risks in the manufacturing and use of biopharmaceuticals

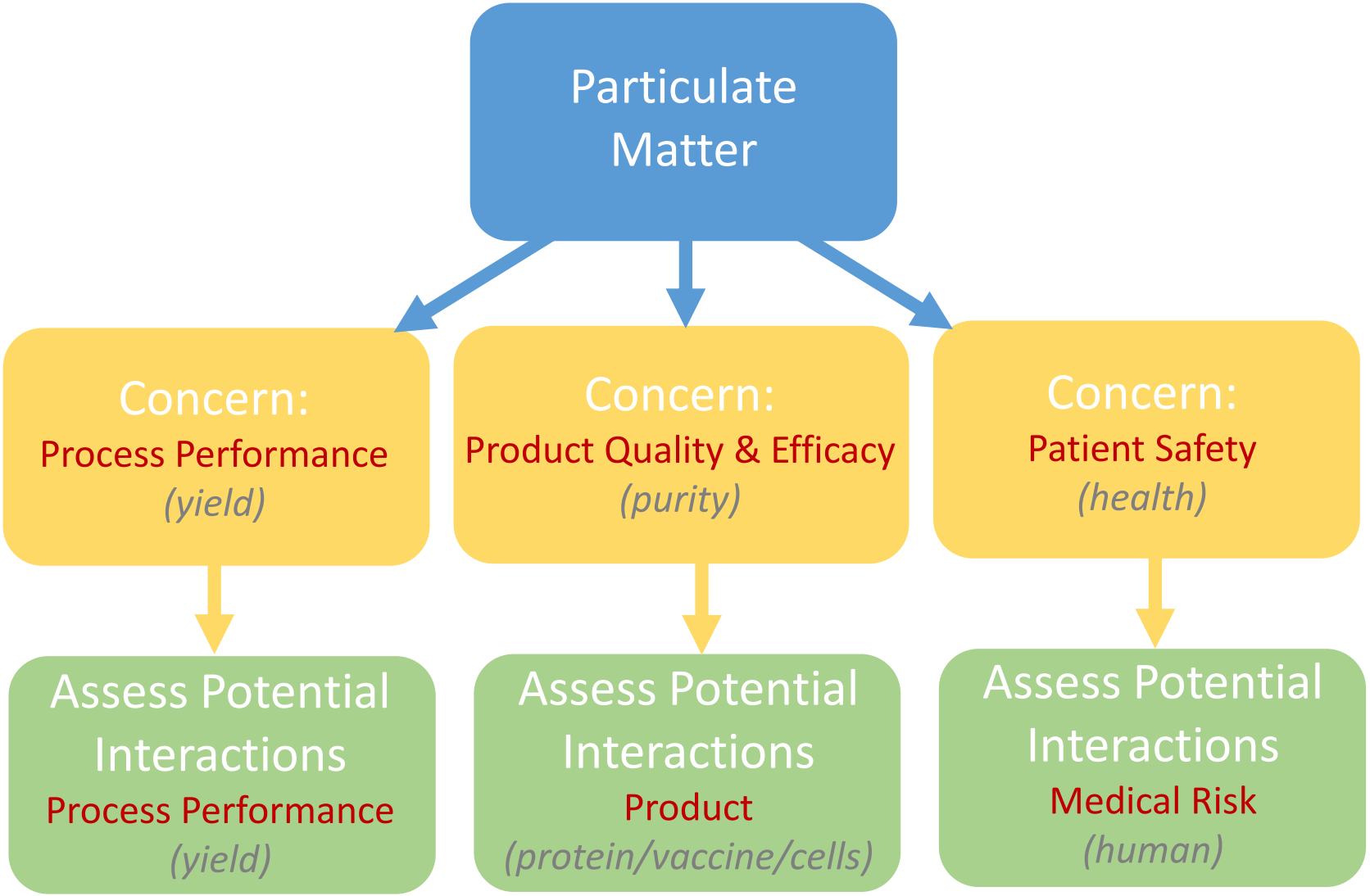


Figure 2
Potential Particle Locations

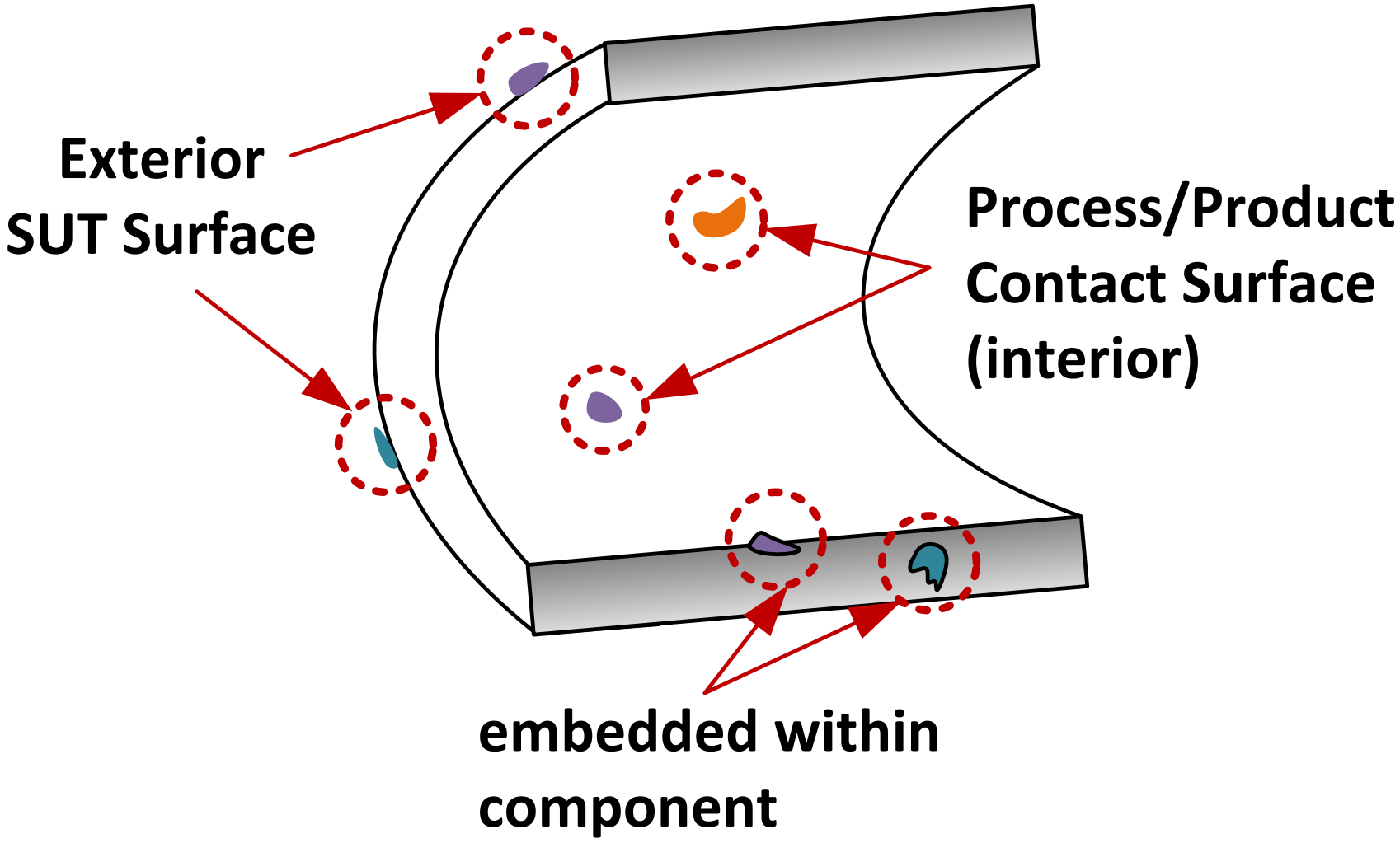
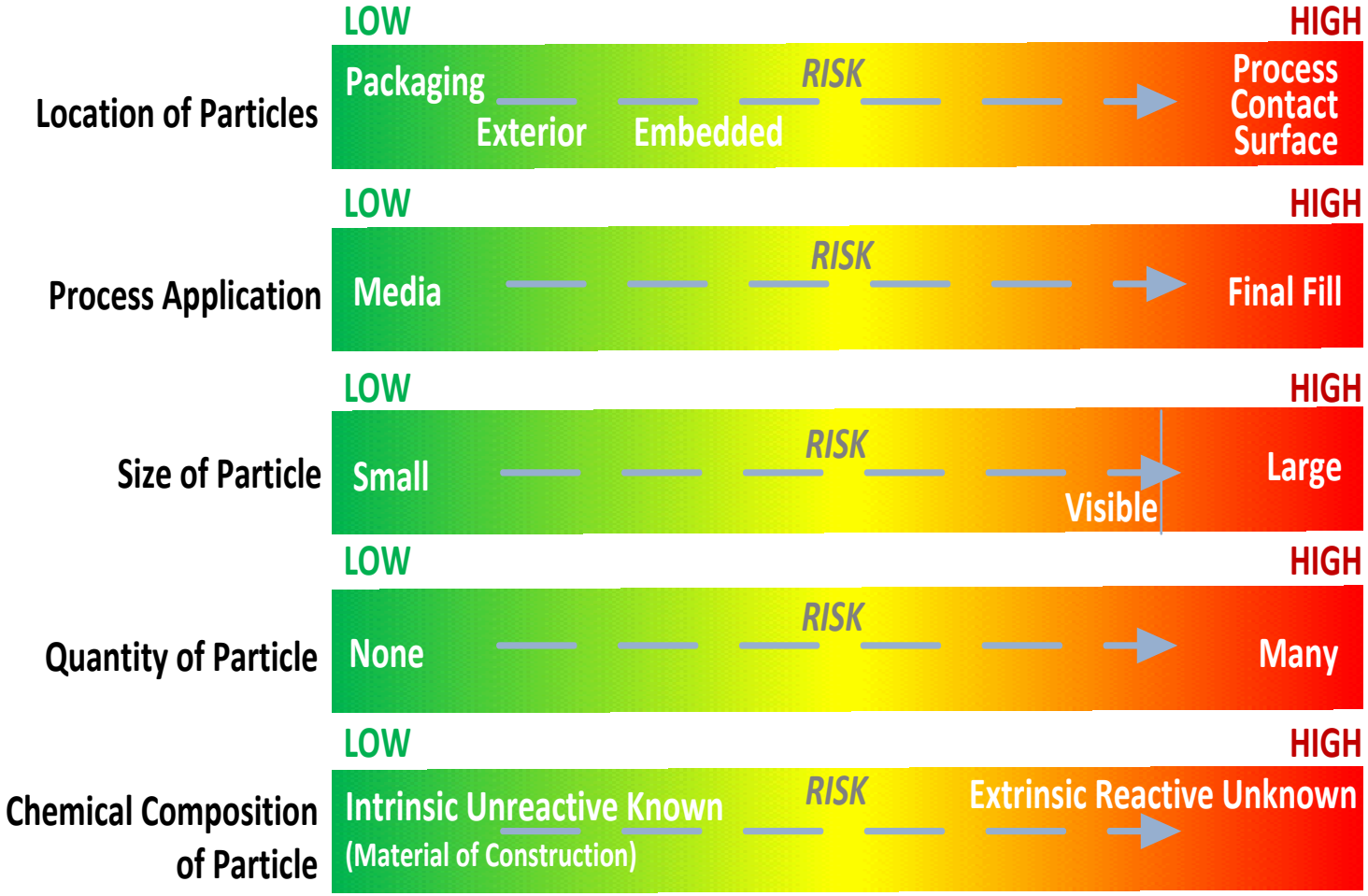


Figure 3
Risk From Particulate Matter By Category



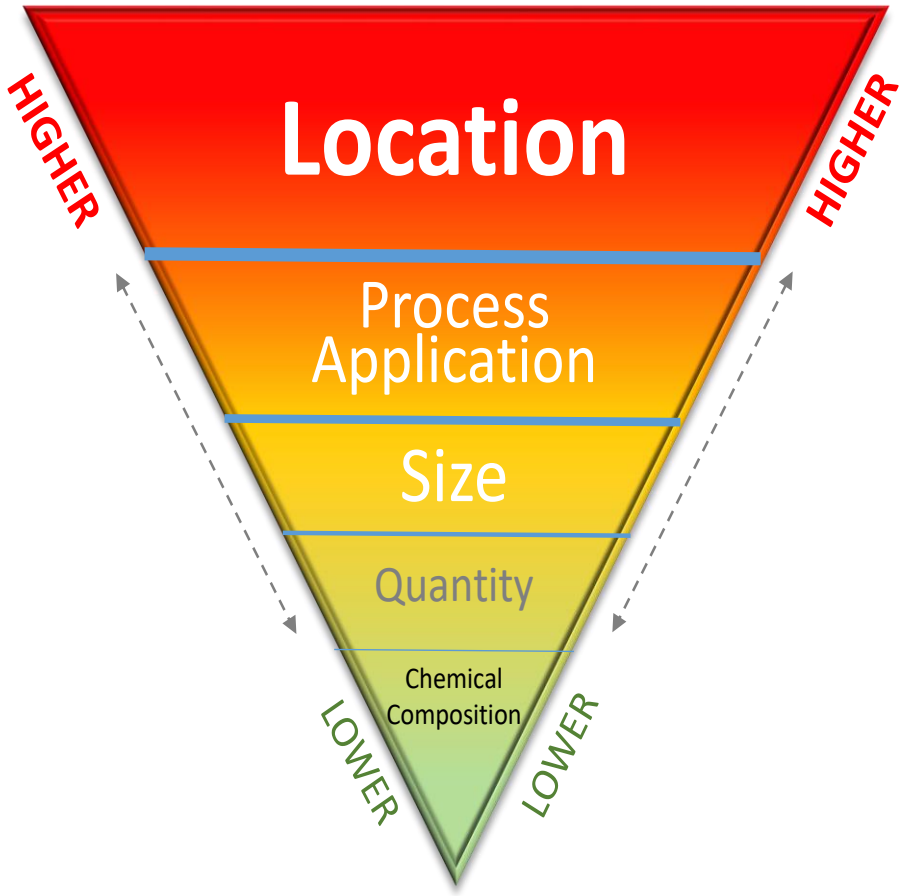
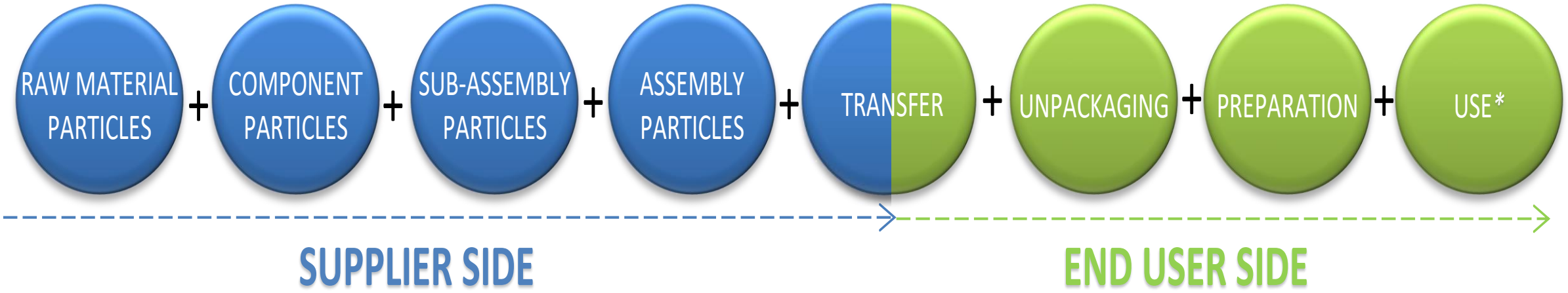
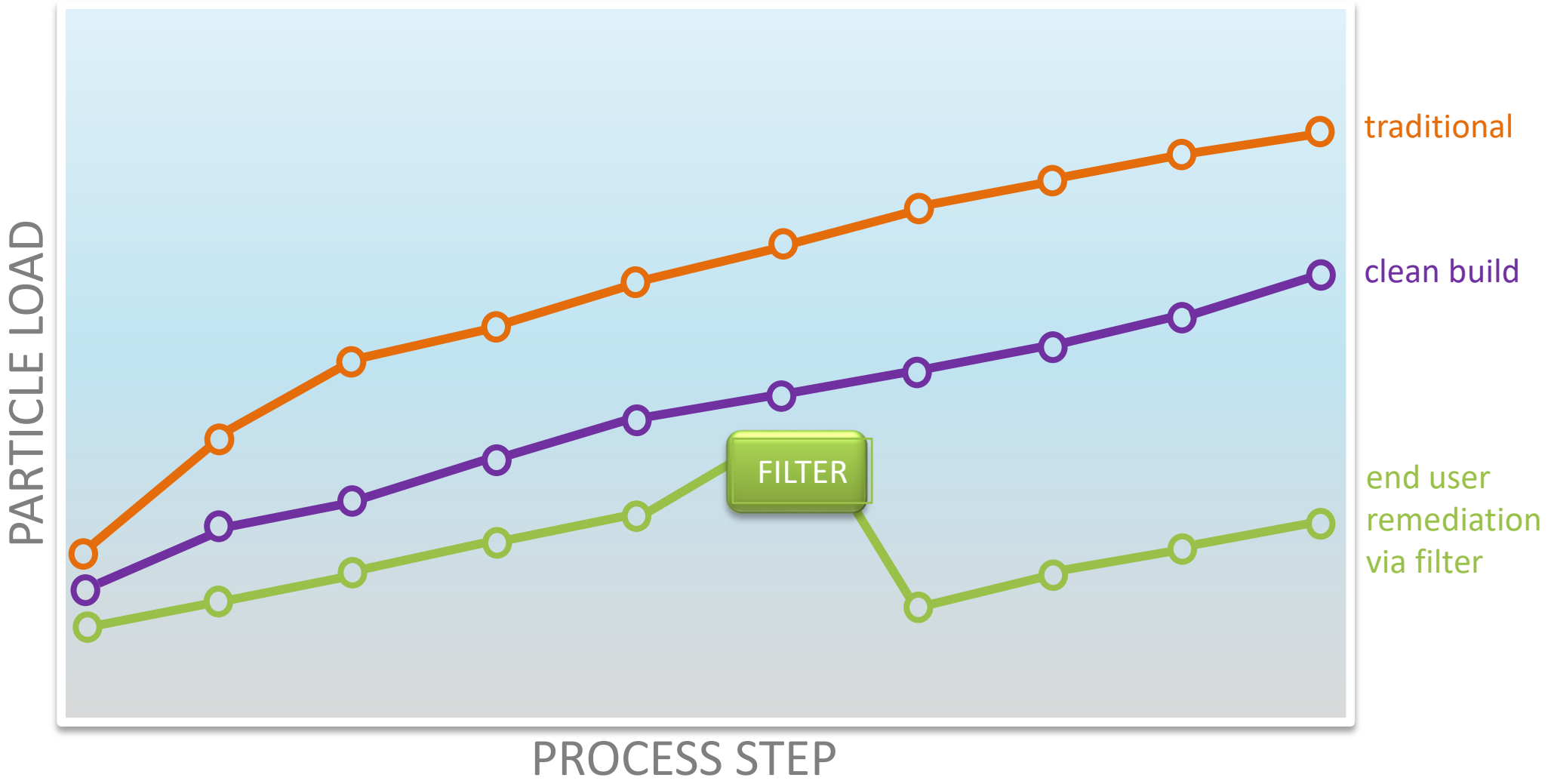


Figure 6
Potential Contributors to Particle Levels in SUT



** The use of a filter by the End User decreases the number of particles.*

Figure 7
Particle Load Can Be Reduced Using Best Practices



Risk

- Higher Risk downstream of the Final Filter.
- Higher Risk with cells.
- Higher Risk from certain Chemicals, USP Class VI vs unknown?
- Higher Risk with viable microorganisms attached to particles.
- Higher risk to nucleate Proteins.

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

Final Drug Product

- **Probability of occurrence**
  - **Reduced by following cGMP**
- **Detectability**
  - **100% visual inspection (USP <790>) and subvisible limits (USP <788>)**
- **Severity of harm**
  - **Particle injected into patient may result in injury**

BioPharmaceutical Processes

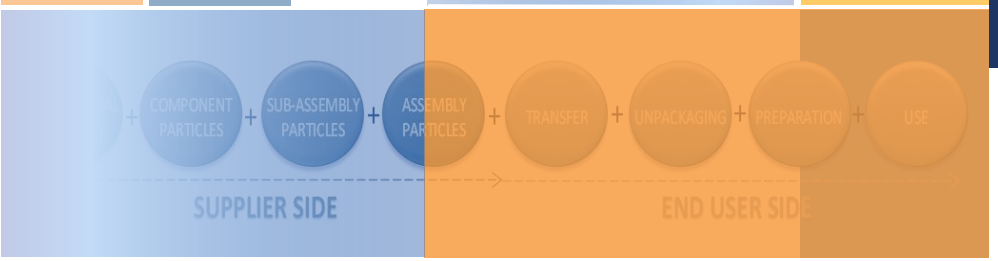
- **Probability of occurrence**
  - **Sterile filtration removes particles ≥ 0.2 micron**
  - **After sterile filtration: some risk that particle from SUS transfers to drug product**
- **Detectability**
  - **Visual inspection, plus destructive sampling (extraction and counting)**
- **Severity of harm**
  - **Depends upon location of SUS in process**

ICH Q9

"the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient."

But it is important to understand that all stakeholders may not necessarily agree on the degree of risk from particulates.

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



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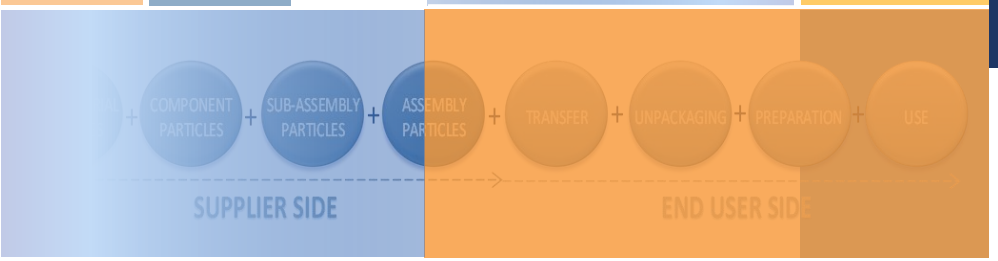
BPSA RECOMMENDATION

The BPSA recommends that suppliers of SUT develop a strong understanding of the particulates (sizes, levels, types, and sources) which might be present within their SUT. Concepts for exchange of information on particulates between suppliers and end users should be developed and implemented.



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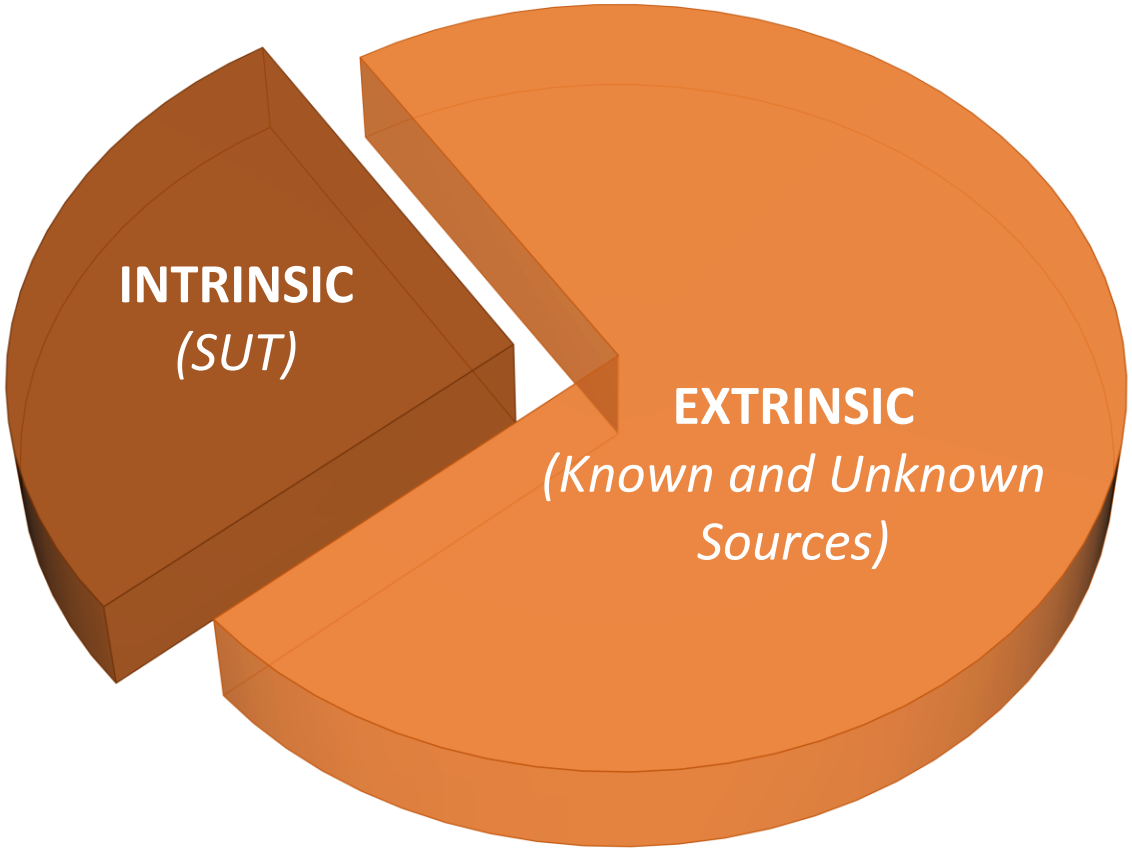
Part IV: Particle Detection & Characterization

Particle Characteristics

Particle Characteristic	Description
Size	sub-visible, visible *(see definition below)*
Shape	round, angular, fiber, irregular, rod-shape, twisted
Appearance	transparent, turbid, opaque, color, polarized
Texture	smooth, rough, irregular
Hardness	soft, viscous, deformable, elastic, brittle

Figure 8
Potential Particle Sources in SUT



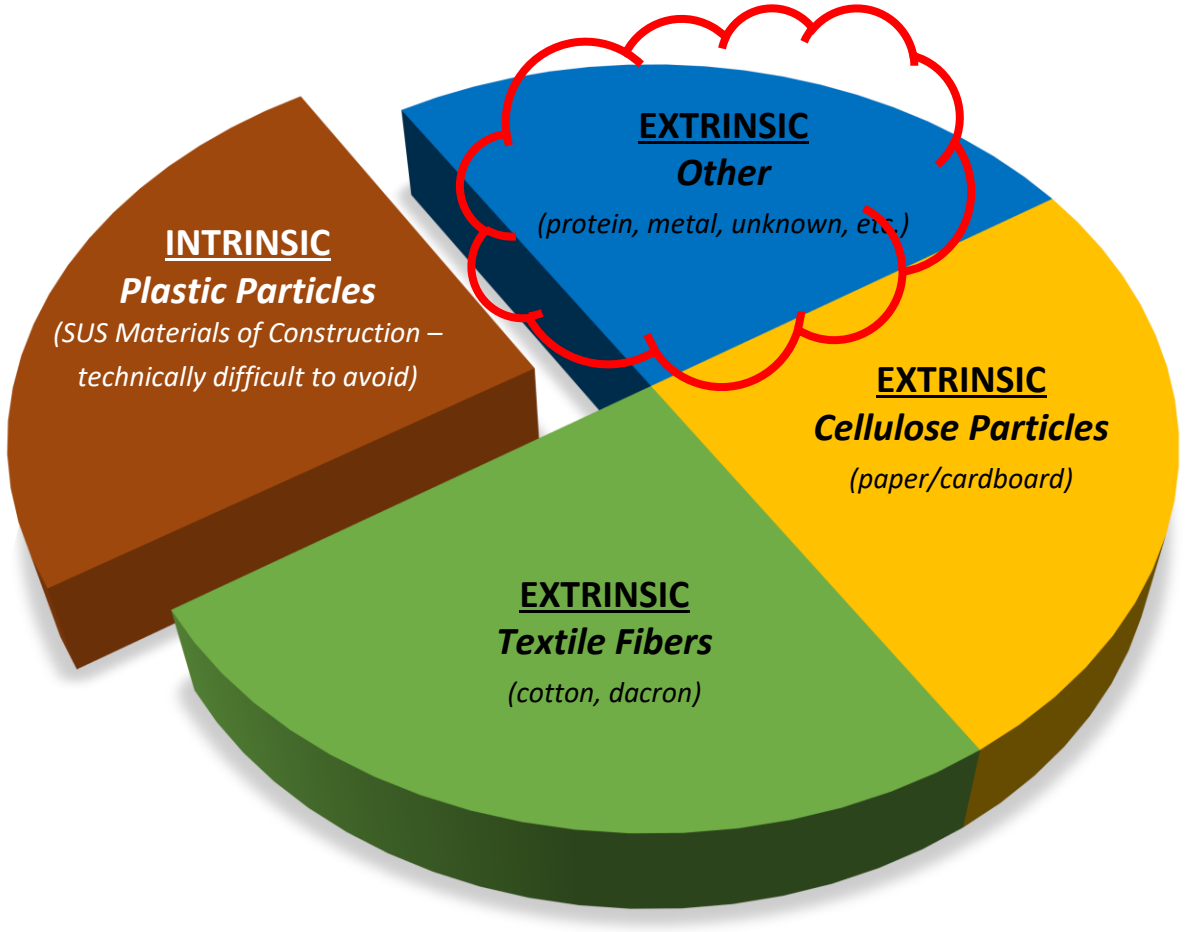
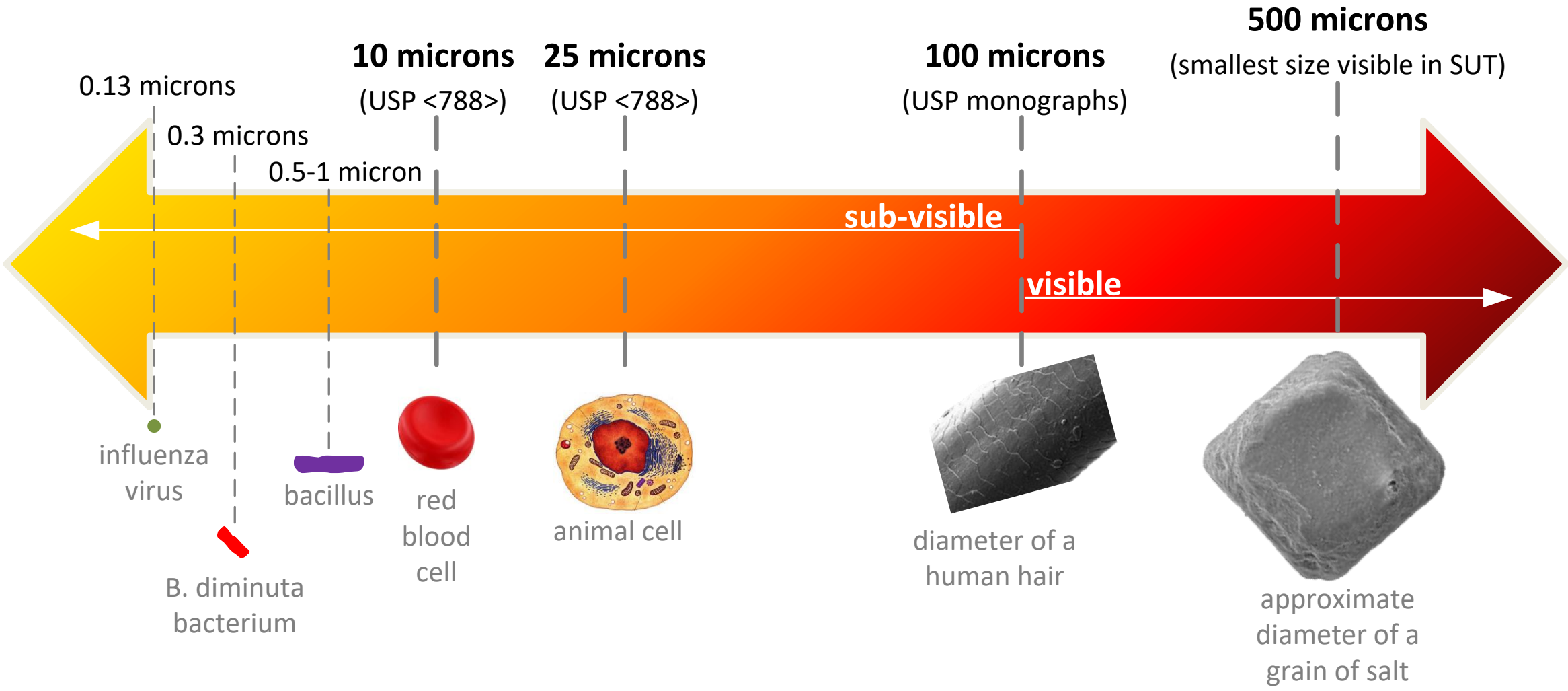
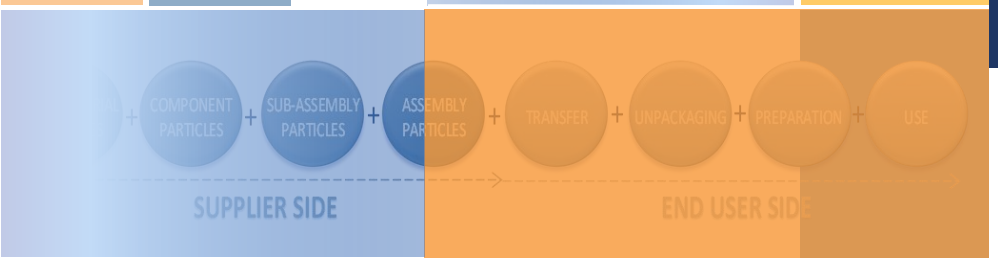


Figure 9
Particle Size Classification (not to scale)





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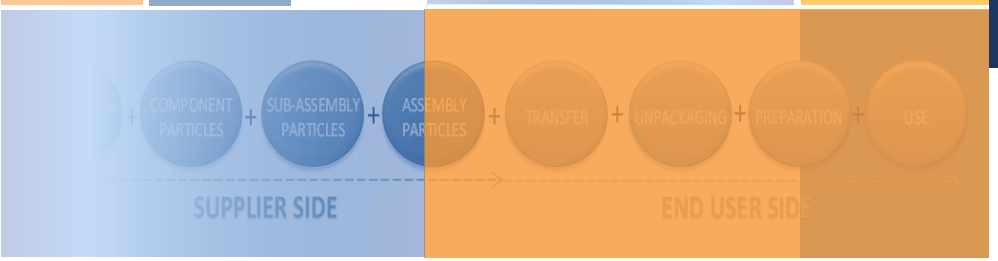
BPSA RECOMMENDATION

The challenges in developing rigorous visual inspection and particle quantification methods for SUT should not be underestimated! The goal of visual inspection and quantification methods is to maximize the probability of detection.



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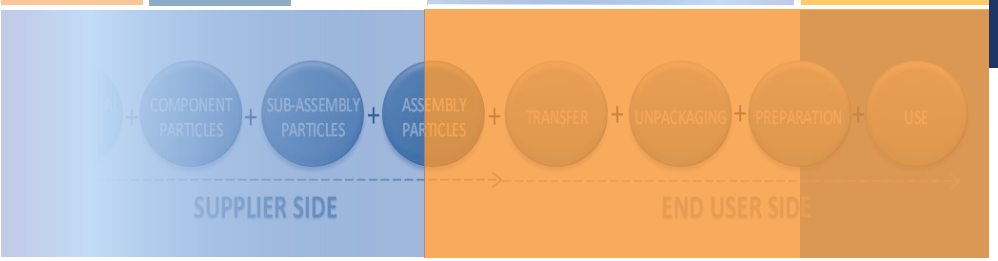
Part V: Particle Inspection & Quantification



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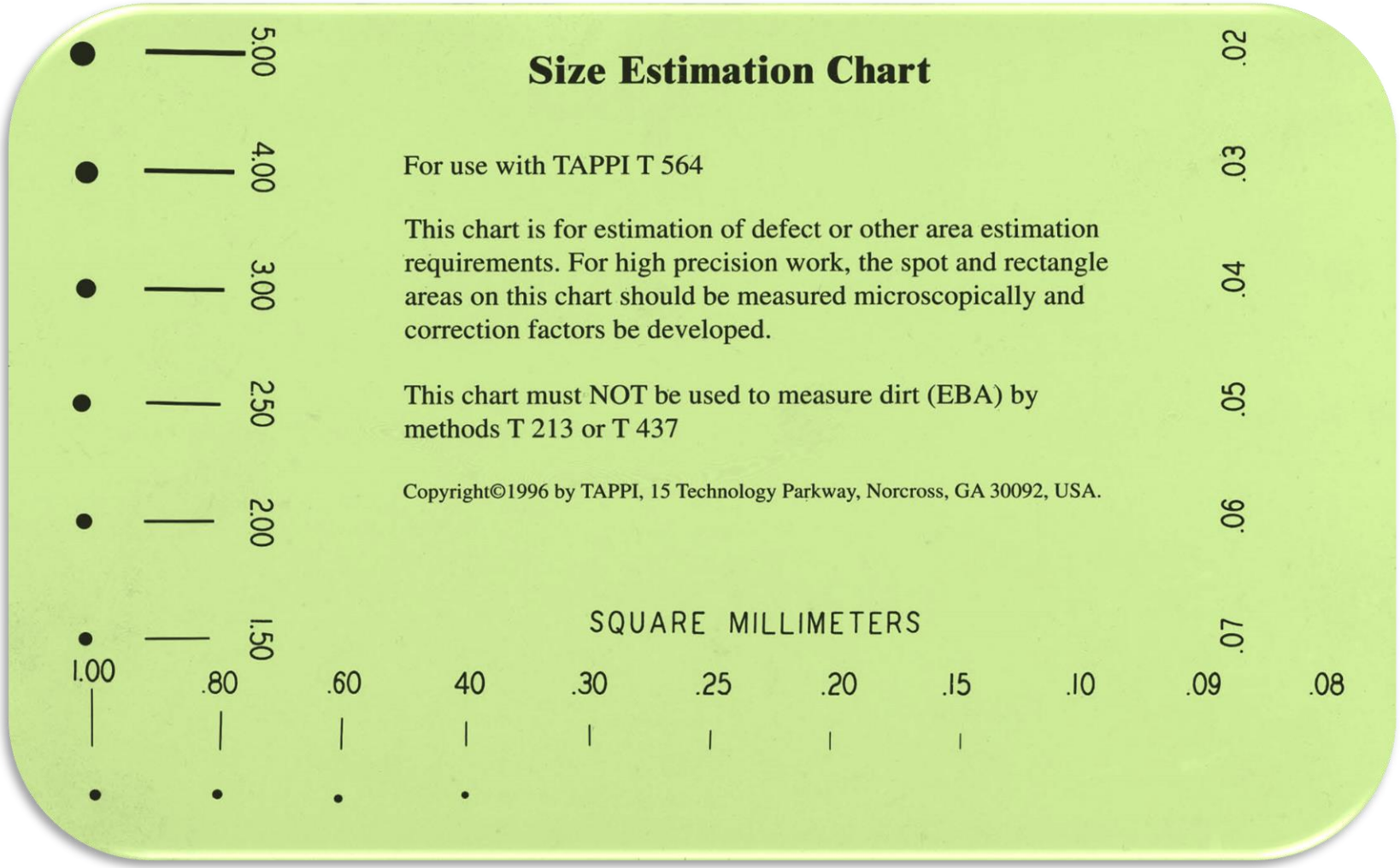
The goal of a chosen particulate extraction protocol for SUT is to maximize the probability that particulates are extracted in a practical, consistent and controlled way, which gives useful information for realistic assessments.

Visual Inspection

SUT bags	• film creases/surface defects • weld delamination/bubbles/misalignment • holes/canals
SUT assemblies	• arrangement of components (tubing, filters, connectors, etc.) as described on the drawing • connection security • holes/canals
Packaging	• overall integrity

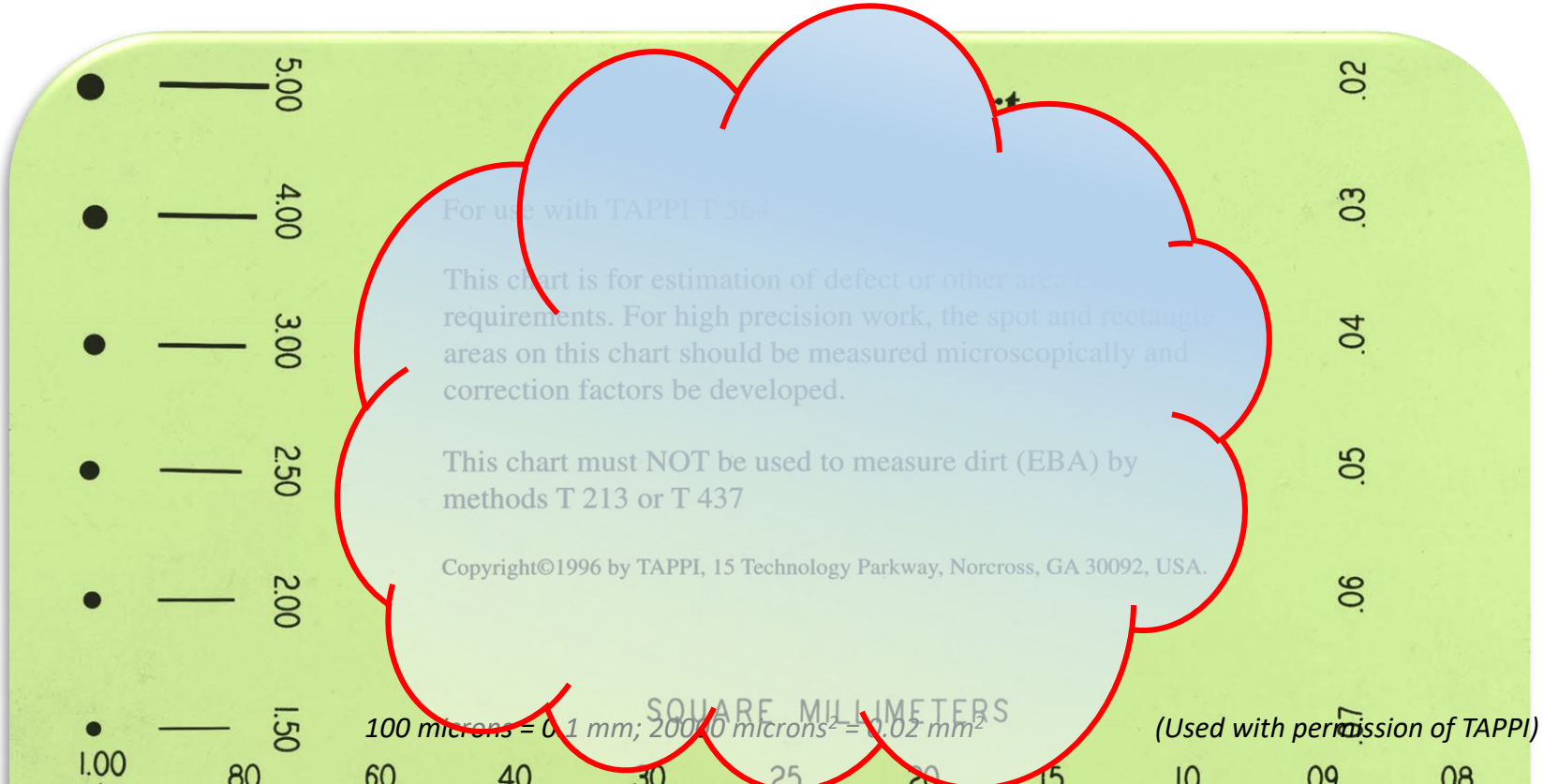
Lighting conditions	intensity, angle (reflected/transmitted), polarization
Background and contrast	white, black (*Ref. 21*)
Presentation/manipulation of SUT	vertical, horizontal
Scanning methodology	top-bottom, left-right
Inspection rate	length of inspection, inspector breaks
Inspector training	training sets with known defects
Inspector fatigue	ergonomics, inspector breaks

Figure 11
TAPPI Size Estimation Chart



100 microns = 0.1 mm; 20000 microns^2 = 0.02 mm^2 *(Used with permission of TAPPI)*

Figure 11
TAPPI Size Estimation Chart
Transparency



100 microns = 0.1 mm; 20000 microns^2 = 0.02 mm^2

(Used with permission of TAPPI)

Figure 10

Approximate gap in particle detectability between visual inspection and USP <788> Method 1 (light obscuration)

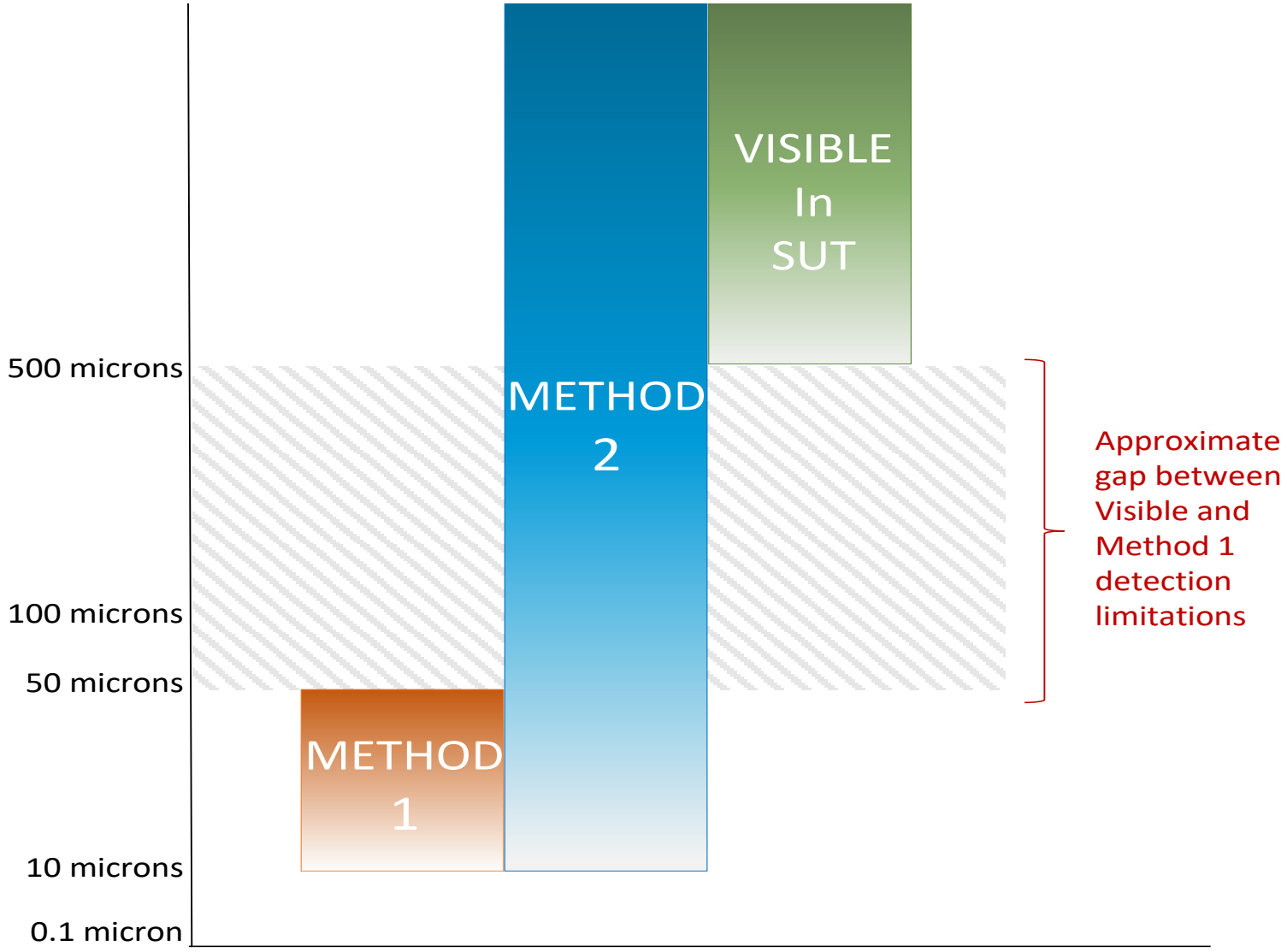
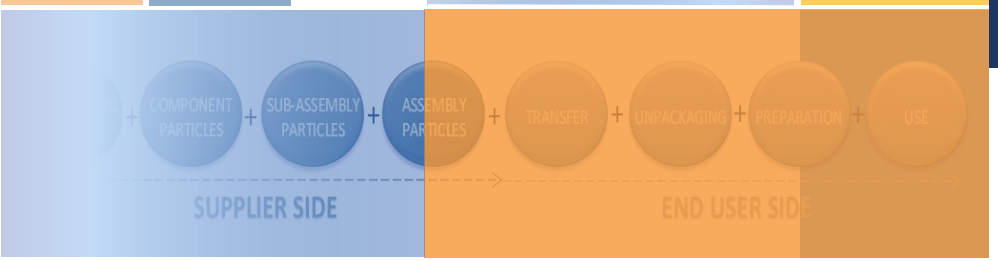


Table 2
Comparison of methods described in USP <788>*

Method 1: Light Obscuration	Method 2: Manual Membrane Microscopy
Indirect measurement using light blockage	Direct visualization of particles on filter membrane using microscope
Particles detected by blockage of light beam	Human operator eye is the detector
Particle size determined by amount of light blockage detected by sensor, relative to amount of light blockage by particle size calibration standard	Particle size determined by comparison with standardized graticule (reticle)
Light blockage signal depends strongly on optical and morphological properties of particle (e.g. transparency, shape) which often differ from properties of particles used for calibration	Visualization depends upon contrast between particle and membrane, lighting conditions, microscope optical quality and operator training
No information on particle morphology and color, and often undersizes fibers and other irregularly shaped particles (e.g. glass fibers)	Direct visualization of particle morphology allows for accurate sizing, and facilitates particle identification based upon morphology. In addition, particles are collected and available for application of more advanced methods of particle identification (e.g. infrared, Raman or electron microscopy)
No filtration required: Directly measure particles in liquid extract	Filtration onto membrane required
Usually dilute: particles dispersed in liquid volume	Usually more concentrated: particles collected on membrane surface
Measures sub-visible particles, but typically does not detect “visible” particles (greater than around 50 to 100 microns). Larger particles in extraction liquid tend to settle during measurement, and may not be dosed into instrument and detected	Will capture all solid sub-visible and visible particles larger than the pore size of the filter membrane
Detection sensitivity may depend upon model/brand of instrument. Newer models often show increased sensitivity, and may also measure any water immiscible liquid droplets present (e.g. from silicones)	Does not measure water immiscible liquid droplets since droplets are not trapped on membrane filter
Detects any air bubbles present	Does not detect air bubbles
Less labor intensive and less subject to human error, since particles automatically counted and sized by instrument	Labor intensive and subject to human detection error, since each particle must be manually detected and sized by comparison with circles in graticule (reticle)



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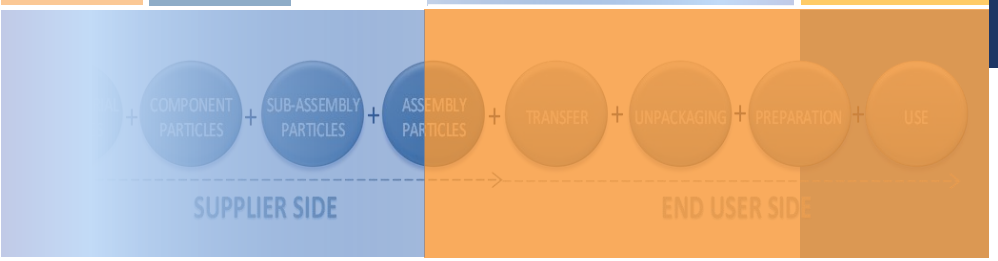
BPSA RECOMMENDATION

In summary, Method 1 and Method 2 both have significant limitations, but Method 2 is preferred. While Method 1 is quicker and easier to apply, light obscuration may not detect particles in the visible size range. Method 2 is labor intensive and subject to human error, but does detect particles in the visible size range

Type of extraction solvent	*most often purified water or buffer, with or without surfactant*
Volume of liquid applied	*relative to the surface area or interior volume*
Type of agitation	*rinsing, shaking, sonication, etc.*
Intensity of agitation	*shake frequency and number of cycles*
Time, temperature	*(varies)*
Liquid flowrate	*(varies)*

USP<788> Limitations

- Standard written for Drug Products, per ml of Drug Product
  - Small Volume
  - Large Volume Parenteral (LVP)
- Not specific to SUT,
  - *Pass-Meets USP<788>? vs Fail does not meet?*
  - *per component, surface area?*
- Extraction Protocols are very different than vials



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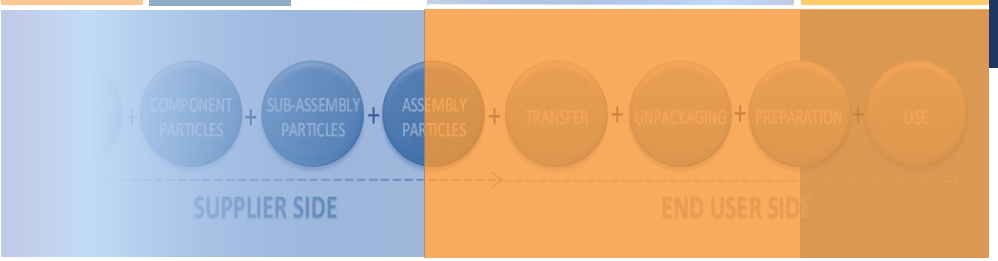
BPSA RECOMMENDATION

The BPSA recommends that suppliers of SUT implement manufacturing processes and environments that reduce the risk of particle contamination



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Part VI: Control of SUT Manufacturing Process

Control of SUT Manufacturing

- Raw components
- Cleanroom operation
- Cleanroom performance
- Manufacturing processes
- Change Management

Figure 12
ISO 7 Cleanroom Particle Counts by Week

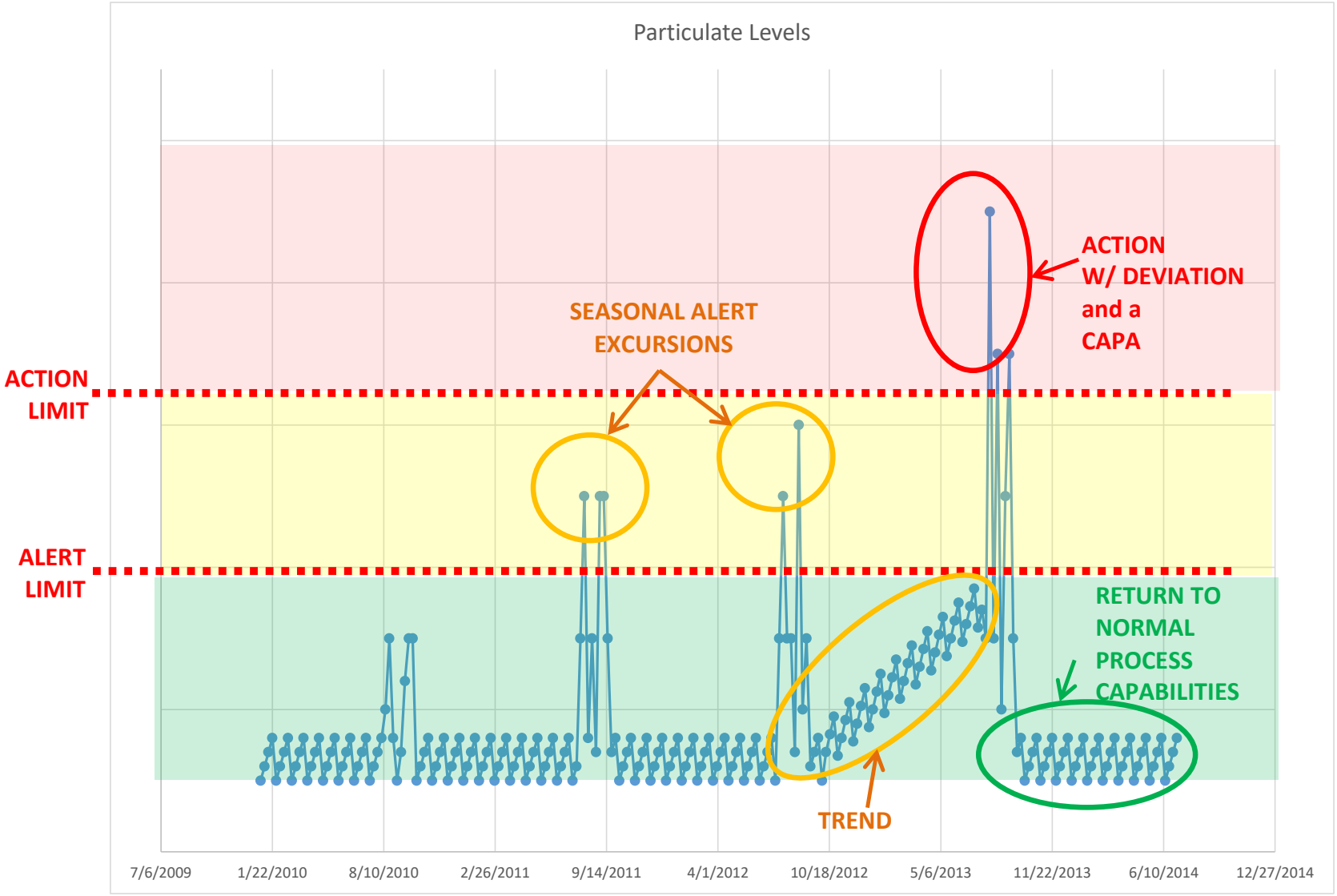
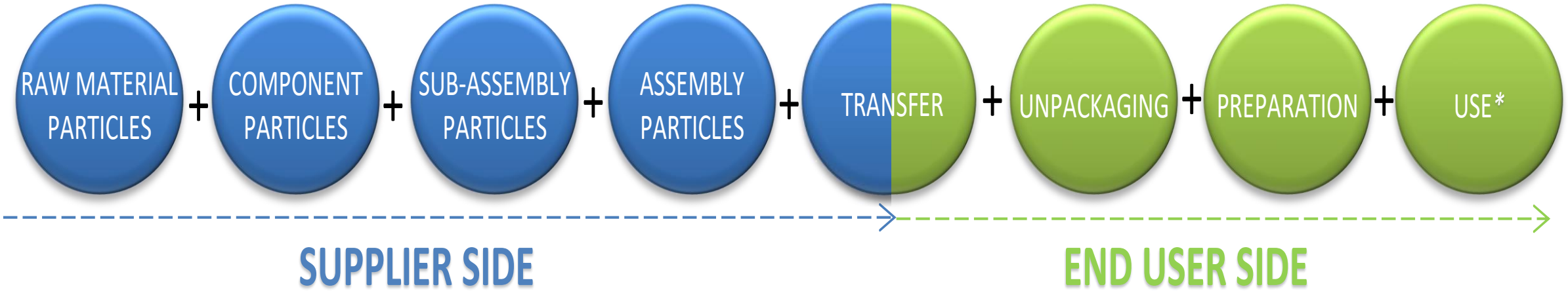
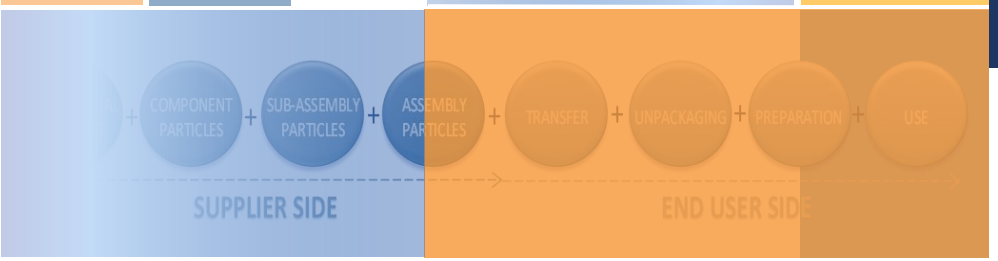


Figure 6
Potential Contributors to Particle Levels in SUT



** The use of a filter by the End User decreases the number of particles.*



2020 RECOMMENDATIONS FOR TESTING, EVALUATION, AND CONTROL OF PARTICULATES FROM SINGLE-USE PROCESS EQUIPMENT

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Part VII: Control of Biopharmaceutical Manufacturing

Table 3

Potential sources of particulates contributed by end user single-use operations

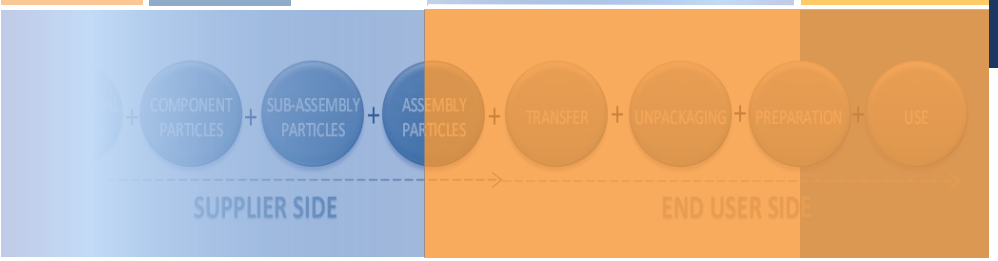
Source type	Manufacturing-induced source
Processing materials and raw material ingredients/product	Particulates from the single-use component (including final drug packaging containers) can interact with components of a protein solution to form precipitates. These can be further exacerbated by process conditions and/or type of single-use component
Manufacturing activities	Connecting and disconnecting assemblies Using fiber-shedding filters with zero-to-minimal flushing Limited use of rinsing/washing/flushing steps Valve use Pump use Onsite or site-to-site transportation conditions and containers Mismatched components, non-optimal component-equipment integration Mixing components chafing inside of container or impeller parts/bearings Rough handling Regular equipment/processing aid wear Abrasive product (e.g. undissolved aluminum salts)
Manufacturing environment	Open system applications of single-use
Personnel	Handling of SUT assembly or part(s)

12 Best Practices

1. Cover sharp parts. Do not remove supplier's protective coverings until necessary.
2. During storage, bags should be contained in a hard-shelled container or, at minimum, covered with a sealed outer bag. Lines should be secured as appropriate, especially when freezing.
3. Flush the systems, especially those that contain filters or fiber-shedding components, where possible.
4. Avoid over-processing: over-mixing or over-handling of components/assembly.
5. Avoid pulling, flattening, rubbing, squeezing, flexing, or twisting of components/assembly.
6. Optimize the welding and sealing conditions to avoid "flashing" or inadequate welds.

12 Best Practices (con't)

7. Keep product fluid contact path as short and with as few components as possible.
8. Do not lift items by their tubing connections.
9. Minimize the stress on tubing junctions. Avoid sharp bend radii.
10. Do not allow sharp objects to be used in the same area as single-use components.
11. Match peristaltic pump tubing type and dimensions to pump heads, process duration, and process fluids. Do not exceed anticipated tubing life.
12. Minimize surfaces that can rub together during shipping, storage, or use.



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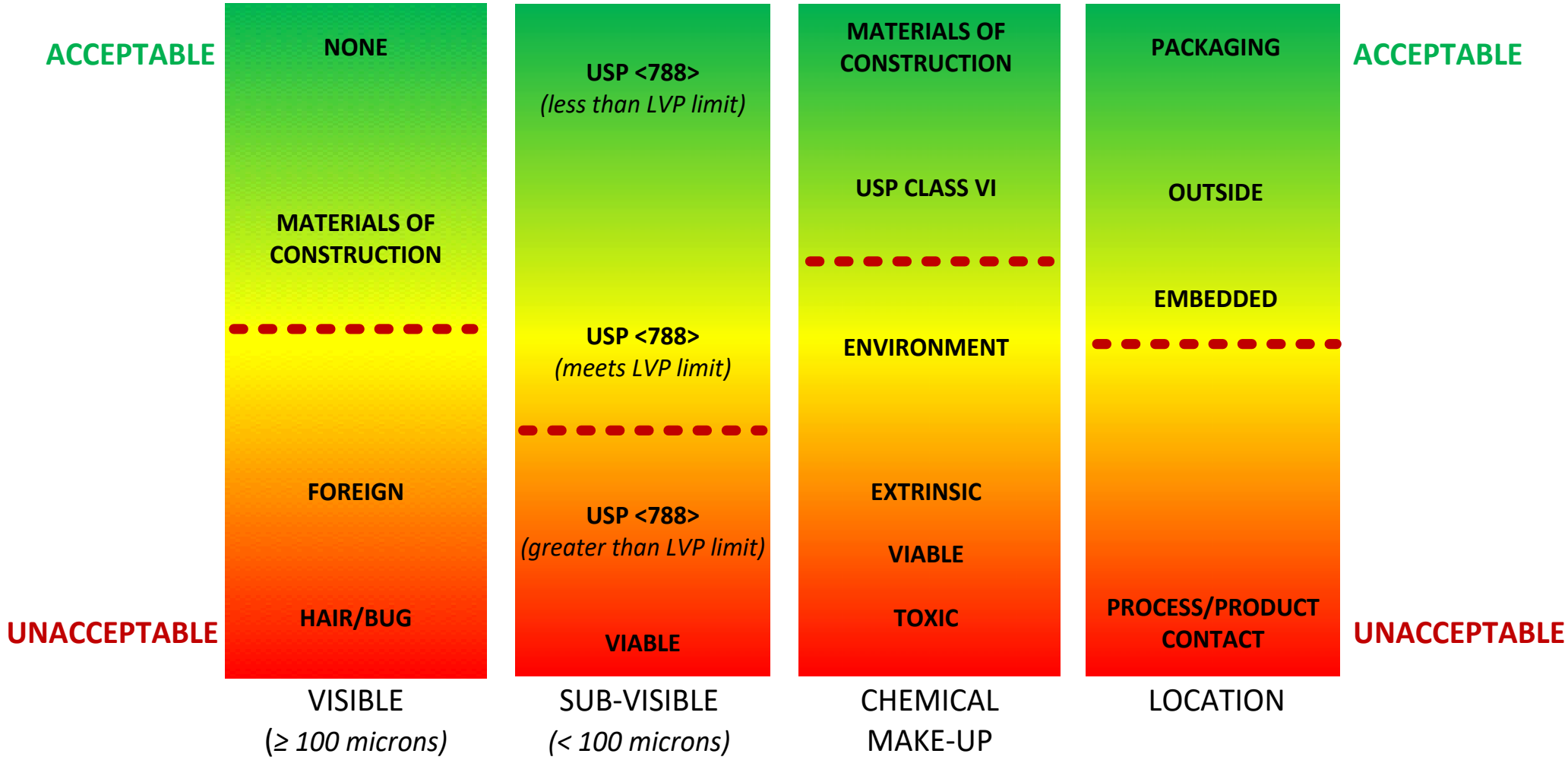
Part VIII: Deviation Response/ Mitigation Plans

Deviation Response/Mitigation Plans

- When in the SUT Lifecycle is the particulate observed?
- Where is the particle observed—on or in the SUT?
- Particle Investigation Steps

Figure 14

Example of End User/Supplier Agreement for Particulate Acceptance Criteria

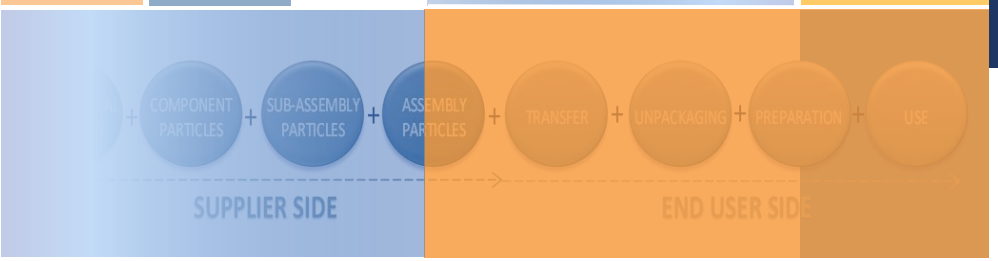


Indicates the agreement level for each application

Appendix A

BPSA User Requirement Template Information Relative to Particulates in SUT

ID	REQUIREMENT DESCRIPTION	SUPPLIER RESPONSE
18	**Endotoxin**: ☐ Aligned to USP <85> or Ph. Eur. 2.6.14 ☐ Other: _____	
19	**Visible particulates**: ☐ Aligned to USP <790>, Ph. Eur. 2.9.20 or JP 6.06 ☐ Other: _____	
	Sub-visible particulates: ☐ Aligned to USP <788>, Eur. 2.9.19, or JP 6.07 ☐ Aligned to USP <789> ☐ Other: _____	
30	**SUS manufacturing/assembly environment classification:** Requirement for the SUS to be manufactured in an environment as indicated, or in a more tightly controlled environment ☐ ISO Class 5 ☐ ISO Class 6 ☐ ISO Class 7 ☐ ISO Class 8 ☐ Controlled non-classified space ☐ Other: _____	



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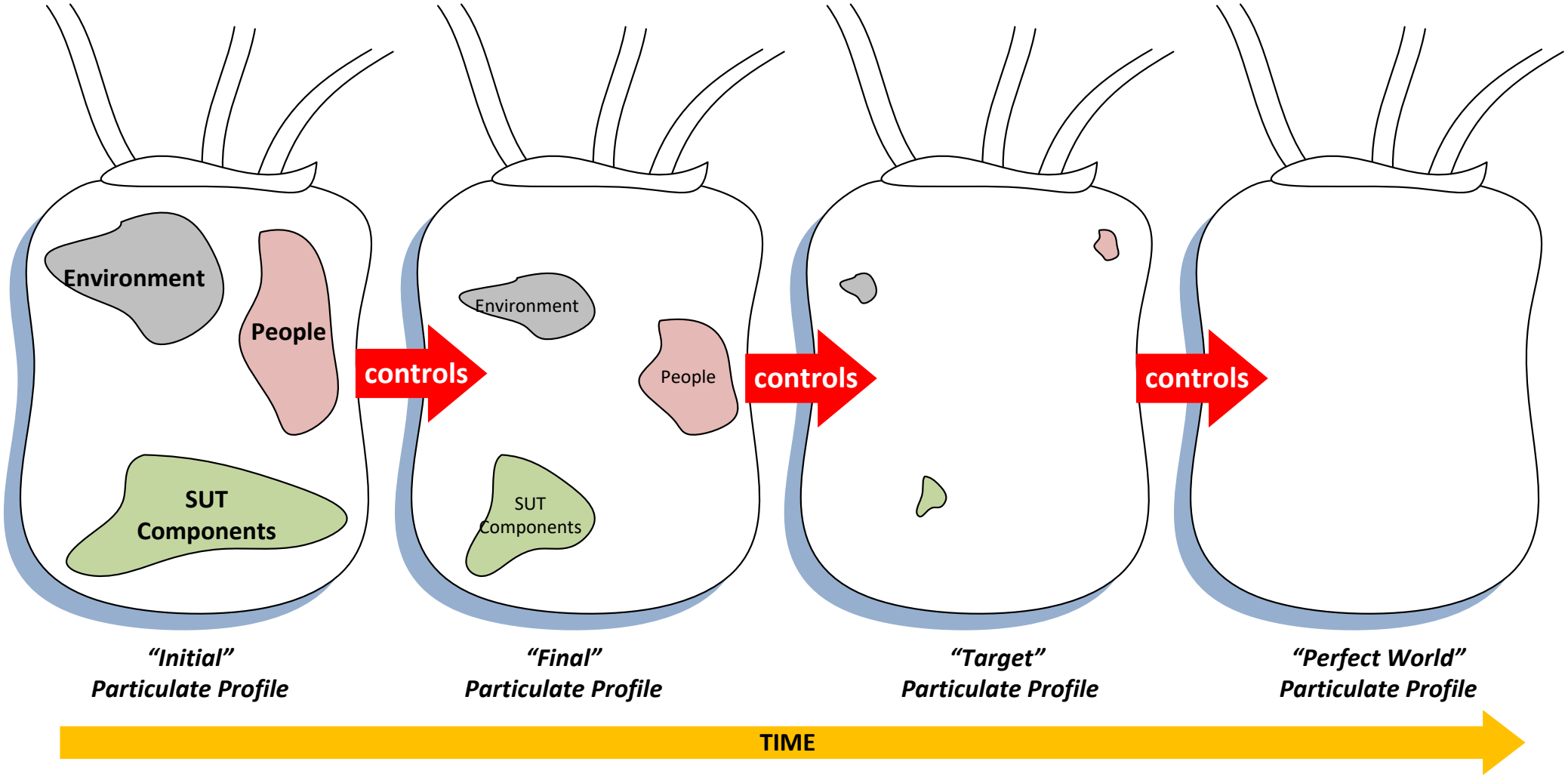
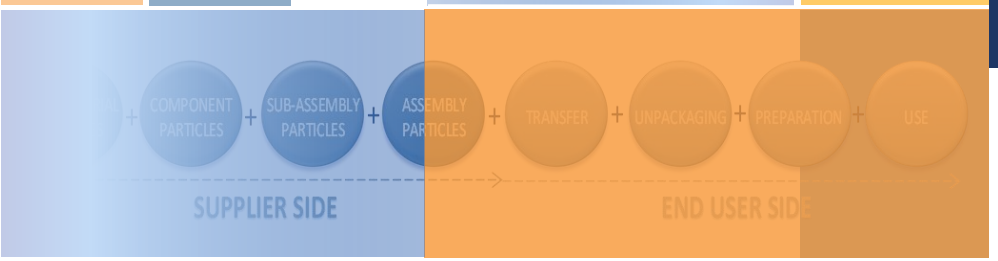
Part IX: Summary & Conclusion

Four Primary Areas that Must be Managed

1. Cleanliness of the incoming materials;
2. Cleanliness of the manufacturing steps and assembly processes;
3. Cleanliness of the operators and associated gowning; and
4. Cleanroom facility and equipment maintenance, monitoring, and controls.

Figure 13
Use of controls over time to reduce particulates





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Part X: BPSA-Recommended Next Steps

BPSA-Recommended Next Steps

1. USP <788> is not adequate for characterization of SUT.
2. Automated detection methods for visual inspection and membrane counting have promise.
3. Application-specific requirements need to be better defined (e.g. cell therapies).
4. Confidential sharing and assessment of industry progress in SUT cleanliness.
5. Particulate generation studies.
6. Acceptance Criteria
7. USP <667> Sub-Visible and Visible Particulates in Packaging and Manufacturing Components and Systems

DISCLAIMER

The information in this document is intended to capture the current state of the Single-Use-Technology Industry in regards to Particulate Control, Testing and Evaluation. The material presented herein is intended to help characterize levels and types of particles, as well as to provide methods to assure minimal levels of particulate in SUT. This information is offered in good faith and supported by the expertise of its contributors. However, BPSA, its members, and contributors do not assume any responsibility or obligation for the reader's compliance to the content of this document. This is not a standard, but a set of recommendations.

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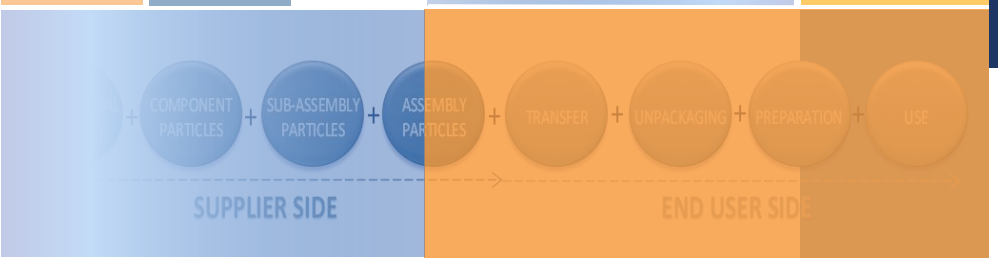
Manufacturers, suppliers and end users should consult with their own legal and technical advisors relative to their SUT use and participation. No part of this document constitutes legal advice.

About BPSA

The Bio-Process Systems Alliance (BPSA) was formed in 2005 as an industry-led corporate member trade association dedicated to encouraging and accelerating the adoption of single-use manufacturing technologies used in the production of biopharmaceuticals and vaccines. BPSA facilitates education, sharing of best practices, development of consensus guides and business-to-business networking opportunities among its member company employees.

For more information about BPSA, visit www.bpsalliance.org



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