The Role of Visual Inspection in Contamination Control

PDA Midwest Meeting 2020
Microbial Contamination and Control

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Overview

1. **Visual Inspection- Product**
2. **Container closure systems- Small and Large Volume Injections**
3. **Common defects types**
4. **Visual Inspection- the Manufacturing Environment**
5. **Control Strategy**
6. **Summary**

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Overview

1. **Visual Inspection- Product**
   - Requirements
   - Methods
2. Container closure systems- Small and Large Volume Injections
3. Common defects types
4. Visual Inspection- the Manufacturing Environment
5. Control Strategy
6. Summary

Visual Inspection- Product/Requirements

Pharmacopeia:

United States Pharmacopeia (USP)

<1> Injections and Implanted Drug Products

"each final container of all parenteral preparations should be inspected to the extent possible for the presence of observable foreign and particulate matter (herein termed visible particulates) in its contents… The inspection for visible particulates may take place during examination for other defects such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product"

Visual Inspection- Product/Requirements

Pharmacopeia:

United States Pharmacopeia (USP)

<790> Visible Particulates in Injections

- Used along with 100% inspection during the manufacturing process, this procedure is sufficient to demonstrate that the batch is essentially free of visible particulates
- Light intensity 2000-3750 lux*
- Inspection time- 10 seconds
- Background- black/white
- Acceptance criteria- ANSI/ASQ Z1.4, General inspection Level II, single sampling plans for normal inspection with an AQL= 0.65%

* Higher illumination may be required for opaque solutions/containers

Visual Inspection- Product/Requirements

Pharmacopeia:

United States Pharmacopeia (USP) related chapters

<1> Injections and Implanted Drug Products

<771> Ophthalmic Products- Quality tests

<787> Subvisible Particulate Matter in Therapeutic Protein Injections

<788> Subvisible Particulate Matter in Injections

<789> Particulate Matter in Ophthalmic Solutions

<790> Visible Particulates in Injections

<1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections

<1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions

<1790> Visual Inspection of Injections

Visual Inspection- Product/Requirements

Regulation

Food Drug and Cosmetic Act Section 501(a)(2)(B):

A drug or device shall be deem adulterated “if the methods…facilities or controls used for its manufacture, processing, packing, or holding do not conform…to current good manufacturing practice…”

Visual Inspection- Product/Methods

Manual Visual Inspection- USP<1790>

"Manual visual inspection (MVI) is the reference inspection method described in all of the major pharmacopeias. It consists of *viewing filled and sealed containers under controlled conditions*. This process may be aided by the use of a tool to allow consistent examination of more than one container at a time. The quality decisions, to either accept or reject the container, is made by a trained person. *Inspection is a probabilistic process, and detection rates <100% are to be expected, especially for smaller or low contrast defects*."

Visual Inspection- Product/Methods

Automated Visual Inspection- USP<1790>

“Automated visual inspection (AVI) combines automated material handling of the containers with electronic sensing of product appearance”

- Vision systems (camera)- physical defects (cracks, cosmetic defects), measurements (i.e. crimping), component confirmation, fill level
- Light obscuration (particulates)
- Container closure integrity (non-visual methods)- vacuum decay, electrical conductivity and capacitance, laser-based gas headspace analysis

Visual Inspection- Product/Methods

Automated Visual Inspection- USP<1790>

"Semi-automated visual inspection combines automated material handling of the containers to be inspected with human vision and judgement to make the decision to accept or reject"

- Offer consistent manipulation and presentation of the units to inspector
- Control of conditions, lighting, pacing
- Attention focused on inspection and not material handling

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1. Visual Inspection- Product
2. **Container closure systems- Small and Large Volume Injections**
   - Characteristics
   - Appearance
3. Common defects types
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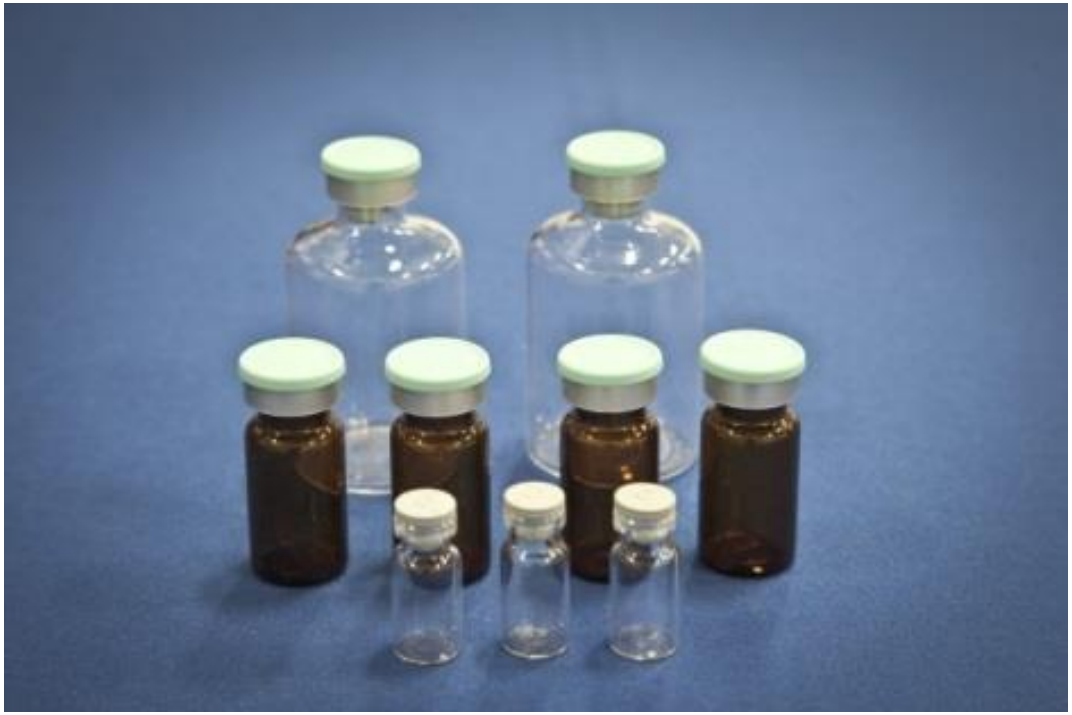
Container and Product Characteristics

- **Container appearance, (glass, plastic) - opacity, color, pattern**
- **Container physical properties- rigid, flexible, size, closures, single and multi chamber**
- **Container shape- round or cylindrical, rectangular, flat**
- **Product appearance- clarity, opacity**
- **Product physical properties- liquid, lyophilized, viscosity, foaming**
- **Secondary container**

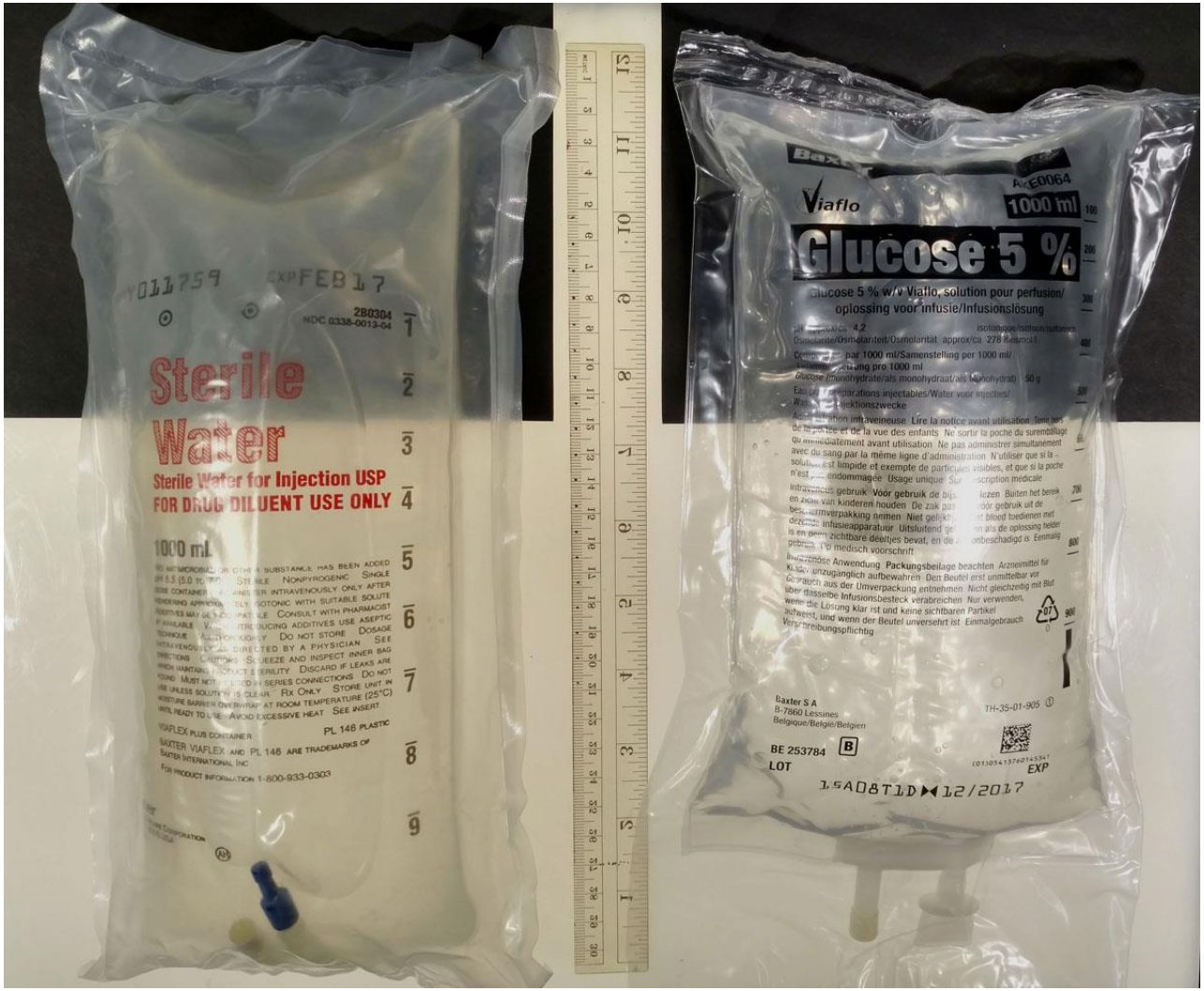
These are variables that impact detection

Containers Closure Systems – Rigid (glass)

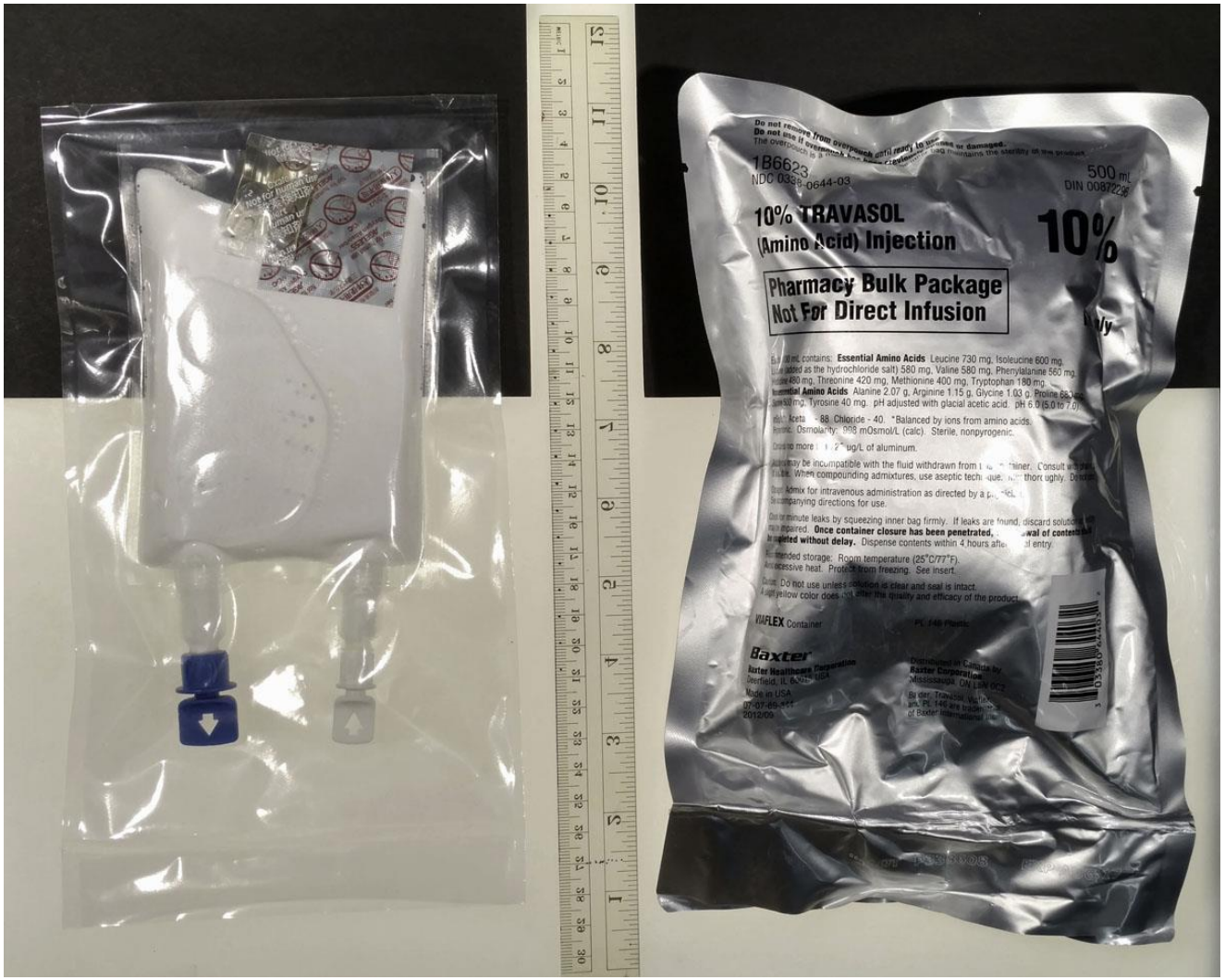


Containers Closure Systems - Flexible

Container and Product Appearances



Container and Product Appearances



Container and Product Appearances

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3. **Common defects types**
   - Definitions
   - Common defect types
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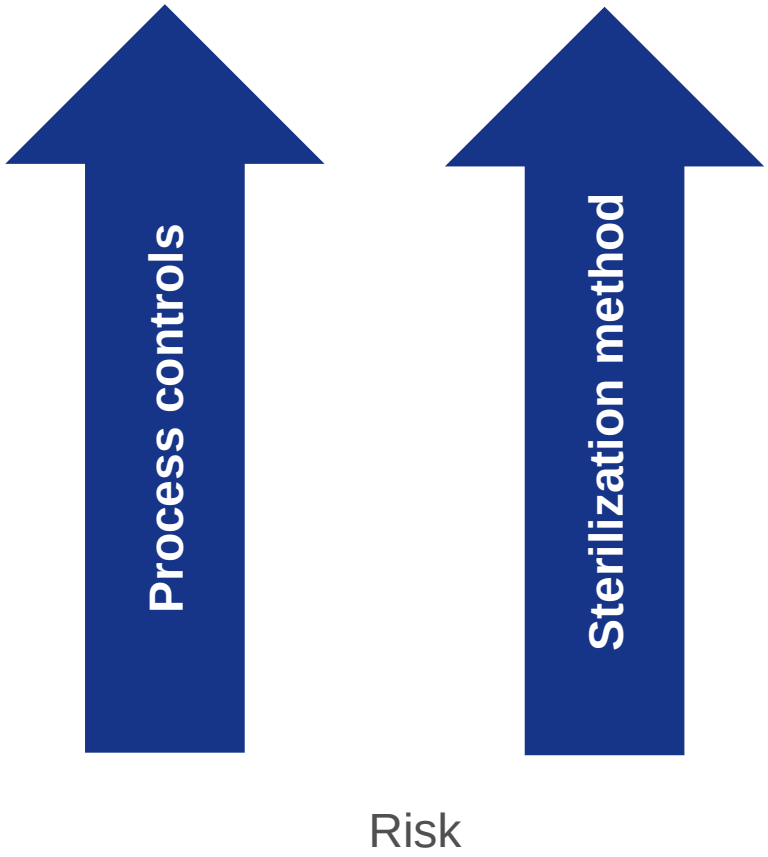
Particulate Matter Definitions

1. **Extrinsic**
   - From outside the process (uncontrolled)
   - Insect parts, hair, fibers, oxidized stainless steel
2. **Intrinsic**
   - from within the process (unplanned)
   - Primary packaging, process equipment, qualified product contact materials (e.g. stainless steel, glass, gasket, silicone oil
3. **Inherent**
   - Part of the formulation (expected and controlled)
   - Protein agglomerates

Particulate Matter

1. **Extrinsic**
2. **Intrinsic**
3. **Inherent**



Common Defect Types

- **Primary container integrity breaches**
- **Secondary (overwrap) integrity**
- **Particulate matter- visible and subvisible**
- **Illegible or incorrect labeling or print**
- **Missing component or closure**
- **Fill level**
- **Physical Dimension**

Common Defect Types

- **Container integrity breaches**
- **Overwrap integrity**
- **Particulate matter- visible and subvisible**
- **Illegible or incorrect labeling or print**
- **Missing component or closure**
- **Fill level**

For flexible containers moisture in the overpouch post-sterilization is an indication of a breach (primary or secondary container)

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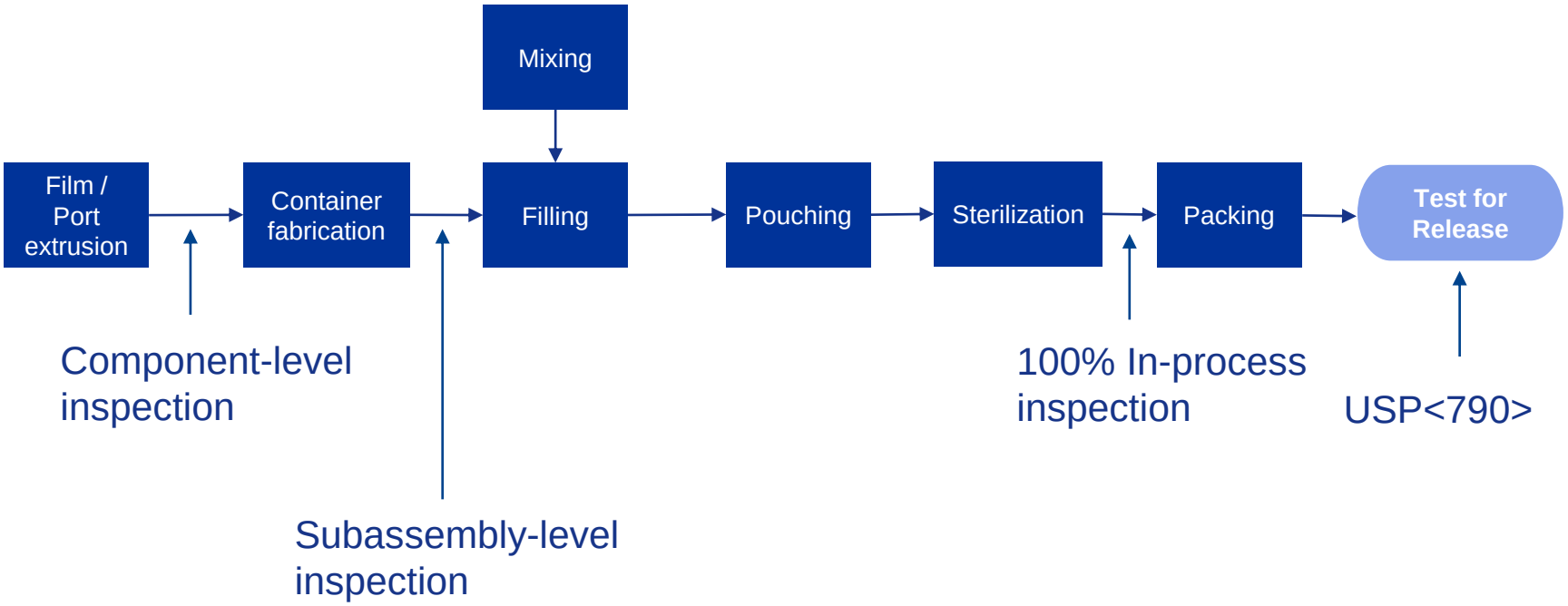
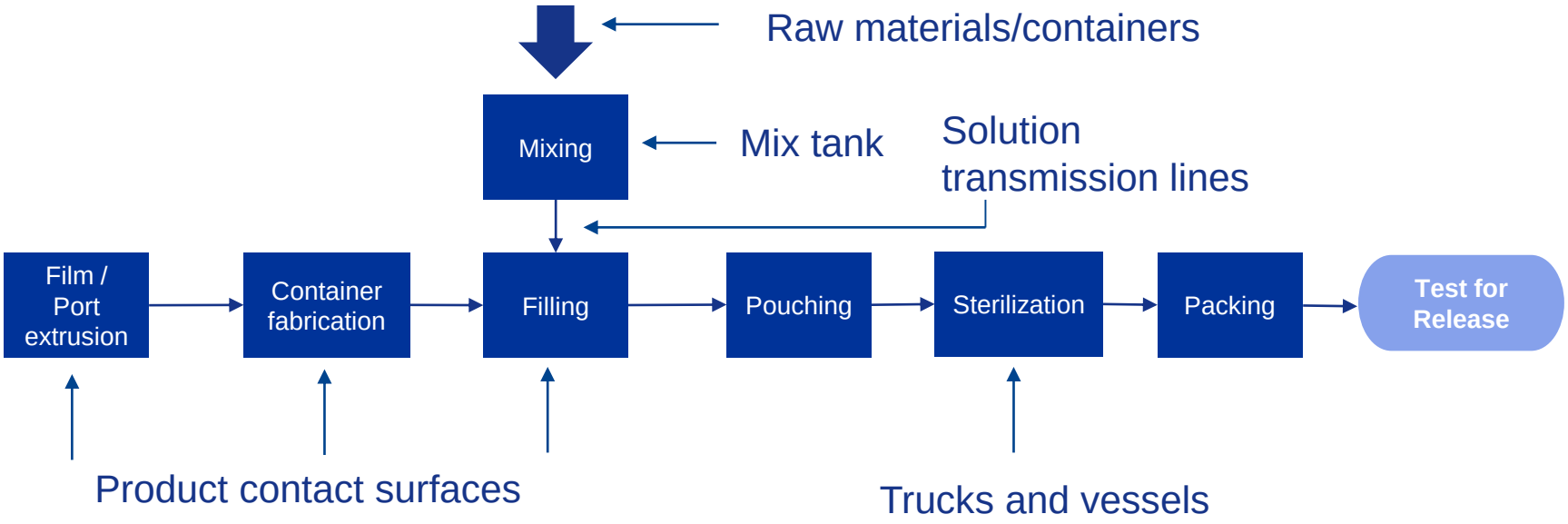
Visual Inspection- the Manufacturing Environment

Visual Inspection- **Product** (Typical Process Flow, flexible containers)



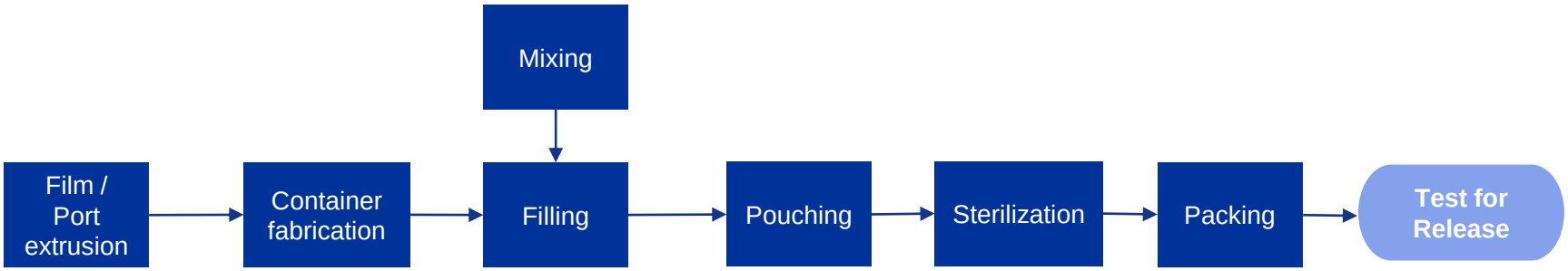
Visual Inspection- the Manufacturing Environment

Visual Inspection- **Production**



Visual Inspection- the Manufacturing Environment

Visual Inspection- **Environment**



- Garbing- condition of and proper donning
- State of cleanliness- standing water, equipment leaks
- HEPA filter checks
- State of validation- occupancy, material flow, behavior
- and many more…

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Control Strategy

Prevention is our greatest ally..

- Inspection, detection, and removal are only one element of a comprehensive control strategy
- Robust product and process design
- Environmental controls
- Defect characterization
- Trending, data review, and feedback loop to the process
- Continuous improvement

Control Strategy- Defect Characterization

Particulate Matter Analysis and Levels of Characterization

Level	Technique	Data	Level of Characterization
1	Visual Observation	morphology (size, color, shape), location of PM	Low
	Stereomicroscopy	morphology	
	Manipulation (probe)	physical characteristics (rigid, flexible, brittle)	
2	Polarized Light Microscopy	morphology, size, crystalline characteristics	
	Fourier Transform Infrared Spectroscopy	chemical composition	
	Energy Dispersive Spectroscopy	elemental composition	
	Scanning Electron Microscopy	morphology	High

Control Strategy

Particulate Matter – Standards and GMP

"Based on a rational consideration of particulate matter occurrence, the numbers of particles in product cannot be further reduced by either additional requirements or tighter limits, since these have no effect on the manufacturing process. The manufacturing process itself is our sole available control on particulate matter. Ample GMP regulations are currently in place to provide for enforcement activities against noncompliant manufacturers. ***GMP's, rather than monitoring or regulatory or compendial requirements, control particles***."

Barber, T. A. 2000. *Control of Particulate Matter Contamination in Healthcare Manufacturing*. Interpharm Press, Inc.

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Summary

- Visual inspection (in-process, AQL) remains a critical element in ensuring process control
- Inspection conditions and methods should be commensurate with the complexity of the container closure system and contents for the defect of concern
- Implementation of visual inspection at upstream process points may provide increase sensitivity to defects
- Establishment of an overarching control strategy
- Visual inspection extends beyond “formal inspection” processes and is an important function to ensure proper cleanroom operations

Conclusion

Thank You