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Particle Determination: Guidance for Parenteral Products

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<788> Particulate Matter in Injections

- Two Methods with 10µm and 25µm size thresholds for counting
  - Primary method is an optical particle counter
    - Light Obscuration (LO)
- Secondary method is filtration, membrane capture, light microscopy count
  - Membrane Microscopy (MM)

	Method 1 – LO		**Method 2 - Microscope**	
Parenteral Volume	**≥ 10 µm**	**≥ 25 µm**	**≥ 10 µm**	**≥ 25 µm**
SVI 100 mL and lower	6000 (per container)	600 (per container)	3000 (per container)	300 (per container)
LVI above 100 mL	25 (per mL)	3 (per mL)	12 (per mL)	2 (per mL)

<788> Particulate Matter in Injections

Revision Topics

- Particulate Matter Type: Inherent (part of the formulation)
  - Protein agglomerates, Suspension, Microparticles
- New specification for Large Volume Parenteral (LVP)
  - Difference between the Small Volume Parenteral (SVP) and LVP specifications

	Method 1 – LO		Method 2 - Microscope	
Parenteral Volume	**≥ 10 μm**	**≥ 25 μm**	**≥ 10 μm**	**≥ 25 μm**
SVP 100 mL and lower	6000 (per container)	600 (per container)	3000 (per container)	300 (per container)
LVP above 100 mL	25 (per mL)	3 (per mL)	12 (per mL)	2 (per mL)

- Potential for a greater total particle load in the LVP case.
  - Example, at 240mL LVP could exceed the SVP ≥10μm limit and be acceptable based on current LVI limits.
- A ceiling (container-based) limit for LVP's similar to that of SVP's

	25/3 per mL
Product (mL)	Current Limit/Unit
100mL	2500/300
125mL	3125/375
150mL	3750/450
200mL	5000/600
240mL	6000/720
250mL	6250/750
500mL	12500/1500
1000mL	25000/3000

<788> Particulate Matter in Injections

Revision Topics

- Eliminating requirement for pooling SVP samples for the Microscopic Test
  - The Microscopic Test currently requires pooling the contents of 10 or more containers for SVP's less than 25 mL
    - Similar to Method 1
  - This requirement is not necessary for the Microscopic Test
- Alternative sample preparation
- Smaller sampling volumes
- Alternate Methods, e.g. Flow Imaging Analysis
- More guidance on for products that are not amenable to <788> Testing
  - Suspension, Microparticles, etc.

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

- Provides LO calibration and control guidance removed from <788> after harmonization
  - Instrument Standardization Tests
    - Flow Rate
    - Volume Accuracy
    - Calibration
    - Sensor Resolution
    - Particle Counting Accuracy
- Provides LO calibration and control guidance removed from <788> after harmonization
- Provides microscopy setup and counting guidance
- Provides discussion regarding pharmaceutical development practices

<787> Subvisible Particulate Matter in Therapeutic Protein Injection

Scope and Purpose

- This chapter can be used as an alternative to *USP* general chapter *Particulate Matter in Injections* <788>.
- It specifically addresses therapeutic protein injections and related preparations, allowing use of:
  - Smaller test product volumes
  - Smaller test aliquots to determine particulate matter content
  - Sample-handling instructions that take into account the issues associated with the analysis of these materials.

<787> Subvisible Particulate Matter in Therapeutic Protein Injection

Highlights

- Dilution is allowed as long as the diluent and methods are demonstrated to be appropriate and the smallest level of dilution that allows for reproducible testing is used
- Specifications same as <788>
  - Limits for > 10 and > 25 µm
  - All sections written assuming measurements below10 µm
- Products that are used with a final filter during administration (in-line) are exempt from these requirements, providing that scientific data are available to justify the exemption

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

Highlights

- Describes the strengths and limitations of specific methods for characterizing protein particle populations between 2 and 100 µm
- Methods that allow assessment of characteristics of the inherent protein aggregates including morphology, conformation, reversibility/dissociation, and covalent modification
- Since the monitoring of the sub-10µm population may be an important product quality parameter, collection of data in the ***2-10 µm range (e.g. 2-5 µm and 5-10 µm) is recommended***
- Focuses on the enumeration, characterization, and when possible, identification of inherent particles, distinguishing them from extrinsic and intrinsic particles

<1787> Methodologies Useful in Measuring Properties of Subvisible Particles

Section I: Size and Distribution		
Technique	Principle of Operation	Range
Light obscuration	The size of the particle in the product fluid is determined by the amount of light that it blocks when passing between the source and the detector.	1–300 µm
Electrical sensing zone (Coulter)	The size of the particle in the product fluid or selected electrolyte is measured in terms of the change in resistance as the particle passes through a micro-channel (orifice).	0.4–1600 µm
Laser diffraction	The size of the particles in product fluid or dilution is determined by measuring the angle of the scattered light.	0.1–3500 µm

<1787> Methodologies Useful in Measuring Properties of Subvisible Particles

Section II: Size and Morphology		
Technique	Principle of Operation	Range
Light microscopy <776>	Photon imaging of substances directly in product fluids or mounts, or of isolated specimens on substrates	0.3 µm to 1 mm
Flow imaging analysis	Digital image capture of the particles' magnified image in streaming product fluid, revealing size, shape, and optical properties	0.7–100 µm for size distribution; 4–100 µm for morphology
Electron microscopy (EM): Scanning EM, scanning transmission EM, and transmission EM <1181>	Electron imaging of specimen isolates on substrates. A high vacuum or near-ambient pressure is required.	Angstroms to mm

<1787> Methodologies Useful in Measuring Properties of Subvisible Particles

Section III: Characterization		
Technique	Principle of Operation	Range
Fourier Transform Infrared (FTIR) microspectroscopy <197>	Photon imaging of isolated specimens on substrates utilizing mid-IR spectral detection	10 µm to 1 mm
Dispersive-Raman microspectroscopy <1120>	Photon imaging of isolated specimens on substrates, or in product fluids or fluid mounts utilizing Raman shift detection	0.5 µm to 1 mm
Electron microscopy (EM) with energy-dispersive X-ray spectrometry (EDX) <1181>	X-ray photon emission from specimens energized by a focused electron beam	Å to mm for imaging; 1 µm to 1 mm for elemental composition
Electron microscopy (EM) with electron energy loss spectroscopy (EELS)	Inelastic scattering from specimens energized by a focused e-beam; e-loss is characteristic of the source element; complementary to EDS	Å to mm for imaging; 0.5 µm to 1 mm for elemental composition
Time of Flight Secondary Ion Mass Spectrometer (TOF-SIMS)	Identification of particles according to their mass spectral profile	µm to near mm

Analytical Gaps and Challenges for Particles in the Submicrometer Size Domain

Scott Aldrich, Shawn Cao, Andrea Hawe, Desmond Hunt, Dean Ripple, Satish K. Singh

ABSTRACT This *Stimuli* article provides a technical discussion of the available technologies for submicrometer particle analysis, including consideration of the advantages, disadvantages, and technical gaps for each application. These methods can be used in the characterization of different protein aggregates as well as other types of particles in this size range. Changes are occurring rapidly in this field, so the *Stimuli* article and discussions focus on measurement principles and comparisons rather than specific instruments.

Visible Particulate

<1> Injections and Implanted Drug Products (Parenterals) — Product Quality Tests

- Foreign and Particulate Matter

  Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed “visible particulates”) in its contents. The inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates *Visible Particulates in Injections <790>.*

<790> Visible Particulates in Injections

- Inspection conditions defined
  - Harmonized with Ph. Eur.
  - 2,000-3,750 lux
  - Black and white backgrounds
  - No magnification
  - 5 sec viewing against each background
  - Swirl and/or invert sample
- Applies to Extrinsic and Intrinsic particles
- Inherent particles addressed in individual monographs or approved regulatory filings

<790> Visible Particulates in Injections

Acceptance Criteria

- At Time of Batch Release
  - 100% inspection followed by acceptance sampling
  - ANSI/ASQ Z1.4-2003 or ISO 2859
  - AQL= 0.65%
  - Alternate and equivalent plans acceptable
- For Product in Distribution
  - n = 20, a = 0
  - AQL= 0.26%

<790> Visible Particulates in Injections

Other Considerations

- A smaller sample (such as the Special sampling plans in the standards) is appropriate for destructive testing of powders and suspensions
- This chapter does not add a new requirement for stability testing
- Alternative light sources such as LEDs are acceptable
- The light intensity range stated is intended to establish a lower limit of 2,000 lux, but it may be appropriate to inspect at levels above 3,750 lux
- Alternative methods and conditions are permitted, but should be shown to be comparable or better in performance

<1790> *Visual Inspection of Injections*

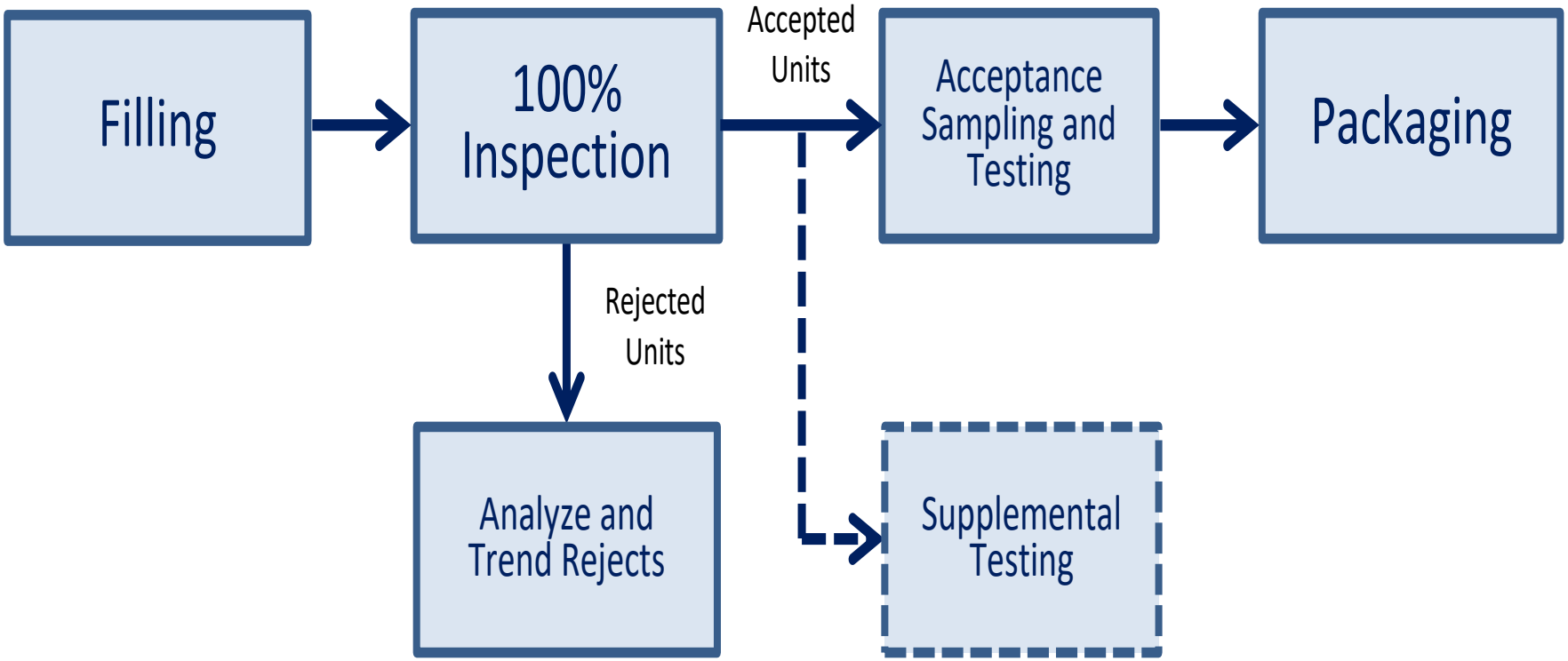
- **Draft Information Chapter**
  - Published for comment in PF 41(1) January 2014
  - Published for comment in PF 42 (6) December 2015
  - Target Official Date: May 1, 2017
- **Contents**
  - Patient Risk
  - Typical Inspection Process Flow
  - Elements of a good inspection process
  - Inspection Lifecycle / Continuous Improvement
  - Interpretation of Inspection Results
  - Inspection Methods and Technologies
  - Qualification and Validation of Inspection Processes

<1790> *Visual Inspection of Injections*

- Scope
  - Inspection for visible particles in filled, sealed containers
  - Applicable to detection and removal of other visible defects e.g. container integrity
  - Primary focus is manual inspection methods, but semi-automated and automated methods are discussed

<1790> *Visual Inspection of Injections*

- Typical Process Flow



Acceptance Sampling

- ANSI/ASQ Z1.4 Sampling Plans
  - General Normal Level II
  - Recommends Tightened Plans when atypical results are observed
- Typical AQL Values
  - Critical 0.010-0.10%
  - Major 0.10-0.65%
  - Minor 1.0-4.0%

Remediation and Alternative Practices

- Re-inspection
  - Repeat of 100% inspection after failure to meet acceptance criteria
- Two-Stage Inspection
  - First stage inspection (often automated) set to accept only good product. Those of uncertain status are separated from the batch and inspected by another method (often manual). Those determined to be acceptable by the second inspection are returned to the batch
  - Used to address high false reject rates which can occur with automated inspection systems and certain product formulations and package types

<1790> *Visual Inspection of Injections*

Preventions

- Inspection Lifecycle
  - Continuous Process Improvement
- Robust Design
- Common Sources of Intrinsic Particles
  - Formulation
  - Packaging Components
  - Processing
- Trending
  - Establishing Alert and Action Levels
  - Periodic review and update

<1790> *Visual Inspection of Injections*

Interpretation

- Defect Classification
  - Critical / Major / Minor
  - Extrinsic / Intrinsic / Inherent
- Unique Product Considerations
  - Lyophilized Products
  - Powders
  - Suspensions
  - Emulsions
  - Amber Containers
  - Translucent Plastic Containers
  - Large-volume Containers
  - Combination Products

Methods and Technologies

- Manual Visual Inspection (MVI)
  - Critical Process Parameters
    - Light intensity
    - Background and contrast
    - Inspection rate
    - Container handling and movement
- Semi-Automated Visual Inspection
  - Critical Process Parameters
    - See MVI
    - Machine parameters
      - Spin speed
      - Rotation rate

Methods and Technologies

- Automated Visual Inspection (AVI)
  - Light Obscuration Methods
  - Imaging Methods
  - Other Technologies
    - Container Integrity / Leak Detection
    - X-ray

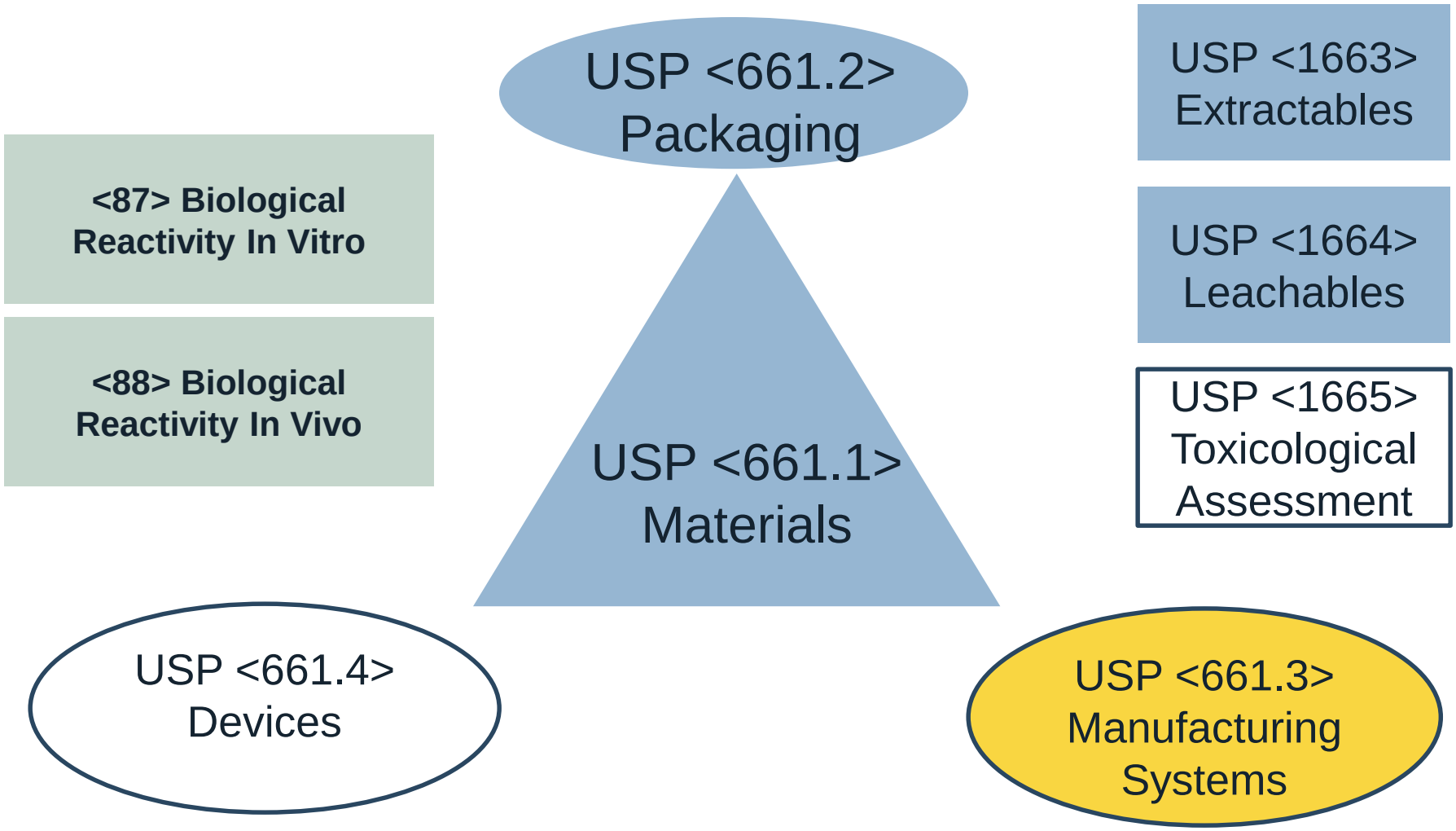
<1790> *Visual Inspection of Injections*

Qualification and Validation

- Standards
  - Preparation
  - Particle Types
  - Defect Rates
  - Test Sets
- Training and Qualification of Human Inspectors
  - Qualification Requirements
  - Requalification

Plastic Components and Systems Used to Manufacturer Pharmaceutical Drug Product

USP Chapters Related to Plastic Materials and Systems: Vision



<661.3> Plastic Components and Systems Used to Manufacturer Pharmaceutical Drug Product

Objective

1. To provide tests and specifications for the characterization of plastic materials so that plastic materials used in manufacturing can be rationally selected for use and so that the selection can be justified, and
2. To provide tests and specifications for the safety qualification of manufacturing, packaging and delivery systems (or components thereof).

Scope

The qualification of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical APIs and DPs.

- Chapter is applicable solely to those components that involve liquid process streams and process intermediates that are expected to have some degree of interaction with liquids.

<661.3> Plastic Components and Systems Used to Manufacturer Pharmaceutical Drug Product

Scope

- The qualification of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical APIs and DPs
- Applicable solely to those components that involve liquid process streams and process intermediates that are expected to have some degree of interaction with liquids
- Single-use systems (SUS) and multiple-use systems (MUS)

Initial Assessment

- Initial assessment examines whether there are factors present that would support the conclusion that the plastic components and systems are fit for their intended use without further characterization
  - Demonstration of equivalence with a comparator component or system would allow acceptance of the component without further characterization
    - Equivalence in purpose and composition of component or system
    - Equivalence in composition of DP(s)
    - Equivalence in processing conditions
    - Equivalence in product dosage form

<661.3> Plastic Components and Systems Used to Manufacturer Pharmaceutical Drug Product

Risk Assessment

- Determine the level of Risk via a risk assessment matrix.
  - Low (Level A)
  - Moderate (Level B)
  - High (Level C)

Risk Level	Dosage Forms	Characterization of Plastic Components or Systems
A	Low-risk dosage forms, e.g., solid oral and liquid oral, where the liquid process stream is part of the manufacturing process for either APIs or DPs	Baseline Assessment
B	Dosage forms other than solid oral and liquid oral	Expanded Baseline Assessment
C	Dosage forms other than solid oral and liquid oral	Full Assessment

<661.3> Plastic Components and Systems Used to Manufacturer Pharmaceutical Drug Product

Testing

- Biological Reactivity
- Physicochemical Test
  - Material and Component Extraction
    - Extraction Conditions

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Questions

Thank You