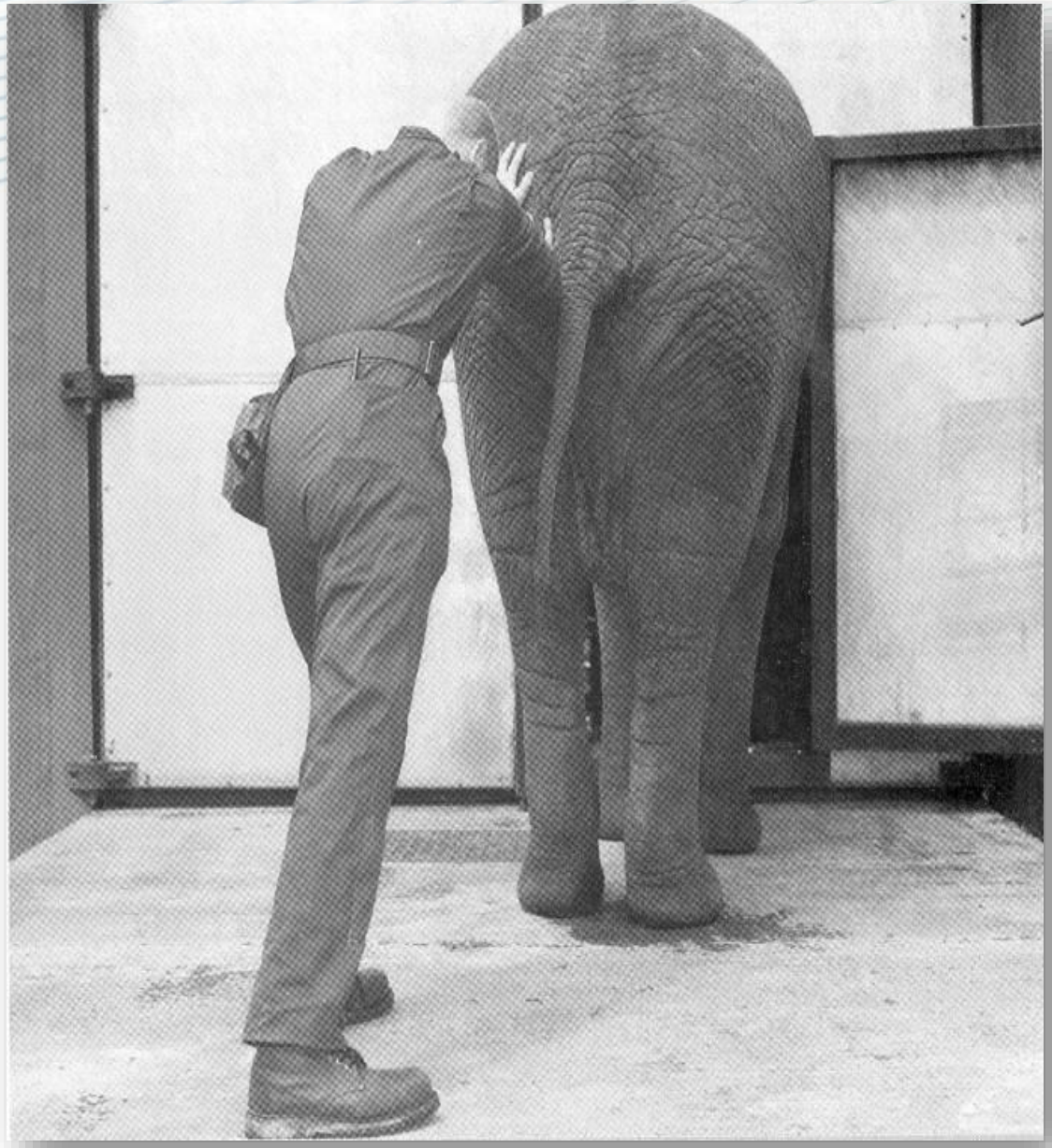
Visual Inspection of Injectable Products:

More than Sorting Good from Bad …

John G. Shabushnig, Ph.D.
Insight Pharma Consulting, LLC
insight!
johnshabushnig@aol.com
October 2021

Agenda

- Patient Risk / Foreign Matter Concerns
- US FDA
- US Pharmacopeia (USP)
- EC GMP's
- European Pharmacopeia (EP) / Pharm Eur
- Other Standards



Why inspect?

Why Inspect?

- Patient Risk
  - Physiological Implications
  - Chemical and Microbiological Implications
- Compendial Requirements
- Regulatory Requirements
- Process Knowledge and Continuous Process Improvement

Particulate Matter Concerns

- Patient Risk Factors to Consider:
  - Particle Size
    - Is the size in the range that will pass through the needle?
  - Quantity
    - Many vs. Single
  - Composition
    - Single 100 µm particle in 1mL dose is equivalent to an impurity level of 4 ppm (v/v)
      - Generally not a tox concern
    - Extrinsic vs. Intrinsic
    - Inert?
    - Biological?

Particulate Matter Concerns (cont.)

- Sterility
  - Extrinsic vs. Intrinsic
  - Aseptic Process vs. Terminal Sterilization
- Duration of Exposure
  - Chronic vs. Single Dose
- Route of Administration
  - IV vs. IM vs. Sub-Q
  - Intrathecal, Intraocular
- Antigenic Potential
  - 1-10µm protein particles
- Intended Patient Population
  - Infant vs. Adult
  - Compromised vs. Healthy

Particulate Size Ranges

<100 nm	100 - 1,000 nm	1 - 100 µm	>100 µm
Nanometer	Sub-micron	Sub-visible	Visible

- SEC (Size Exclusion Chromatography)
- FFF (Field Flow Fractionation)
- SDS-Page Gels
- AUC (Analytical Ultra-Centrifugation)

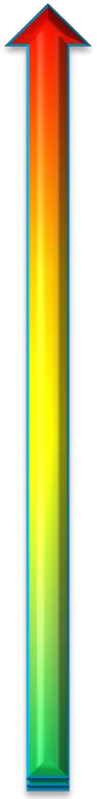
- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter

- Manual / Human
- Semi-Automated
- Automated

Narhi, et al. J Pharm Sci, 2012

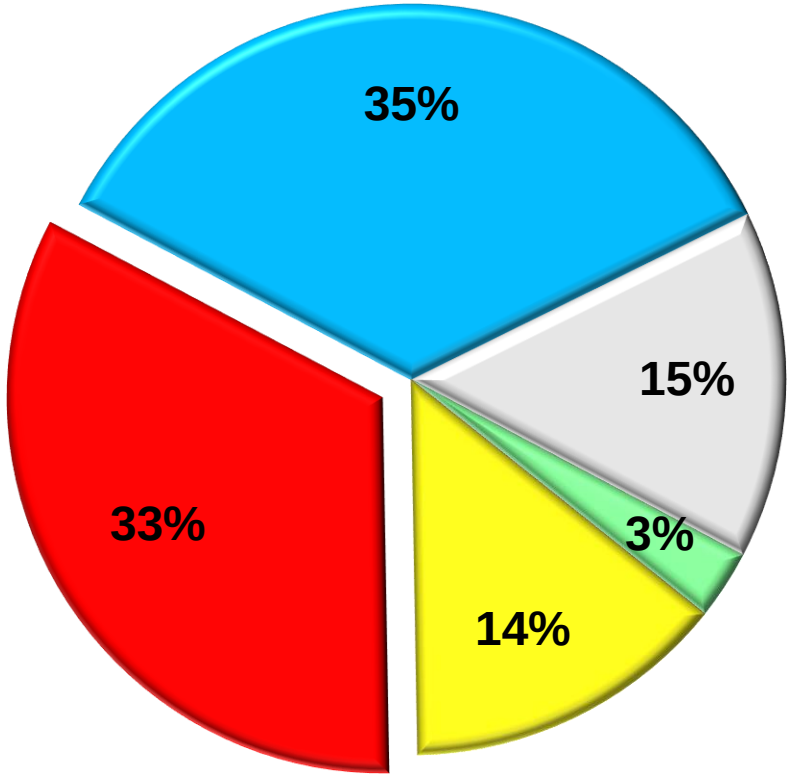
Particulate Matter Definitions

- Extrinsic (from outside the process, uncontrolled)
  - Environmental Contaminants
    - insect parts, hair, fibers, paint, rust
- Intrinsic (from within the process, unplanned)
  - Processing Equipment, Primary Package
    - qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)
- Inherent (part of the formulation, controlled and expected)
  - Protein agglomerates



RISK

FDA Sterile Injectable Drug Recall Notices 2017-2021

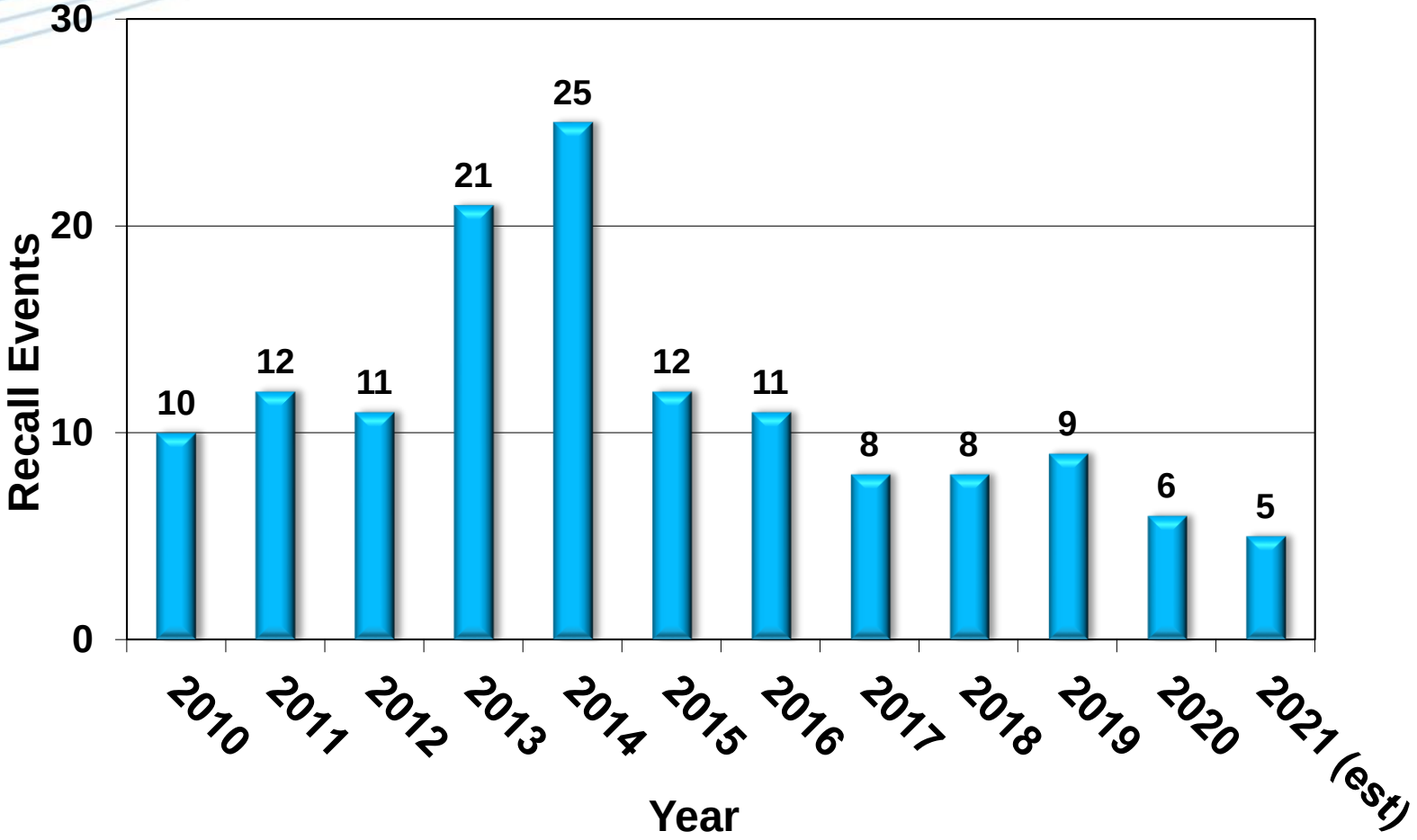


- Visible Particles
- Lack of Sterility Assurance
- Labeling
- Container
- Other*

* Incl. incorrect potency or dose, discoloration, impurities/degradation products and storage temp excursions.

Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

Visible Particulate Recall Notices



Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

Recent FDA Recalls

- 1-8-2019 Sun Pharmaceutical Industries, Inc. Issues Voluntary Nationwide Recall of Vecuronium Bromide for Injection Due to the Presence of Particulate Matter Identified as Glass
  - Glass particles
- 1-5-2019 Lupin Pharmaceuticals, Inc. Issue Voluntary Recall of Ceftriaxone for Injection USP, 250mg, 500mg, 1g and 2g
  - Rubber particles
- 6-4-2018 Hospira Issues a Voluntary Nationwide Recall for Two Lots of Naloxone Hydrochloride Injection, USP, in the Carpuject™ Syringe System due to the Potential Presence of Particulate Matter
  - Loose and embedded particles
- 1-16-2018 Baxter Expands Voluntary Nationwide Recall to Include Second Lot of Nexterone Injection Due to Presence of Particulate Matter
  - Polyethylene particles

US FDA 483 Themes

- Must establish a maximum allowable reject rate.
- Must control reinspection of product, including when appropriate, inspection conditions and number of reinspections permitted.
- Inspectors must be trained and training documented.
- Inspectors must be periodically recertified.
- Training and certification conditions must align with routine 100% inspection conditions.
- Address inspection fatigue during qualification.

US FDA 483 Themes

- Must conduct thorough investigations. Identify particulate matter when performing investigations.
- Must use statistically sound sampling plan(s) for AQL inspection.

US FDA FD&C Act

- Food Drug and Cosmetic (FD&C) Act
  - 501(a)(1): “if it consists in whole or in part of any filthy, putrid, or decomposed substance”
  - 501(a)(2)(A): “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health”
  - 501(a)(2)(B): “if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice”

US FDA CFR

- Code of Federal Regulations (CFR)
  - 21 CFR 211.94 Drug Product Containers and Closures
    - (a) Drug product containers and closures shall not be reactive, additive, or absorptive …
    - (b) Container closure systems shall provide adequate protection …
    - (c) Drug product containers and closures shall be clean …
  - 21 CFR 211.165 Testing and Release for Distribution
    - (f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

US FDA Compliance Program Guidance Manual 7356.002A

- 100% Inspection of Injectable Products
  - Verify written procedures that define the defects removed and actions taken if the number of critical defects exceeds a pre-determined level.
  - Defect categories should be identified. Results of inspection of each batch should be compared to established levels.
  - Evaluate appropriateness of pre-determined action levels.
  - Evaluate firms investigations, including units rejected for cracks and visible particulates.

US FDA Compliance Program Guidance Manual 7356.002A

- Observe the inspection process.
- Challenge inspection rates through observation.
- Evaluate adequacy of written procedures.
- Evaluate personnel qualification and requalification and equipment qualifications. Evaluate personnel qualification including the use of reference samples.
- Evaluate the firm's program for sampling and examination of inspected vials.
- Evaluate the firm's assessment of units rejected during filling or any separate inspection prior to 100% inspection, established alert/action limits and investigations where appropriate.

US FDA Compliance Program Guidance Manual 7356.002A

- The following list of deficiencies represents examples of practices that CDER believes could warrant regulatory and/or administrative action:
  - Failure to provide adequate training to employees who work in critical operations, such as … those who perform the 100% inspection of filled injectable products.
  - Failure to perform adequate 100% inspection of injectable products for particulate matter and other defects.

Pharmacopeial Requirements

	USP <790>	EP 2.9.20	JP 6.06
Illumination Intensity (lux)	2,000-3,750	2,000-3,750	2,000-3,750 lux (8,000-10,000)*
Inspection Time (sec)	10 sec	10 sec	10 sec
Background	Black/White	Black/White	Black/White
Acceptance Criteria	"essentially free from visible particulates" ANSI/ASQ Z1.4 AQL=0.65%	"clear and practically particle-free"	"free of readily detectable foreign insoluble matter"

* Illumination intensity for plastic containers

United States Pharmacopoeia USP 43

- USP <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
  - Foreign and particulate matter: Articles intended for parenteral administration should be prepared in a manner designed to exclude particulate matter … Each final container of all parenteral preparations should 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 should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates …

United States Pharmacopoeia USP 43

- USP <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
  - Qualification of the inspection process should be performed with reference to particulates in the visible range and those particulates that might emanate from the manufacturing or filling process. Every container in which the contents show evidence of visible particulates must be rejected. The inspection for visible particulates may take place during examination for other critical defects such as cracked or defective containers or seals or when characterizing the appearance of a lyophilized product.

United States Pharmacopeia USP 43

- USP <790> *Visible Particulates in Injections*
  - Inspection conditions defined
    - Harmonized with EP
    - 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

USP <790> Acceptance Criteria

- At Time of Batch Release
  - 100% inspection followed by acceptance sampling
  - ANSI/ASQ Z1.4 or ISO 2859
  - AQL= 0.65%, UQL= 2.3-3.3% typical
  - Alternate and equivalent plans acceptable
- For Product in Distribution
  - n = 20, a = 0
  - AQL= 0.26%, UQL= 10.9%

USP <790> Acceptance Criteria

- Supplemental Inspection
  - Where the nature of the contents or the container–closure system permits only limited capability for inspection of the total contents, the 100% inspection of a batch shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container, suspensions, highly colored liquids) contents of a sample of containers from the batch. The destructive nature of these tests requires the use of a sample smaller than those traditionally used for non-destructive acceptance sampling after 100% inspection.

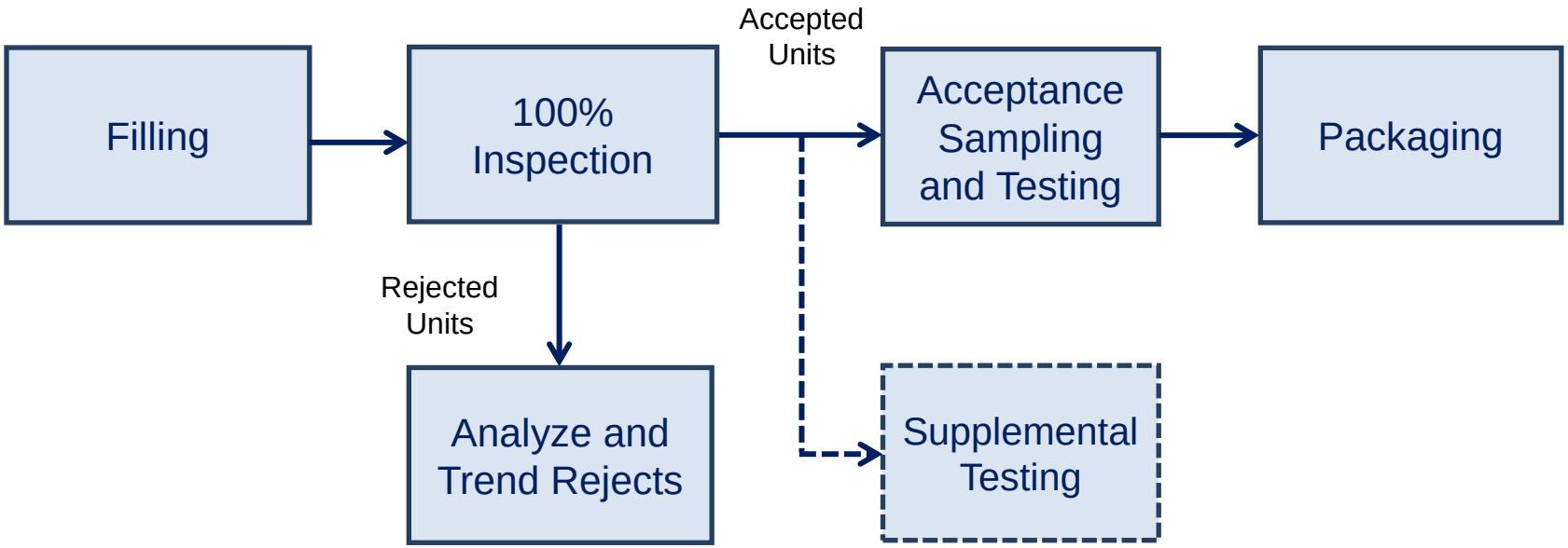
USP <790> Acceptance Criteria

- At Time of Batch Release
  - 100% inspection followed by acceptance sampling
  - ANSI/ASQ Z1.4 or ISO 2859
  - AQL= 0.65%, UQL= 2.3-3.3% typical
  - Alternate and equivalent plans acceptable
- For Product in Distribution
  - n = 20, a = 0
  - AQL= 0.26%, UQL= 10.9%

USP <1790>

- <1790> *Visual Inspection of Injections*
  - Information Chapter
  - Key elements of an inspection process
    - Patient Risk
    - Elements of a good inspection process
    - Lifecycle / Continuous Improvement
    - Visible Defect Types
      - Extrinsic, Intrinsic and Inherent
    - Inspection Technologies
  - Published in USP 40 1st Supplement
    - Official Aug 2017

USP <1790>



Other USP Related Chapters

- Related Chapters
  - <771> *Ophthalmic Products – Quality Tests*
  - <787> *Subvisible Particulate Matter in Therapeutic Protein Injections*
  - <788> *Particulate Matter in Injections*
  - <789> *Particulate Matter in Ophthalmic Solutions*
  - *<1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections*
  - <1788> *Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions*

EC GMP Annex 1 / WHO Annex 6

- Finishing of Sterile Products

  EC 124 / WHO 11.3. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. …

EC GMP Annex 1 / WHO Annex 6

- Finishing of Sterile Products

  EC 124 / WHO 11.3. … Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Proposed Revisions to Annex 1

Manufacture of Sterile Medicinal Products

Published Dec 20, 2017

Additional comments requested Feb 18, 2020

8. Finishing of Sterile Products

8.21 *Sealing/Container Integrity*

8.29 *General Visual Inspection*

8.30 *Manual Inspection*

8.31 *Automated Inspection*

8.32 *Trending*

8.21 Sealing/Container Integrity

- Containers should be closed by an appropriate validated method
- Containers closed by fusion (BFS, FFS, flex bags, glass or plastic ampoules) should be 100% integrity tested
- A sample of other containers should be checked for integrity using a validated method
  - A statistically valid sampling plan should be used
  - "… visual inspection alone is not considered an acceptable integrity test method."

8.29 General Visual Inspection

- 100% inspection of all filled containers for extraneous contamination and other defects required
- Defects should be classified based on risk and history, assessing:
  - Impact to patient
  - Route of administration
- Batches with unusual levels of defects should be investigated
- A defect library should be generated with all known classes of defects
- Critical defects should not be found during sampling of acceptable containers
  - Accept on zero plans for critical defects

8.30 Manual Inspection

- Inspection should be done under suitable and controlled conditions
  - EP 2.9.20 provides reference conditions
- Operators must be qualified and requalified at least annually
  - Should address worst-case inspection rate/speed, component size and fatigue
  - Eyesight checks should be performed as part of requalification
- Operators should be given frequent breaks

8.31 Automated Inspection

- Automated methods should be validated with known defects
- Method should provide sensitivity equal to or better than manual inspection
- Equipment should be checked prior to start-up and at regular intervals

8.32 Trending

- Reject rates for various defect types should be trended
  - Adverse trends should be investigated
  - Impact to product on the market should be assessed as pat of investigation

European Pharmacopeia

- EP 10.0 Parenteral Preparations - Parenteralia

  Containers for parenteral preparations are made as far as possible from materials that are sufficiently transparent to permit the visual inspection of the contents, except for implants and in other justified and authorised cases.

- EP 10.0 Parenteral Preparations - Injections

  Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles.

European Pharmacopeia

- EP 2.9.20 *Particulate Contamination: Visible Particles*

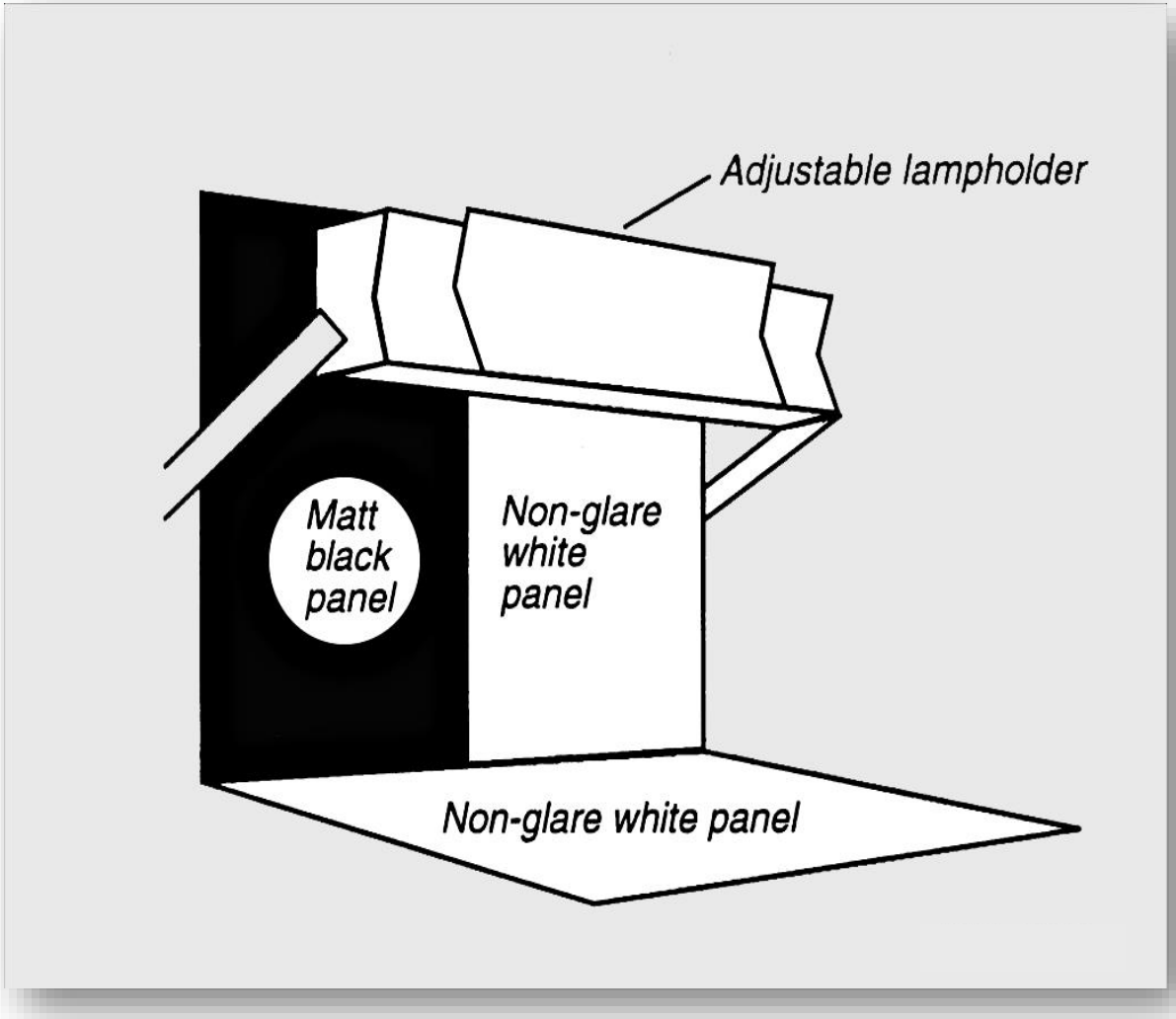
  Particulate contamination consists of mobile undissolved substances other than gas bubbles, unintentionally present in liquid preparations.

  The test is intended to provide a simple procedure for the visual assessment of the quality of liquid preparations, if applicable after reconstitution, as regards visible particles.

European Pharmacopeia

- Apparatus
  - Vertical matte black panel
  - Vertical non-glare white panel next to black panel
  - Lamp holder … with … shaded, white light source and … diffuser (… two 13W fluorescent tubes, each 525 mm (20.7 in) in length, or an … LED light source). … illumination at the viewing point is … between 2000 and 3750 lux, although higher values may be required for for coloured glass and plastic containers and for coloured or turbid preparations.

European Pharmacopeia



European Pharmacopeia

- Changes …
  - Official Jan 2020
  - Applicable to reconstituted solutions
  - Increased light levels for turbid or colored solutions, as well as plastic or colored glass containers
  - Transfer to clear containers for evaluation when needed
  - Addition of LED as acceptable light source

European Pharmacopeia (cont.)

Chapter 5.17.2 *Recommendations on Testing of Particulate Contamination: Visible Particles* (new)

- Official Jan 2021
- General considerations and workflow agree with recommendations in USP <1790>.
- Definitions of Extrinsic and Intrinsic particles do not align with USP <790> and <1790>.
  - Those derived from primary packaging and equipment are considered extrinsic
  - Those resulting from the formulation are intrinsic
  - No inherent particle definition

EP 5.17.2

- "… although there is little supporting evidence generated by clinical studies, visible particles are … a potential safety concern, and their presence should … be minimized as far as possible in any product … for humans or animals."
- Recommend ISO 2859-1 sampling plans for acceptance sampling (AQL inspection) but no specific recommendations for AQL values are made.
- Visible particles should be classified as "at least a major defect".
- Inspector training and qualification with prepared defect sets is described.
- Probabilistic nature of inspection is discussed.

Other Standards

- World Health Organization
  - International Pharmacopeia
- Other National Pharmacopeia
  - Chinese Pharmacopeia
  - British Pharmacopeia
- Guidelines for Particulate Matter Control in Injections (1998)
  - Legislation of the Russian Federation

Conclusions

- High concern with visible particulates by global authorities.
- Requirements are often ambiguous (but getting better).
- Movement towards global harmonization of manual inspection conditions.

Acknowledgements

- USP Visual Inspection Expert Panel
  - D. Scott Aldrich - Ultramikro
  - John Ayres - Pharma Safety Solutions
  - Roy Cherris - Bridge Associates International
  - Mary Lee Ciolkowski - Bausch & Lomb
  - Desmond Hunt - USP
  - Steve Langille - ValSource
  - Russell Madsen - The Williamsburg Group
  - John Shabushnig (Chair) - Insight Pharma Consulting
  - Deborah Shnek - Alder Biopharmaceuticals
  - Hailin Wang – FDA
  - Neal Zupec - Baxter

Questions?