Visual Inspection of Injectable Products:

More than Sorting Good from Bad …

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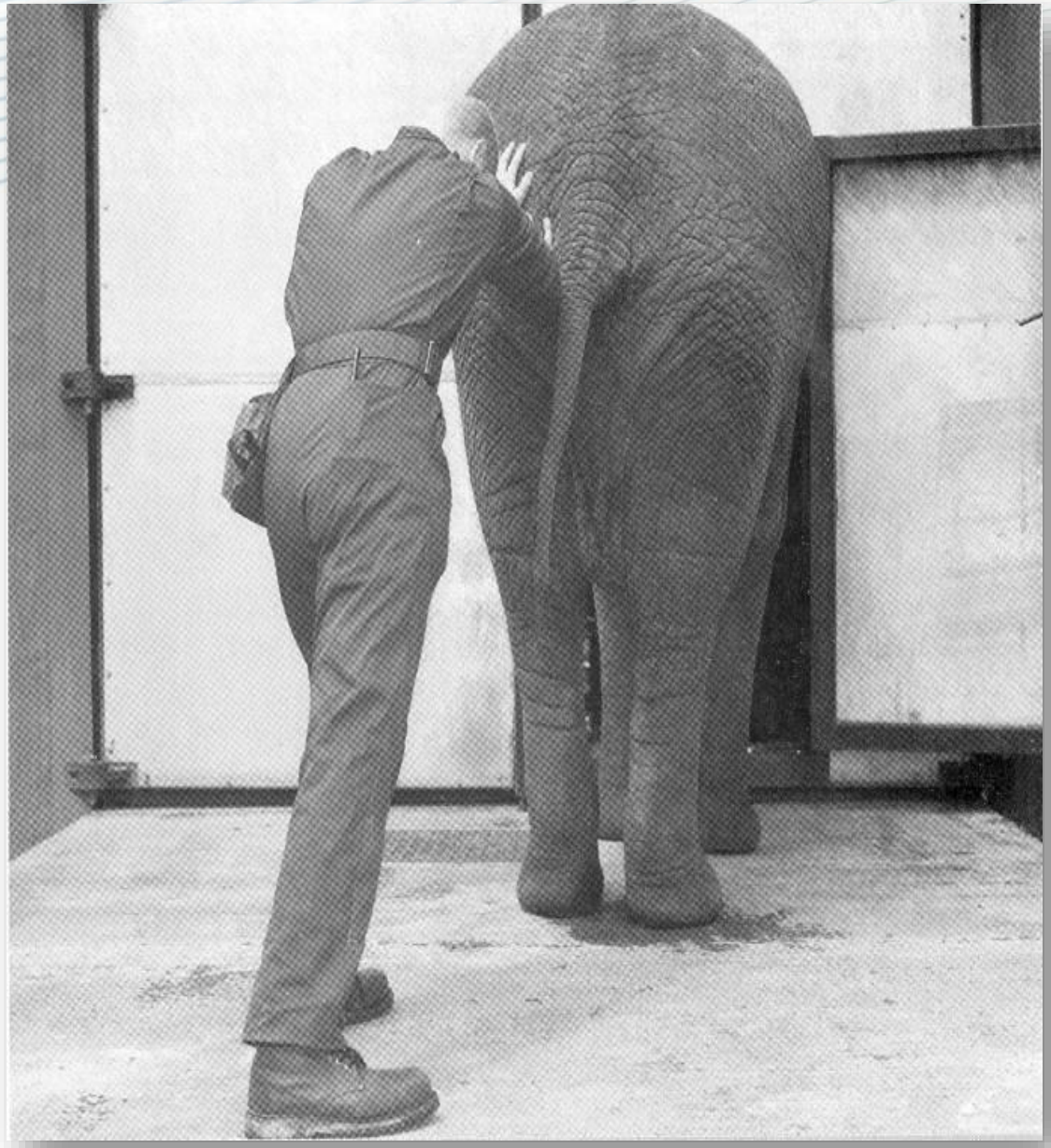
Agenda

- Patient Risk / Foreign Matter Concerns
- US FDA
- US Pharmacopeia (USP)
- EC GMP's
- European Pharmacopeia (EP) / Pharm Eur
- WHO Pharmacopeia
- Japanese Pharmacopeia (JP)
- Chinese Pharmacopeia (ChP)
- 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 (How big is it?)
    - Is the size in the range that will pass through the needle?
  - Quantity (How many?)
    - Many vs. Single
  - Composition (What is it?)
    - 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
- Route of Administration
  - IV vs. IM vs. Sub-Q
  - Intrathecal, Intraocular
- Duration of Exposure
  - Chronic vs. Single Dose
- Intended Patient Population
  - Infant vs. Adult
  - Compromised vs. Healthy

Particulate Size Ranges

<100 nm	100 - 1,000 nm	1 - 100 µm	>100 µm
Nanometer	Submicron	Subvisible	Visible

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

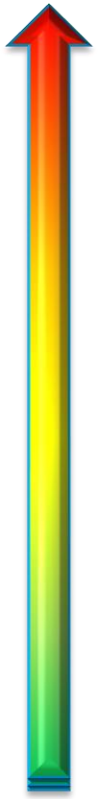
- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter

- Manual / Human
- Semi-Automated
- Automated

Narhi, et al. J Pharm Sci, 2012

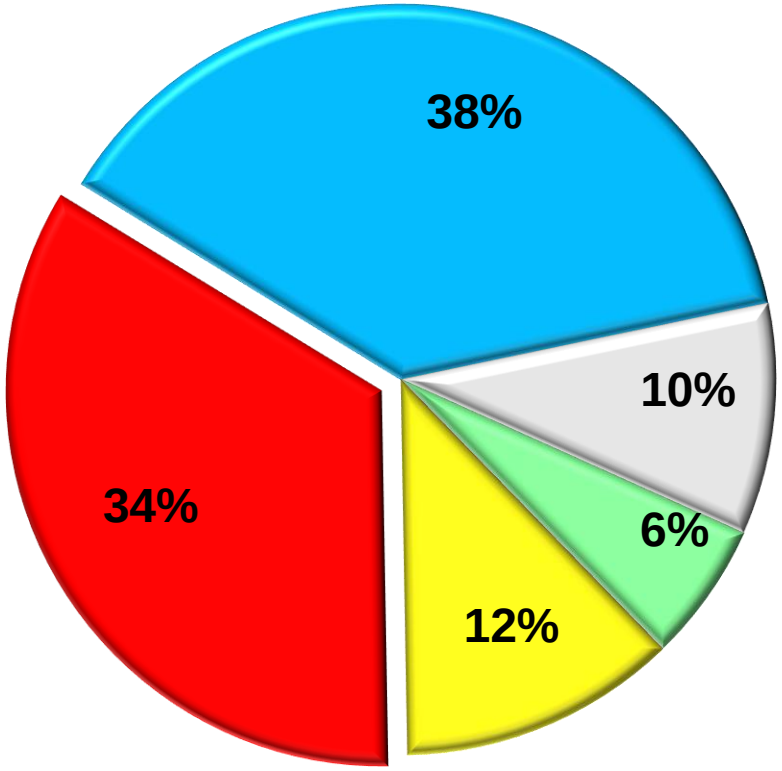
Particulate Matter Definitions

- 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

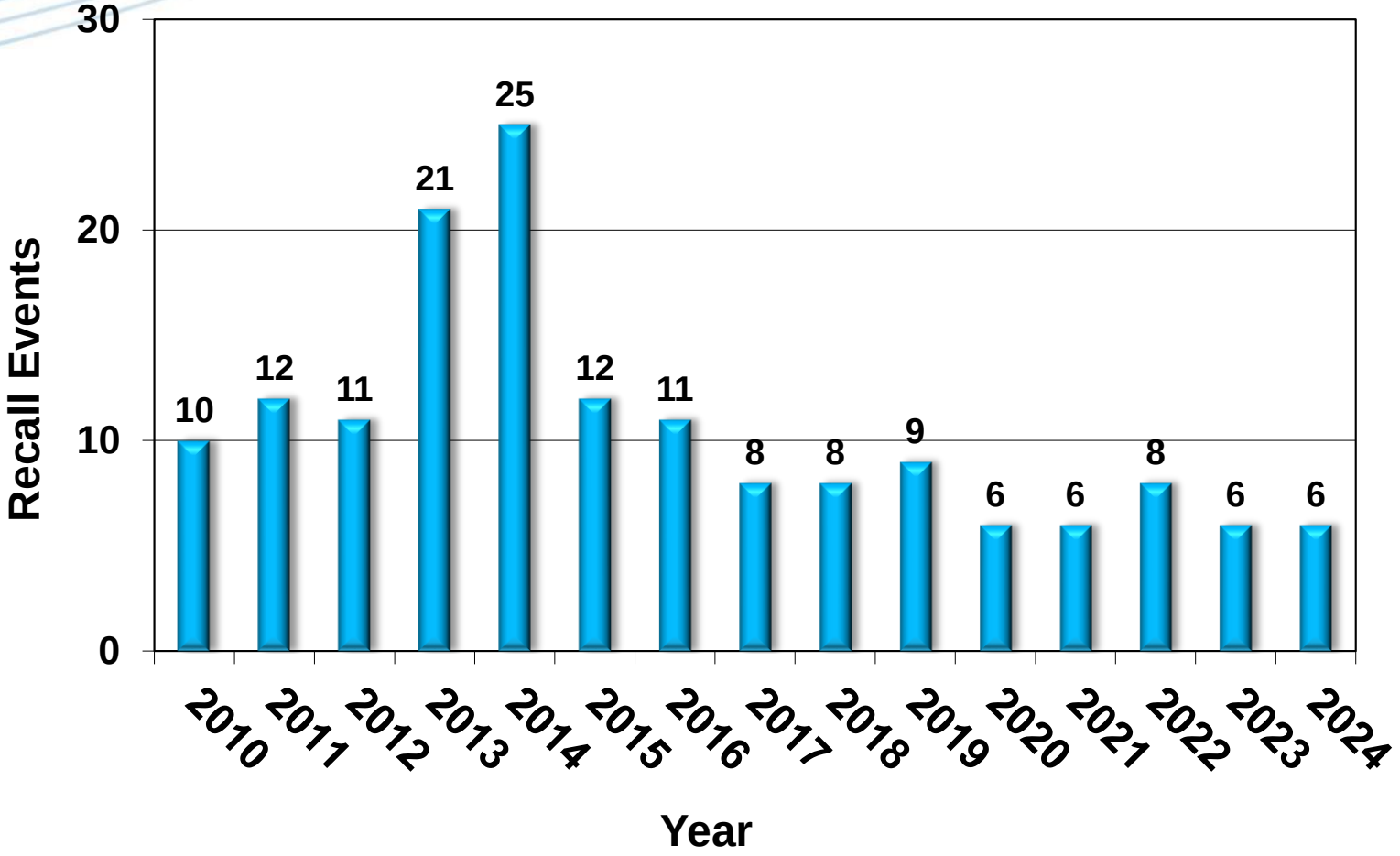
FDA Sterile Injectable Drug Recall Notices 2020-2024



* 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

- 9-29-2024 Gilead Issues Voluntary Nationwide Recall of One Lot of Veklury (Redesivir) for Injection 100 mg/vial Due to the Presence of Glass Particles
  - Glass particles
- 3-28-2024 Eugia US LLC (AuroMedics Pharma LLC) Issues Voluntary Nationwide Recall of Methocarbamol Injection, USP 1000 mg/10 mL (100mg/mL) (Single Dose Vial) Due to the Presence of White Particles
  - White Particles
- 3-12-2024 Par Pharmaceuticals Issues Voluntary Nationwide Recall of One Lot of Treprostinil Injection Due to Potential for Silicone Particulates in the Product Solution
  - Silicone Particles

Typical FDA Recall Risk Statement

- "The administration of an injectable product that contains … particles may result in local irritation or swelling in response to the foreign material. Particles can potentially travel, through the blood vessels, to various organs and block blood vessels in the heart, lungs or brain which can cause stroke or even lead to death. To date … has not received any reports of adverse events related to this recall."

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 Guidance for Industry

- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)

  Inspection of Container Closure System … Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. … Any defects or results outside the specification established for in-process and final inspection are to be investigated in accord with § 211.192.

US FDA Guidance for Industry

- Inspection of Injectable Products for Visible Particulates (2021, draft)
  - Draft published 14 Dec 2021
    - rumored for >5 years
  - Issued jointly by CDER, CBER, CVM
  - Scope limited to visible particles
  - Comments submitted 1Q2022 from PDA, USP, many others
  - "Meeting an applicable … USP … standard alone is not generally sufficient for meeting … CGMP … requirements …"

US FDA Guidance for Industry (cont.)

- Generally, aligns with USP <790> and <1790>
- particle definitions (extrinsic, intrinsic, inherent)
- risk based
- recognizes probabilistic nature of VI, use of threshold studies
- Importance of prevention and life-cycle approach
- Expects understanding of particles that may be present to begin during development

US FDA Guidance for Industry (cont.)

- Concerns
  - "FDA does not recommend more than one reinspection … to release a batch with atypical defect levels."
  - "Extrinsic particulates … during 100% inspection or AQL … - which suggest the presence of filth, sterility assurance issues, or other CGMP violations – may result in product that could be adulterated, even if statistical sampling acceptance criteria are met."
  - Roles and responsibilities of Quality Unit
    - Prepare and control vs. approve defect test sets
    - Collect AQL samples

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.

US FDA 483 Themes

- Must establish a maximum allowable reject rate.
  - Total, plus other specific categories and types
- Inspectors must be trained, and training documented.
- Training and certification conditions must align with routine 100% inspection conditions.
- Address inspection fatigue during certification.
- Inspectors must be periodically recertified.

US FDA 483 Themes

- Must control reinspection of product, including when appropriate, inspection conditions and number of reinspections permitted.
- Must conduct thorough investigations. Identify particulate matter when performing investigations.
- Must use statistically sound sampling plan(s) for AQL inspection.

US FDA Advisory

- 3-25-2011 Formation of Glass Lamellae in Certain Injectable Drugs
- Conditions associated with higher incidence of glass delamination:
  - Glass vials manufactured from tubing
  - High pH drug solutions
  - Use of citrate and tartrate buffers
  - Contact time / shelf life
  - Room temperature storage (compared with refrigerated storage
  - Terminal sterilization

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 42

- 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 42

- 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 42

- 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

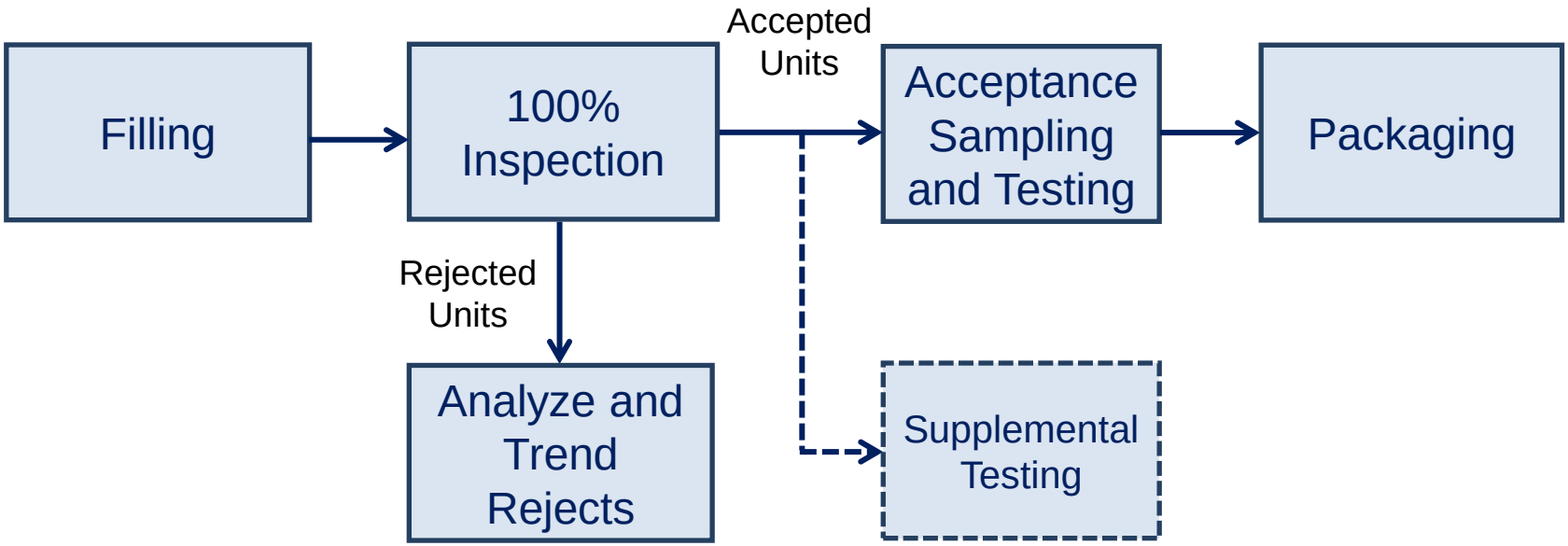
USP <790> Acceptance Criteria

- 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 <1790>



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
  - Originally published in USP 40 1st Supplement
    - Official Aug 2017, Revision Official May 2022

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

- Final version published 22 Aug 2022
  - effective 25 Aug 2023
- 59 pages in new version vs. 12 pages in previous version
- New version 4 chapters on VI vs. 1 chapter in previous version
  - chapters 8.30, 8.31, 8.32, 8.33
- New version 5 chapters CCIT vs. 2 chapters in previous version
  - chapters 8.21, 8.22, 8.23, 8.24, 8.25

EC GMP Annex 1 (cont.)

- Finishing of Sterile Products
  - Generally, aligns with USP <1790>
  - Adds detail on:
    - risk assessment
    - operator qualification
    - critical MVI parameters
  - Adds expectations for:
    - creating a defect library
    - no critical defects found during sampling inspection
    - trending

EC GMP Annex 1 (cont.)

- Concerns
  - "… visual inspection is not considered as an acceptable integrity test method."
  - "The performance of equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch"

European Pharmacopeia

- EP 7.0 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 7.0 Parenteral Preparations - Injections

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

European Pharmacopeia

- EP 7.0 Parenteral Preparations – Powders for injections or infusions

  Powders for injections or infusions are solid, sterile substances distributed in their final container and which, when shaken with the prescribed volume of a prescribed sterile liquid rapidly form either clear and practically particle-free solutions or uniform suspensions.

European Pharmacopeia

- EP 2.9.20 Particulate Contamination: Visible Particles

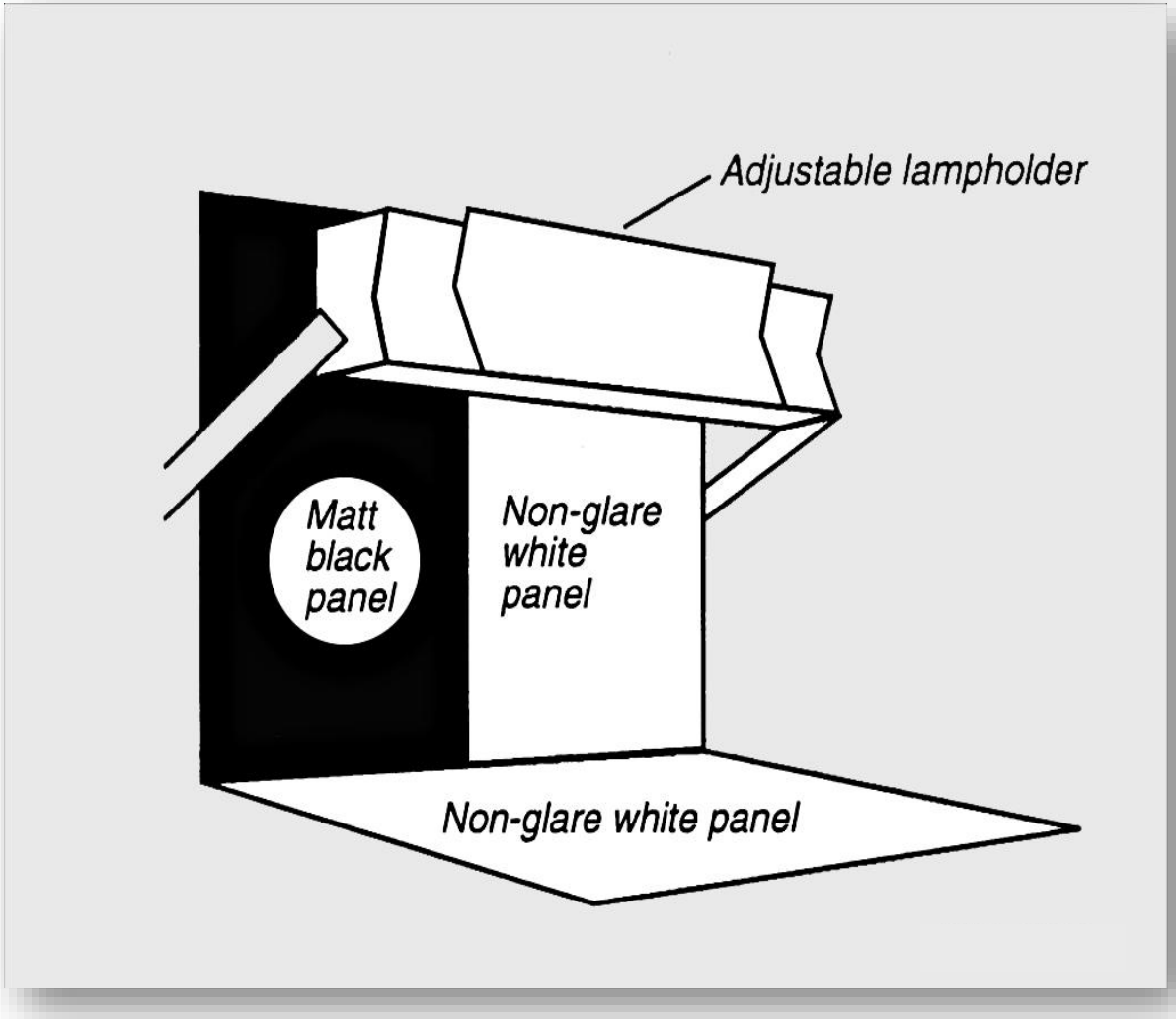
  Particulate contamination of injections and infusions consist of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

  The test is intended to provide a simple procedure for the visual assessment of the quality of parenteral solutions as regards visible particles. Other validated methods may be used.

European Pharmacopeia

- Apparatus
  - Vertical matte black panel
  - Vertical non-glare white panel next to black panel
  - Adjustable lamp holder with shaded, white light source and … a diffuser (… two 13W fluorescent tubes, each 525 mm (20.7 in) in length is suitable). … illumination at the viewing point is … between 2,000 and 3,750 lux for clear glass ampoules. Higher values are preferable for coloured glass and plastic containers.

European Pharmacopeia



European Pharmacopeia

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

European Pharmacopeia (cont.)

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

- Effective Jan 2021

This is a "Recommendation Chapter". Unusual for EP but good to see additional guidance. Generally good alignment with USP <1790>. Concerns:

- Naming conventions and terminology
  - Establishing new naming conventions that are different than existing compendia and industry naming conventions. Special concern with use of "extrinsic" and "intrinsic" and lack of "inherent" terminology.

Monoclonal Antibodies

- EP 01/2008:2031 Monoclonal Antibodies for Human Use

  Appearance. Liquid or reconstituted freeze-dried preparations are clear … without visible particles.

- PharmEuropa Supplement 11.2 (Nov 2022)

  "'Without visible particles' replaced with 'practically free from visible particles', while retaining the escape clause 'unless otherwise justified and authorised' (as currently expressed in the monograph)."

  Reference to 2.9.20 and 5.17.2 added

WHO International Pharmacopoeia

- Visual inspection of particulate matter in injectable preparations

  Particulate contamination of injections and parenteral infusions consists of extraneous, undissolved particles unintentionally present in the solutions. Disregard any gas bubbles. …

WHO International Pharmacopoeia

- Visual inspection of particulate matter in injectable preparations

  … The test is not intended for use by a manufacturer for batch release purposes. To ensure that a product will meet pharmacopoeial specifications with respect to visible particulate matter, if and when tested, manufacturers should carry out a 100% inspection and rejection of unsatisfactory items prior to release or use other appropriate means.

WHO International Pharmacopoeia

- Recommended procedure
  - Gently swirl or invert each individual container, making sure that no air bubbles are introduced, and observe for about 5 seconds in front of the white panel. Repeat … in front of the black panel.
  - Record the presence of any particles. Repeat the procedure for a further 19 containers.
  - The preparation fails … if one or more particles are found in more than one container.
  - When … applied to reconstituted solutions …, the test fails if particles are found in more than two containers.

Japanese Pharmacopoeia

- JP 17: 6.06. *Foreign Insoluble Matter Test* ... *Method 1*

  ... observe for about 5 seconds each against the backgrounds of a white and a black inspect with the unaided eyes at a position of light intensity of approximately 2000 to 3750 lx under an white lamp: Injections or vehicles must be clear and free from readily detectable foreign insoluble matters. As to Injections in plastic containers … light intensity of approximately 8000 to 10,000 lx … . When the observation is not easy, prolong the observation time as appropriate.

Chinese Pharmacopoeia

- Effective 2020, English Translation.
- 0904 *Test for Visible Particles*

  *"*Visible particles are defined as insoluble substances that present in injections, ophthalmic liquid preparations or sterile drug substances and can be observed under the required conditions by visual test. Their size or lengths are usually more than 50 µm."
- Method

  Describes both visual inspection by diffuse illumination (lamp test, Method 1) and a light scattering method (Method 2).

Chinese Pharmacopoeia 0904

- Apparatus

  An inspection station with a non-glare white and black background. A light source with a daylight lamp with panel for obstructing from light … with illumination between 1,000-4,000 lux.

  (Similar to those described by USP/EP/JP)

- Requests for Inspector

  "Inspector's vision of distant and near distance should be 4.9 or more than 4.9 (vision after correction should be 5.0 or more than 5.0). Inspector should not be color blind."

Chinese Pharmacopoeia 0904

- Procedure

"… gently swirl and invert the container … observe … in front of black background and white background."

"… keep appropriate distance from inspectors' eyes to the container(… usually 25 cm to inspect clearly) …"

"Repeat several times within 20 seconds."

"Hold 2 ampoules (vials) for each observation if the volume of solution … is not more than 10 mL …"

"… illumination should be 1,000-1,500 lux for colorless solution. …should be 2,000-3,000 for coloured solution, …brown glass or transparent plastic … 4,000 lux for suspensions or emulsions."

Chinese Pharmacopoeia 0904

- Solutions, Suspensions for Injection

  "… take 20 containers examined randomly."

- Sterile Powder for Injection

  "… take 5 containers … dissolve the contenst completely with appropriate solvent …"

- Sterile API

  "… weigh 5 portions …, weight equal to maximum strength of preparation …"

- Solutions for Eye Drops

  "… take 20 containers being examined randomly."

Chinese Pharmacopoeia 0904

- Acceptance Criteria

  "The obviously visible foreign matters such as broken bits of metal or glass, fibres with lengths of more than 2mm or block with size dimension of more than 2mm, …smokey precipitate …, and protein flocculus … should not be found"

  "Unless other wise specified, … tiny visible particles … insoluble substance, short fibres … less than 2mm and protein flocculus … of less than 1mm comply with the requirements listed in the tables …"

Biological Injections and Eye Drops

Category	1st Test: 20 Containers	1st and 2nd Test 40 containers
Injections	≤50mL, ≤3 visible particles in each container. >50mL, visible particle ≤5 in each container. Accept if no more than 1 container fails test. Retest if 2 containers fail test. Batch fails if 3 or more containers fail test.	Batch fails if more than 2 containers fail test.
Eye Drops		Batch fails if more than 3 containers fail test.

Non-biological Injections and Eye Drops

Category	**1st Test: 20 Containers**	**1st and 2nd Test 40 containers**
Injections, IV	Retest if 1 cont fails test. Batch fails if 2 or more cont fail test.	Batch fails if >1 cont fails test.
Injections Non-IV	Retest if 1 or 2 cont fail test. Batch fails if more than 2 cont fail test.	Batch fails if >2 cont fail test.
Eye Drops	Batch passes if ≤1 cont fails test. Retest if 2 or 3 cont fail test. Batch fails if >3 cont fail test.	Batch fails if >3 cont fail test.

Sterile Powder for Injections

Category	Small visible particle limit (number of particles)
Biologicals <50mL	≤3
Biologicals ≥50mL	≤5
Non-biological, lyophilized	≤3
Non-biological, Non-lyophilized	≤5

Other Guidance and Standards

- Annex 1 to the Good manufacturing practices guide - Manufacture of sterile drugs (GUI-0119) (2024)
  - Heath Canada
- Biopharmaceutical Foreign Product Inspection Management Guidelines (2022)
  - Ministry of Food and Drug Safety, S. Korea
- Visual Inspection of Sterile Products Best Practices Document (2021)
  - Indian Pharmaceutical Alliance (IPA)
- DAC Probe 5 (2006)
  - Germany

Conclusions

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

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Questions?