Visual Inspection of Injectable Products:

More than Sorting Good from Bad …

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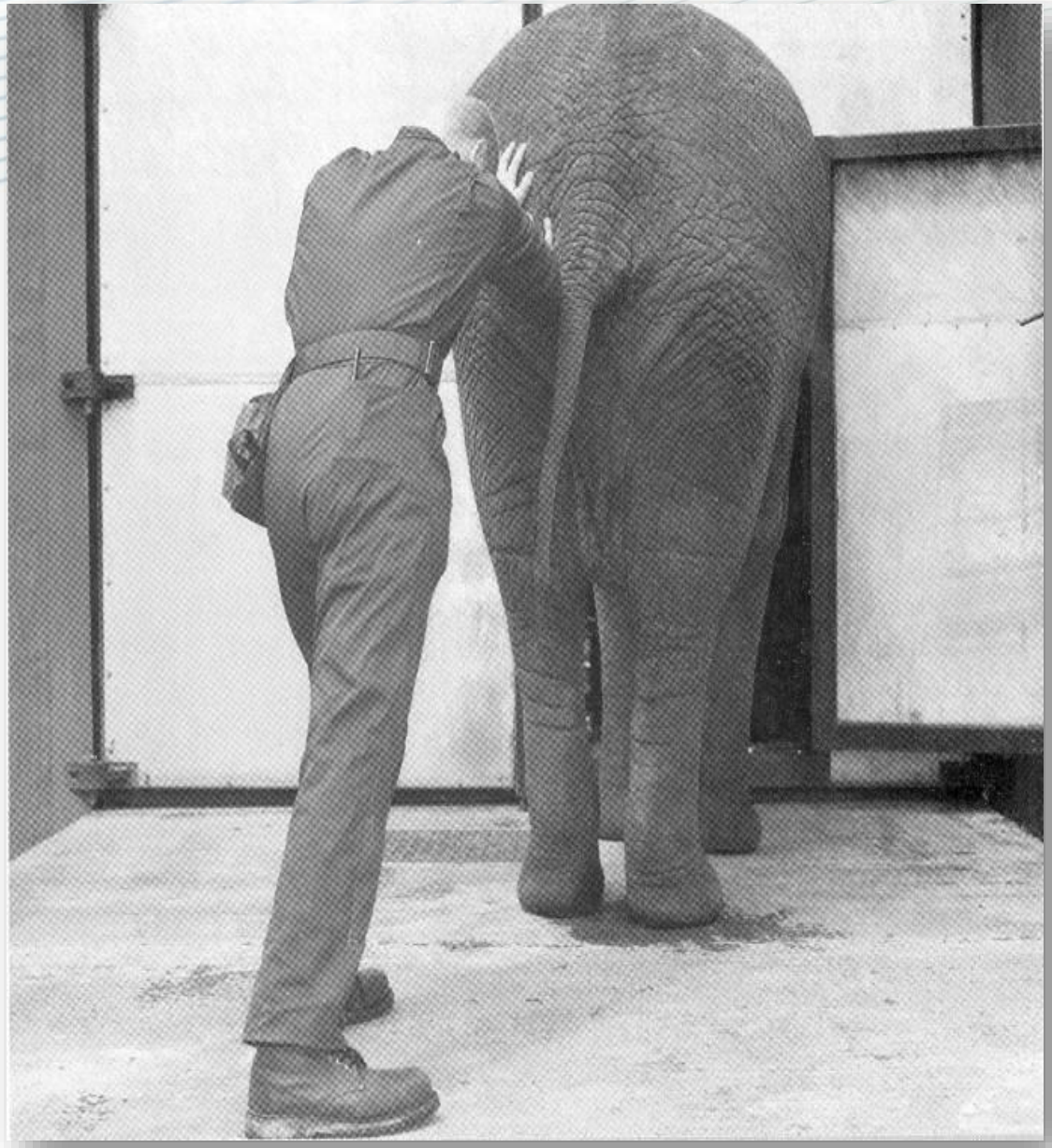
Agenda

- 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
    - 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)

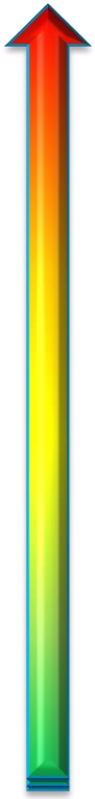
- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter

- Manual / Human
- Semi-Automated
- Automated

Narhi, et al. J Pharm Sci, 2012

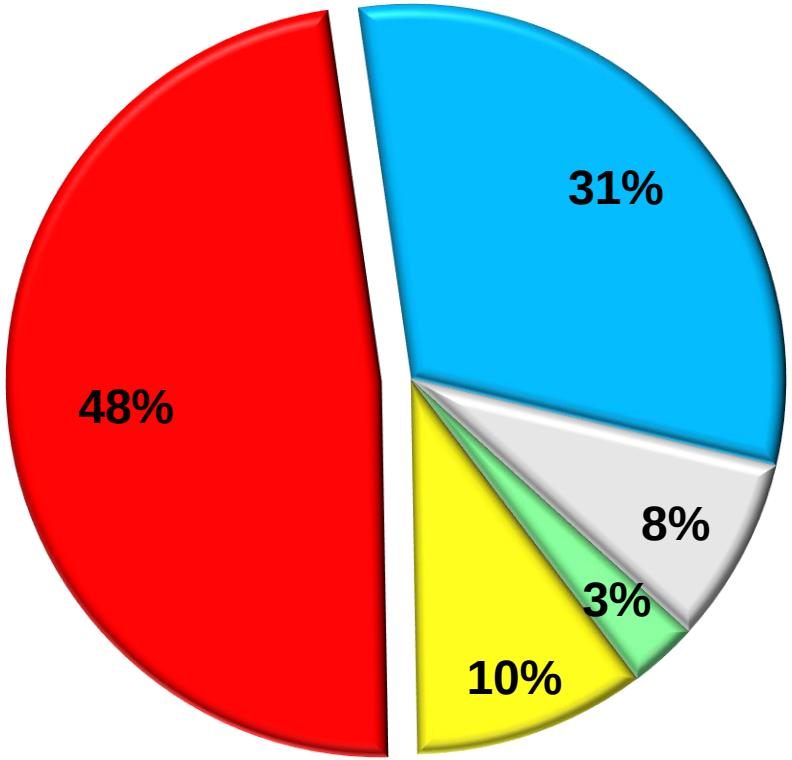
Particulate Matter Definitions

- 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 2010-2017

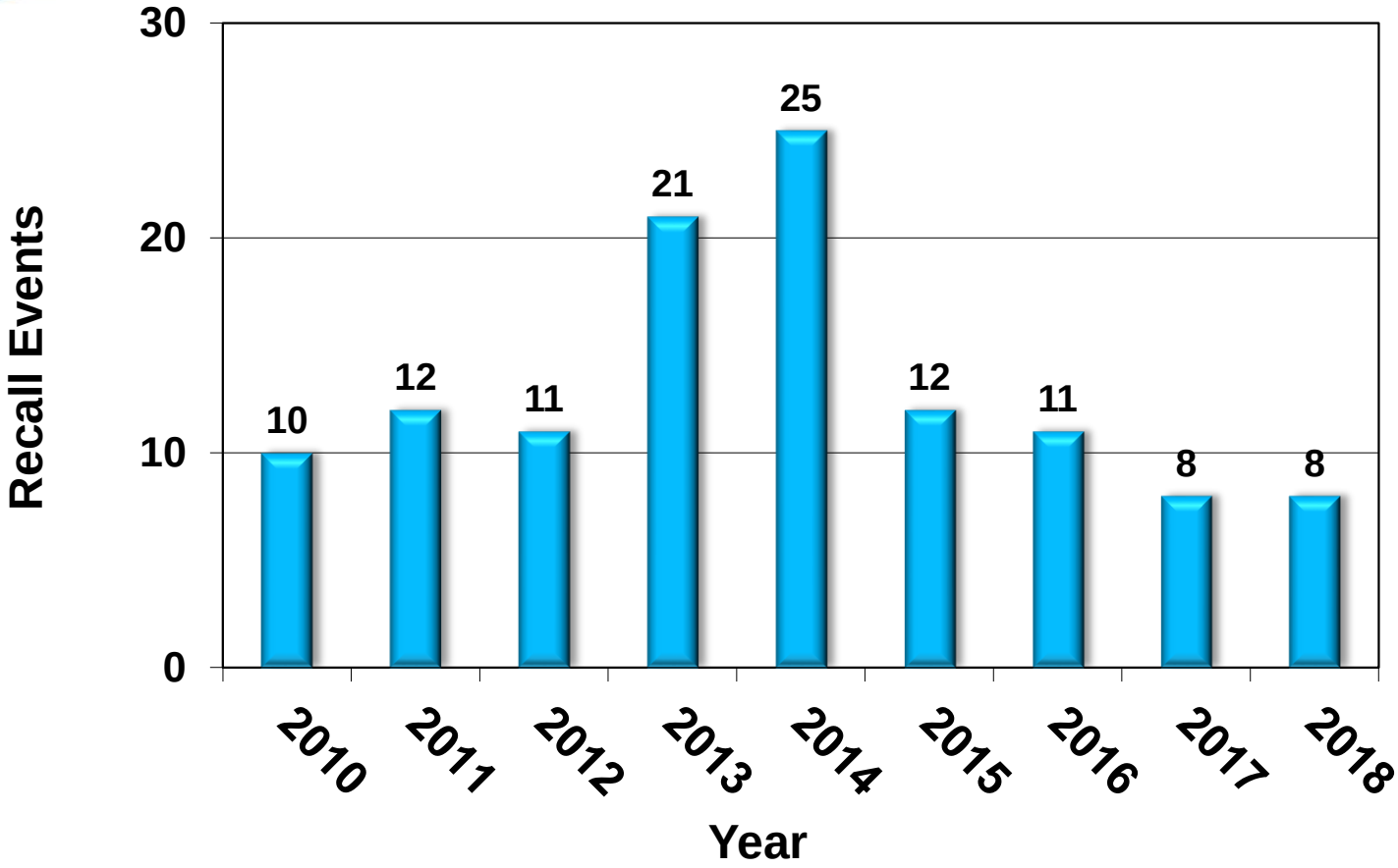


- Visible Particles
- Lack of Sterility Assurance
- Labeling
- Container
- Other*

* 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

- 1-16-2018 Baxter Expands Voluntary Nationwide Recall to Include Second Lot of Nexterone Injection Due to Presence of Particulate Matter
  - Polyethylene particles
- 1-5-2019 Pharmaceuticals, Inc. Issue Voluntary Recall of Ceftriaxone for Injection USP, 250mg, 500mg, 1g and 2g
  - Rubber particles
- 1-9-2019 Pharmaceutical Industries, Inc. Issues Voluntary Nationwide Recall of Vecuronium Bromide for Injection Due to the Presence of Particulate Matter Identified as Glass
  - Glass 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

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 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.

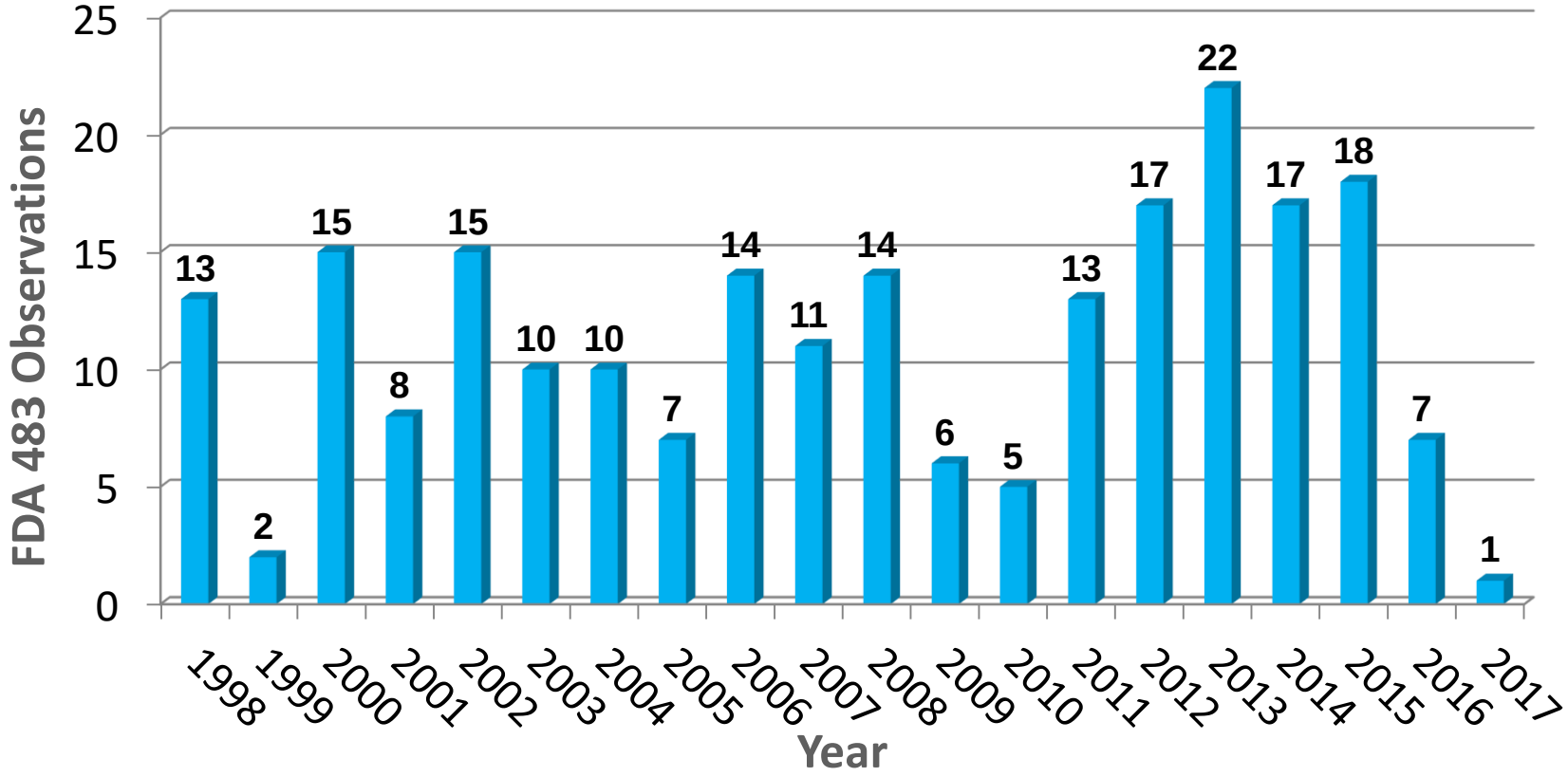
US FDA Compliance Program Guidance Manual 7356.002A

- 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 Observations Regarding Visual Inspection



From GMP Trends

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 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>

- <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

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

8. Finishing of Sterile Products

- 8.18 *Sealing/Container Integrity*
- 8.26 *General Visual Inspection*
- 8.27 *Manual Inspection*
- 8.28 *Automated Inspection*
- 8.29 *Trending*

8.18 Sealing/Container Integrity

- Containers should be closed by an appropriate validated method
- Containers closed by fusion (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.

8.26 General Visual Inspection

- 100% inspection of all filled containers for extraneous contamination and other defects
- Defects should be categorized, QRM to set defect classifications
  - Impact to patient
  - Route of administration
- Batches with unusual levels of defects should be investigated
- A defect library should be generated with all known defects
- Critical defects should not be found during sampling of acceptable containers
  - Accept on zero plans for critical defects

8.27 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

8.28 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

8.29 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 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

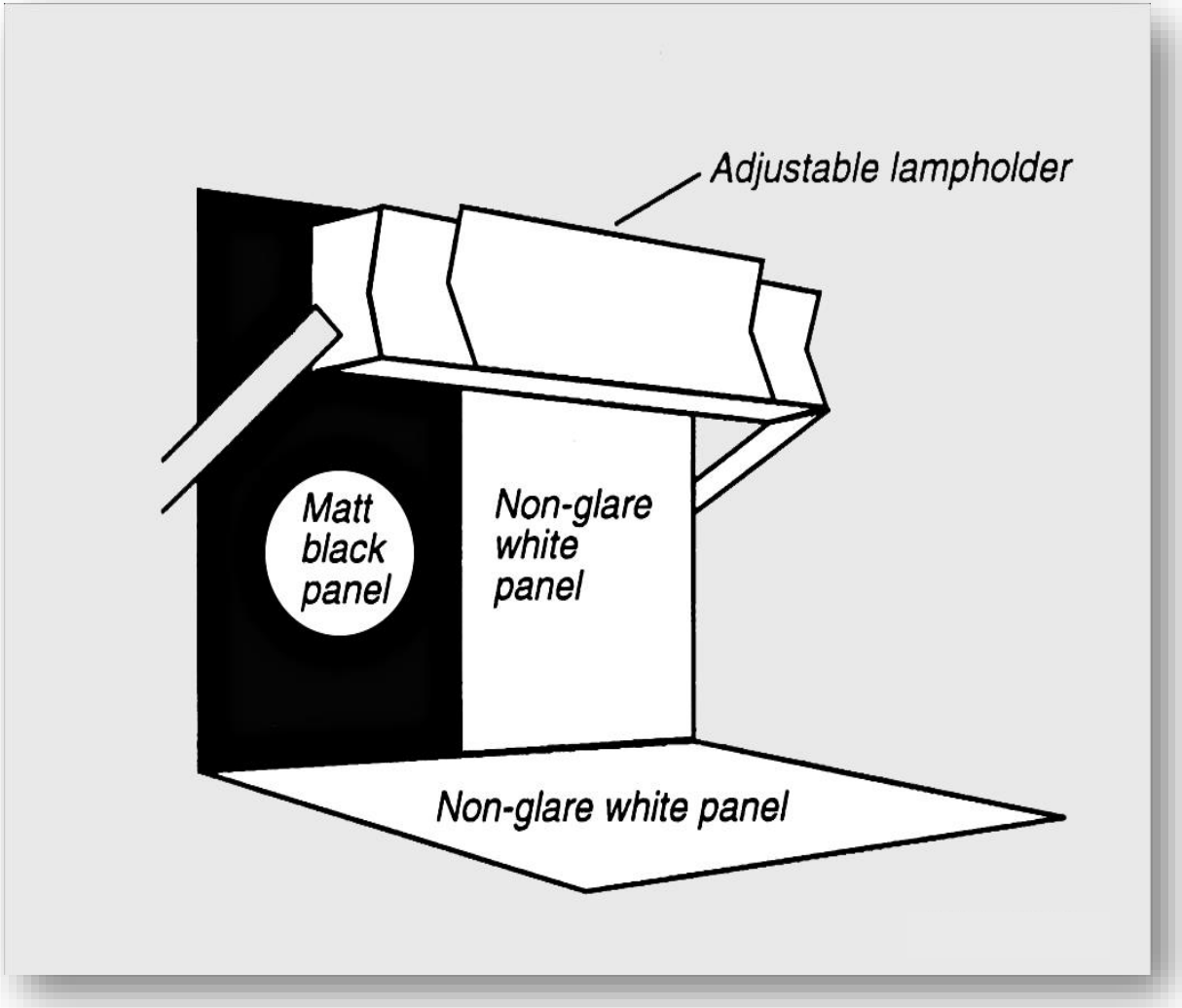
  Particulate contamination of injections and infusions consist of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

  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)

- Comment period closed at end of 2018
- Comments were submitted by PDA VI IG

This is a "Recommendation Chapter". Unusual for EP but good to see additional guidance. 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.

- EMA Communication

  "The formation of aggregates, sub-visible and visible particulates in the drug product is important and should be investigated and closely monitored on batch release and during stability studies. In addition to the pharmacopeial test for particulate matter, other orthogonal analytical methods may be necessary to determine levels and the nature of particulates".

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 2015, English Translation. *Test for Visible Particle in Injections*

  Visible particles are defined as insoluble substances that present in injections, eye drops or sterile API (raw material) and can be observed under the required conditions by visual test. Their size or lengths are usually more than 50 μm.

  …

  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 is also not color blind.

Chinese Pharmacopoeia

- Apparatus

  An inspection station with a non-glare white and black background. A light source with a daylight lamp …

- Procedure

  The test is carried out in a dark room.

  The intensity of illumination should be 1,000-1,500 lx for colorless injections or eye drops. The intensity of illumination should be 2,000-3,000 lx for samples with colored glass, transparent plastic containers or colored solutions. For suspensions or emulsions for injections or eye drops … the intensity of illumination should be 4,000 lx.

Chinese Pharmacopoeia

- Procedure (cont.)

  Remove adherent labels and clean …, then gently swirl and invert each container …

  … retain appropriate distance to inspector's eyes (common distance 25 cm) …

  … The total observation time is 20 seconds … If each containers is no more than 10 mL of solution, the inspector can hold two containers …

- Light scattering test added in addition to "Lamp Test" in 2015.

Chinese Pharmacopoeia

- Solutions, Suspensions for Injection

  … take 20 containers examined randomly.

- Sterile Powder for Injection

  … take 5 containers, use an appropriate solvent and method to dissolve the powder completely.

- Sterile API

  … take 5 samples with the maximum amount listed.

- Solutions for Eye Drops

  … take 20 containers

Chinese Pharmacopoeia

- Acceptance Criteria

  After standing for a while … no floating smoky particles; innumerable agglomerates, precipates … or protein flocculent material are observed. Any visible particles like a bit of glass, metal, fiber (> 2 mm) and specks (> 2 mm) should not be detected. If other small visible particles (< 2 mm) … is observed, or for biological drug product or biological raw material, if there are protein particles or protein flocculent materials that are < 1 mm, unless otherwise specified, the following criteria should be met:

Chinese Pharmacopoeia

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.

Chinese Pharmacopoeia

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.

Chinese Pharmacopoeia

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 Standards

- US Federal Standard 142a (1970)
  - Procurement of drug products by US government
  - Discontinued
- DAC Probe 5 (2006)
  - German standard
- WHO Pharm/92.206 Rev. 2 (1992)
  - Not implemented
- 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

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Questions?