Visible Particles: Regulatory and Compendial Requirements

John G. Shabushnig, Ph.D.
Insight Pharma Consulting, LLC

insight!

June 2014
Agenda

• Visible Particle Definitions
• US FDA
• US Pharmacopeia (USP)
• EC GMP’s
• European Pharmacopeia (EP) / Pharm. Eur.
• Japanese Pharmacopeia (JP)
• Other Standards
• Conclusions
Particulate Size Ranges

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

- SEC (Size Exclusion Chromatography)
- FFF (Field Flow Fractionation)
- SDS-Page Gels
- AUC (Analytical Ultracentrifugation)
- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter
- Manual / Human
- Semi-Automated
- Automated

Particulate Matter Definitions

• Extrinsic (from outside the process)
  – Environmental Contaminants
    • insect parts, hair, fibers, paint, rust

• Intrinsic (from within the process)
  – Processing Equipment, Primary Package
    • qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)

• Inherent (part of the formulation)
  – Protein agglomerates
• 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”
• 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.
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 483 Observations Regarding Visual Inspection

© 2014 John G. Shabushnig
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.
• USP 37: <1> Injections - Foreign and Particulate Matter

All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* <788> and other foreign 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.
US Pharmacopoeia

• USP 37: <1> Injections - Foreign and Particulate Matter (cont.)

The inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container that shows evidence of visible particulates shall be rejected.
US Pharmacopoeia

• USP 37: <1> Injections - Foreign and Particulate Matter (cont.)

The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

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 lot shall be supplemented with the inspection of constituted (e.g. dried) or withdrawn (e.g. dark amber container) contents of a sample of containers from the lot.
US Pharmacopoeia

• USP 37: <788> Particulate Matter in Injections

  Particulate matter in injections and parenteral infusions consists of mobile, undissolved particles, other than gas bubbles, unintentionally present in the solutions.
US Pharmacopoeia

• USP 37: <1> Injections – Packaging, Containers for Injections

  … The container is made of material that permits inspection of the contents. …
**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 Z1.4-2003 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%
• What’s next …
  – Clarifications added:
    • A smaller sample (such as the Special sampling plans in the standards) is appropriate for destructive testing of powders and suspensions
    • Now states that this chapter does not add a new requirement for stability testing
    • Alternative light sources such as LED’s are acceptable
    • The light intensity range stated is intended to establish a lower limit of 2,000 lux, but that it may be appropriate to inspect at levels above 3,750 lux
  – Published in USP 37 1st Supplement
    • Official August 1, 2014
• 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. …
• 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.
• **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.
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.
• 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.
• 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

Adjustable lampholder

Matt black panel

Non-glare white panel

Non-glare white panel

WHO 98430
• JP 16: 6.06. Foreign Insoluble Matter Test … Method 1

... inspect with the **unaided eye** at a position of light intensity of approximately 1,000 lx under an **incandescent lamp**: Injections or vehicles must be clear and free from readily detectable foreign insoluble matters. As to Injections in **plastic containers** … the inspection should be performed with the unaided eyes at a position of light intensity of approximately **8,000 to 10,000 lx**, with an incandescent lamp at appropriate distances above and below the container.
• JP 16: 6.06. Foreign Insoluble Matter Test ... Method 2

This method is applied to solid injections to be dissolved before use.

Clean the exterior of containers, and dissolve the contents with vehicles or with Water for Injection carefully, avoiding any contamination with extraneous foreign substances. The solution thus constituted must be clear and free from foreign insoluble matters that is clearly detectable when inspected with the unaided eyes at a position of light intensity of approximately 1,000 lx, right under an incandescent lamp.
Other Standards

- WHO International Pharmacopeia (IP)
- Chinese Pharmacopeia (CP)
- DAC Probe 5 (Germany)
Conclusions

• High sensitivity to 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 - Eli Lilly
  - Roy Cherris - Bridge Associates International
  - Desmond Hunt - USP
  - Steve Langille - US FDA
  - Russell Madsen (Chair) - The Williamsburg Group
  - John Shabushnig - Insight Pharma Consulting
  - Deborah Shnek - Amgen
Questions?