# USP <790> and USP <1790>: Status and Recent Experience

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## Agenda

- USP <790> *Visible Particulates in Injections*: History and Content
- USP <1790> *Visual Inspection of Injections*: History and Content
- Related Chapters
- Comparison with Global Compendial Requirements
- What's Next?
- Conclusions and Acknowledgments

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# USP <790> History and Contents



## USP <790> Chapter Development

- Stimuli Published
  - USP Pharmacopeial Forum Vol. 35(5) Sep-Oct 2009
- Stakeholder's Forum - May 13, 2010
- Meeting with FDA - March 28, 2011
- Drafts Published for Comment
  - USP Pharmacopeial Forum Vol. 38(2) Mar- Apr 2012
  - USP Pharmacopeial Forum Vol. 38(6) Nov-Dec 2012
- Official
  - USP 37 1st Supplement, August 1, 2014

## USP <790> Key Points

- Robust 100% inspection is a prerequisite
- Inspection conditions defined
- Acceptance criteria provided to define "essentially free of visible particulates"
- Supplemental testing for difficult to inspect products retained from USP <1>
- Guidance on how to assess continued compliance with "essentially free" if a complaint is received

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## USP <790> Contents

- 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 are addressed in individual monographs or approved regulatory filings

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## 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%

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## <790>

- Implicit…..
  - A controlled inspection process is in place
  - The process has metrics and feedback
  - Particles can be characterized
  - Sources can be identified

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## Particulate Matter Categories

| Extrinsic | Intrinsic | Inherent |
|---|---|---|
| Wild, Outside the System | Inside the System | **Is** the System:<br>Solutions<br>Suspensions<br>Micelles<br>Emulsions<br>Colloids<br>Protein Assembly |
| Extremes are "Filth" | Product-contact | n/a |
| Likely Microbial Vector | May have Microbial Content | Formulation-Relevant |
| Uncontrolled | Unplanned | Controlled, Expected |
| Additive | Additive or Changing | Stable<br>Same T.O.R. as E.O.S. |
| Single to Many Particles | Various Physical States | Defined active ingredient |
| May be Considered Most Objectionable | Needs Planning & Control | Most Acceptable, Known |

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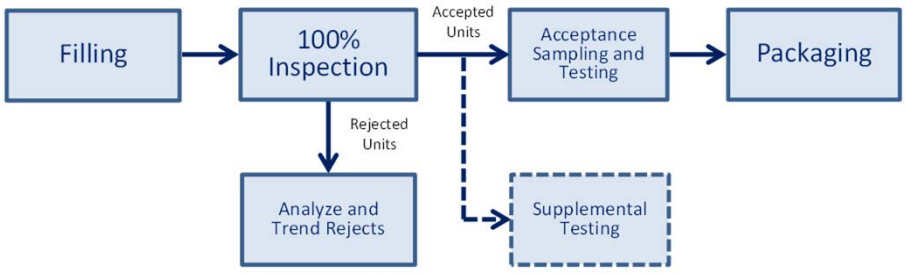
## USP <1790> Typical Process Flow

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## USP <790> Supplemental Testing

- Required when the nature of the product or package limits effective inspection
- Sample size based on ANSI/ASQ Z1.4 Special Sampling Plans
  - S-3 or S-4 plans recommended in USP <1790>
- Opaque Products
  - Reconstitute powders or lyo products
  - Inspect samples prior to lyophilization
  - Dissolve suspensions
  - Dilute strongly colored solutions
- Colored, Translucent or Opaque Containers
  - Transfer product to a clean, clear container

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## USP <1790> History and Contents

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## USP <1790> Chapter Development

- Information Chapter
- Drafts Published for Comment
  - USP Pharmacopeial Forum Vol. 41(1) Jan- Feb 2015
  - USP Pharmacopeial Forum Vol. 41(6) Nov-Dec 2015
- Official
  - USP 40 1st Supplement, August 1, 2017

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## USP <1790> Key Points

- Scope includes particles and other visible defects
- Summarizes risk to patients
- Emphasizes prevention / Inspection Lifecycle
- Describes inspector training and qualification methods
- Describes acceptance sampling (AQL inspection) methods and interpretation
- Describes typical inspection methods
  - Manual, Semi-Automated and Automated Inspection
- Further guidance regarding investigation in the event of a complaint for product in distribution

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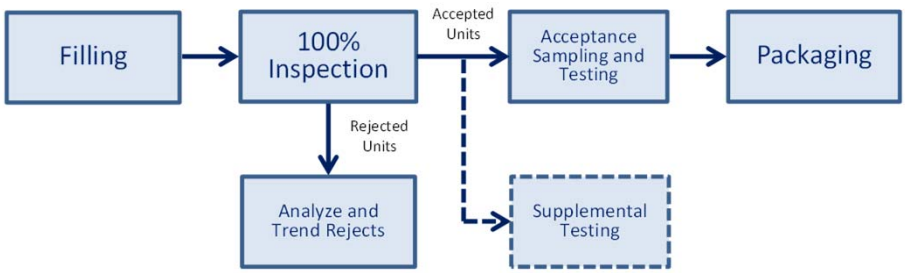
## USP <1790> Typical Process Flow

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## USP <1790> Prevention

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

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# Related USP Chapters

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## USP Related Chapters

- Related Chapters
  - <1> *Injections*
  - <771> *Ophthalmic Products*
  - <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 DRAFT*
  - <1788> *Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions*

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# Global Compendial Requirements

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# 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

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# 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. …

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# 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".

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## What's Next?



## What's Next?

- Publish updated version of USP <1790> with reference numbering corrected.
- Listen to feedback from stakeholders on experience with USP <790> and new USP <1790>.
- Currently, USP <790> treats all products, routes of administration and particles as having equal risk. Should this change? (USP <1790> gives some additional guidance.)
- Is more guidance needed on the use of statistical tools with visual inspection data?

# Conclusions and Acknowledgements

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# Conclusions

- Visual inspection is a probabilistic process. 100% detection and removal is not achieved for all particles, even with the best inspection technology/process.
- "Zero defects" is a valuable goal, but not a practical limit for particulate matter.
- Acceptance limits should be practical; based on patient risk and process capability.

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# Conclusions

- Informal harmonization has brought the three major pharmacopeias closer together in inspection method and the definition of visible.
- Industry and regulators have benefited from a clearer description of inspection methods and acceptance criteria for particulates in injectable products.
- Prevention driven by the inspection process should be part of the product and manufacturing life-cycle.

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# Acknowledgements


- USP Visual Inspection Expert Panel
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  - Deborah Shnek - Amgen


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# Questions?

Remember, everyone is an inspector …

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