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2023 PDA VISUAL INSPECTION FORUM

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EXHIBITION: 17-18 APRIL

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Visual Inspection Approaches for Ophthalmic Solutions Packaged in Opaque and Semi-Transparent Containers

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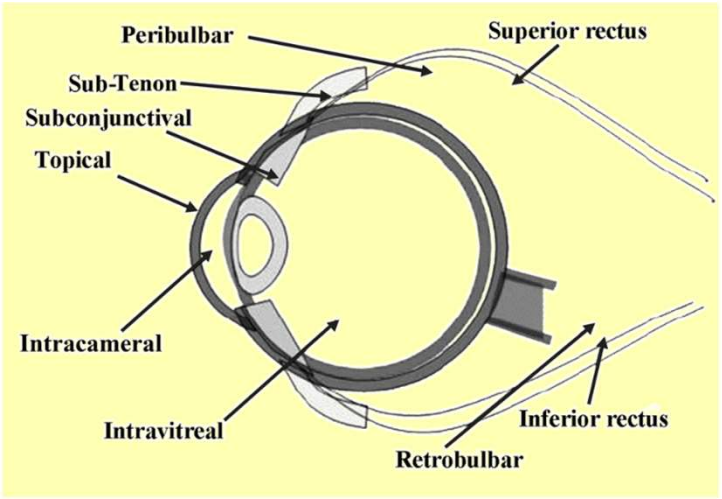
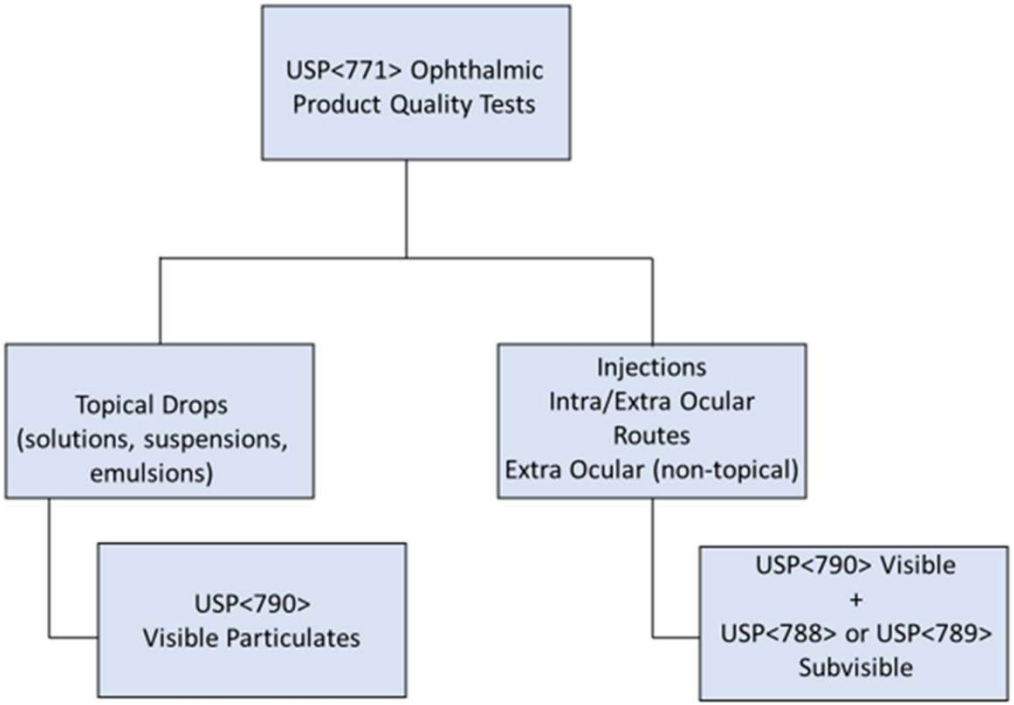
Outline

- USP<771> Ophthalmic Products-Quality Tests
  - Dec 2022 revision: Particulate and foreign matter test changes based on route of administration
- Ophthalmic products packaged in opaque/semi-transparent plastic packaging
  - Alternative test strategies for VI aligned with USP<790>
- Particle prevention measures: evaluating cleanliness of incoming packaging components
- Use of manufacturing process capability and competitor product bench marking as a strategy to establish acceptance criteria aligned with “essentially free” concept

USP Changes Impacting Ophthalmic Products (official Dec 2022)

USP <771> : Particulate and Foreign Matter Requirements for Ophthalmic Solutions





Visual Inspection: Ophthalmic Dosage Forms

- Applies to all sterile ophthalmic products, drops and injections
- Sterile ophthalmic products – many in low volume polymeric packaging
  - Visual Inspection (VI) according to <790> is required, but may require alternate strategies
  - Standard industry practices expected
  - Consider defect category classification and patient risk
    - Topical eye drop vs parenteral injection
      - ***Reduced risk profile for topical drop, thus AQL <0.65% (major) probably not appropriate***

- Guidance Documents
  - *USP* <790> General Chapter requirements
  - *USP* <1790> Informational Chapter background
  - FDA "Inspection of Injectable Products for Visible Particulates"
    Guidance for Industry, Draft December 2021
  - **PDA TR 79, "Particulate Matter Control in Difficult to Inspect Parenterals," 2018**

Destructive testing options:

- Conduct testing in class 100 cleanroom conditions:
  - Transfer sample to a verified-clean glass inspection container and conduct VI
    - high viscosity formulations may require dilution to allow swirl/movement; observed particles further analyzed microscopically to classify type: plastic, fiber etc.
  - Membrane Microscopy: Filter individual units, microscopically examine filter membrane, count and size particles in visible size range (typically ≥ 100 µm); useful for emulsions and dissolved suspensions

Opaque Plastic Container Challenges: USP<790> Acceptance Sampling and Testing

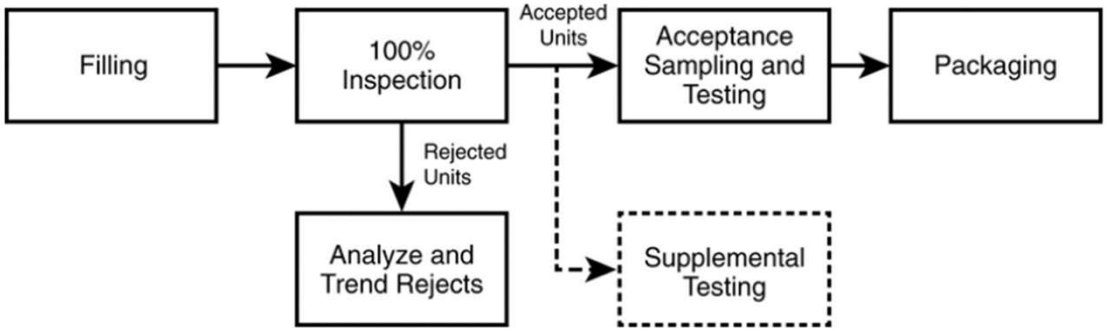


Figure 1. Typical process flow chart.

- Using ANSI/ASQ Z1.4 Tables for sampling procedure:
  - Typical manufacturing batch size: 500L – 1700L ⟶ yields 20,000 – 200,000 filled units
  - AQL of 0.65 (upper limit of major defect category range) and Normal II level
  - Sample size for visual inspection batch release: **300 – 800 units**
- Destructive testing is necessary: 100% “as-is” inspection not possible

- Alternative strategy for lot acceptability is necessary due to destructive nature of the visual inspection test and size of statistically valid sample number

Particle Prevention Measures and Evaluation of Manufacturing Process

- Evaluation of the process stream:
  - Cleanliness of incoming packaging
  - Water fills to gain additional knowledge about filling process capability
  - API cleanness evaluation for suspension products (metal or inorganic particulates if API is milled)
  - Characterize amount, size and types of particulate matter

ISO 5/Class 100
Filling Line

Incoming cleanliness of packaging components: dropper bottles, dropper tips and caps

Incoming Bottles, dropper tips and caps from packaging supplier were evaluated for subvisible/visible particulate matter load

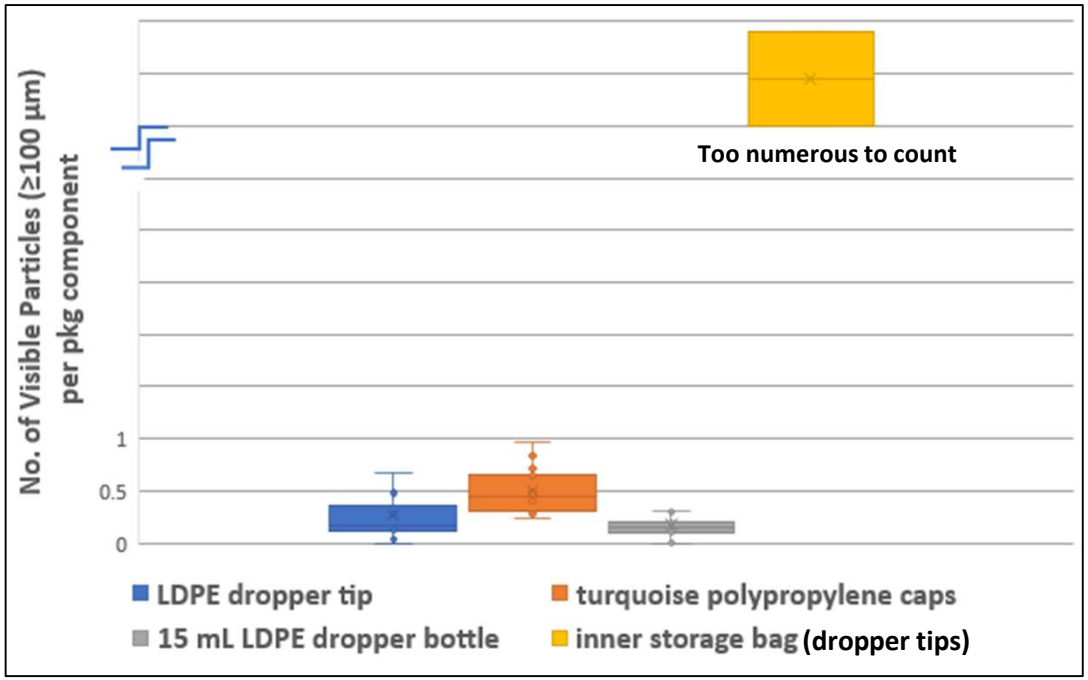
Components rinsed with 0.2 µm filtered water in Class 100 clean hood

Subvisible and Visible particulate load was quantified using light obscuration and membrane microscopy (for visible > 100 µm)

On avg. less than 0.5 particles/component ≥ 100 µm observed for bottles, tips, caps – **good cleanliness**

Largest source of ≥ 100 µm particles: inner storage bag of shipping carton

Best practice in manufacturing: Avoid inverting shipping carton over the hopper when loading pkg components on filling line



Alternative Approach to 100% Visual Inspection: Acceptance Limits?

Use of product stability data to evaluate manufacturing process capability (retrospective analysis):

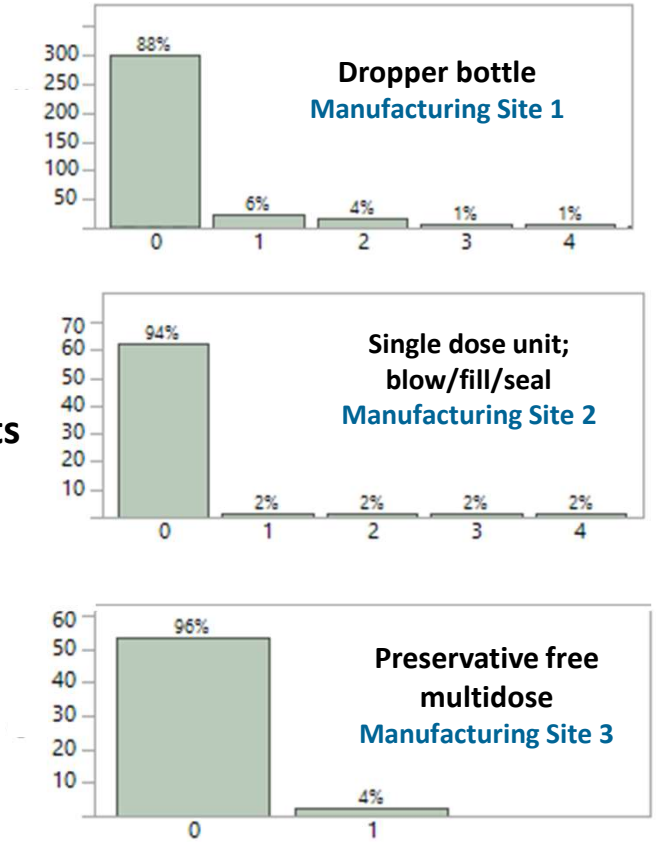
- Assumptions:
  - Visible particulates, if present, “introduced” into to the batch at time of filling; randomly distributed, no trending with stability timepoint or storage condition (stable)
  - Sufficient units are pooled to achieve a 25 mL visual inspection sample
  - Inspection data generated by two trained/experienced analysts (similar performance)
- Different packaging configurations
- Different manufacturing plants, fill sizes and filling processes

Dropper bottle

Single dose unit

Preservative free multi-dose container/closure

Alternative Approach to 100% Visual Inspection: Acceptance Limits?



On average across packaging types and manufacturing sites:

93% of VI tests revealed 0 visible particles

97% of VI tests revealed 0 or 1 particle

99% of VI tests revealed 0, 1 or 2 particles

Visual Inspection Bench Marking: Ophthalmic Solutions in Dropper Bottles: Rx and OTC

Product	Container Fill Vol.	# Visible particles per inspection aliquot (25 mL)
Rx		
Acular™ (ketorolac tromethamine 0.5%)	5 mL	0
Zymar™ (Gatifloxacin 0.3%)	5 mL	0
Quixin™ (Levofloxacin 0.5%)	5 mL	0
Vigamox™ (moxifloxacin HCl 0.5%)	3 mL	2
Voltaren™ (diclofenac Na 0.1%)	5 mL	3
Trusopt™ (dorzolamide HCl 2%)	10 mL	0
Cosopt™ (dorzolamide HCl-timolol maleate)	10 mL	0
Xalatan™ (latanoprost 0.005%)	2.5 mL	0
Generic/OTC		Avg of 3 replicates
Visine	15 mL	0.3 ± 0.6
Thera Tears	15 mL	0
Blink	15 mL	2.3 ± 0.6

- Analysis of Rx and OTC products revealed 1 and up to 3 visible particles per inspection aliquot in some cases
- “Essentially Free” not necessarily defined as 0 particles
- Production performance appears similar across Rx and OTC manufacturers

Summary

- Alternative approaches to visual inspection testing per USP<790> are necessary for topical ophthalmic solutions filled in opaque/semi-transparent packaging
- A strategy utilizing: process capability, cleanliness of process streams (e.g. packaging component) and competitor bench marking can be used to establish acceptance limits aligned with compendial expectations

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