Challenges and Strategies for Assessment of Visible Particles in C&GT and High Concentration Products

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Introduction and background

- What are CGT and high concentration products?
- Scope:
  - Visible particles in:
    - 100% Visual Inspection (last part of the manufacturing process)
    - Visible Particles as part of QC release
- Why are visible particles a concern?
  - Patient safety
  - Product quality/ Process consistency
  - Regulatory compliance

Unique Challenges in Particle Control of CGT and High Conc products

Manufacturing	Purification	Equipment (SUS)	Analytical methods
			
Less automated Manual manipulations Small batch sizes	No sterile filtration	Not optimized for particle shedding	Visual inspection constrained: Containers, product attributes (turbidity, low fill volume)

High concentration products: high viscosity and opalescence

Particle Sources and Specific Challenges

Single Use System Manufacturing Equipment

- Low volume products, short market history
- Sterile not particle free
- Often adopted from R&D laboratories

Filtration

- No sterile filtration (cell therapy products)
- Only cell strainers
- Process not optimized to reduce particles
- Development required

Container Closure System

- Often very high particle load
- Freeze-thaw cycles, transportation
- Challenging to inspect

Regulatory expectations

- **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.

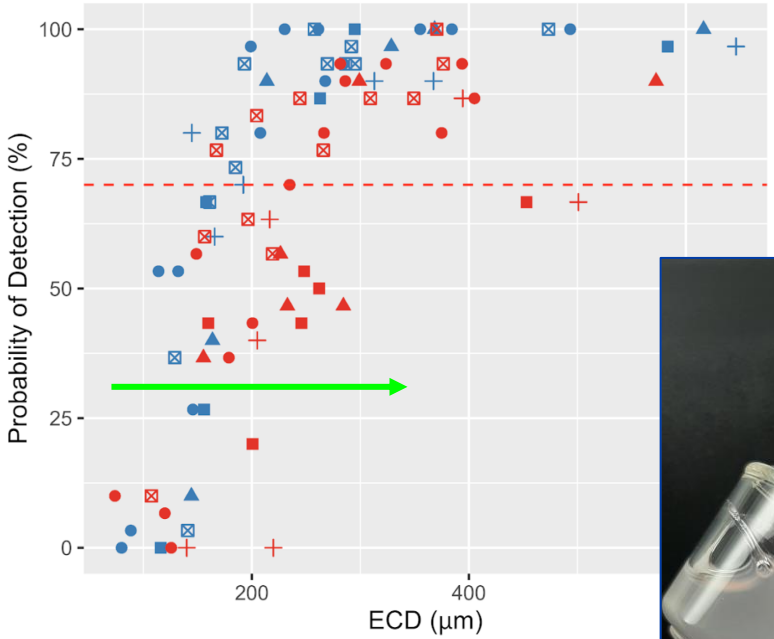
The inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates …

- Harmonization across major markets (US, Europe, Japan): 100% visual inspection mandated
- Recent FDA enforcement trends

Visual Inspection	USP <790>	EP 2.9.20	JP 6.06
Methodology	>2,000-3,750 10s (black/white)	2,000-3,750 10s (black/white)	2,000-3,750 10s (black/white)
GMP requirements	Specification for VP	Specification for VP	Specification for VP,SVP
Cell Therapy	-	Eudralex Vol 4: Part IV GMP for ATMPs	-

Technical Limitations

- High turbidity
- Temperature sensitivity of the product
- Storage conditions
- Short shelf life
- Small batch sizes



Case Studies and Examples

- Real-world examples of particle control challenges and solutions
  - FDA warning letters or observations related to particle control

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

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1. **Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)].** Specifically, your firm's sampling plan and test procedure for (b) (4) freezing bags ("Cryobags"), the primary container for [redacted], are not appropriate to assure that Cryobags are "free of…particulate matter" as required by your acceptance criteria. Between December 2018 and the date of the inspection, you identified approximately one hundred (100) batches of [redacted] contaminated with foreign particulate matter, such as wood, cellulose, brass, and steel. In November 2020, your firm concluded the Cryobags were the

(b) Your procedure for removing particulates detected in [redacted] in final product does not provide assurance that all particulates, including particulates that are not easily visible, can be identified and removed such that the final product, delivered through intravenous infusion, is free from contamination with foreign particulate matter. You have identified "sterility issue[s]" and "thrombosis issue[s]" as potential risks associated with particulate contamination.

  - Successful implementation of prevention, detection, or control strategies

Discussion and Q&A

- Share experiences and best practices
- Brainstorm solutions to specific challenges
- Encourage questions and interaction
- Provide insights and guidance based on co-facilitator expertise

Risk Mitigation and Prevention Strategies

- Implementing Quality by Design (QbD) principles
  - Understanding and mitigating particle risks throughout the process
  - Life cycle management programs
- Establishing appropriate material specifications
- Rigorous incoming material inspections
- Destructive testing (e.g., water runs, rinse tests)
- Visual inspection at the point of use for components
- Using high-quality, low-particle shedding materials and systems
- Optimizing manufacturing steps to minimize particle generation
  - Reducing manual manipulations where possible
  - Controlling the environment (e.g., cleanrooms, isolators)

Detection and Control Strategies

- Optimizing visual inspection methods
  - Inspection durations
  - Light intensity
  - Sample handling procedures
- Training and qualification of personnel
- Alternative Sampling Plans and Technologies
  - Addressing challenges of small batch sizes:
    - 200% inspection
    - Enhanced inspection conditions
    - Alternative sampling plans
  - Exploring novel technologies:
    - Flow imaging microscopy
    - AI-based technologies

Seed questions

- What strategies are typically employed to address the technical challenges we discussed?
- What challenges from the HAs have you encountered?
- What innovative methods/ approaches has your company used to address these challenges?
- How does the strategy with regard to VI change throughout the development lifecycle (phase-appropriate approaches)?
- How do we qualify VI operators to consistently detect inherent particles?