REGULATORY PERSPECTIVE ON INSPECTION OF INJECTABLE PRODUCTS FOR VISIBLE PARTICULATES

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Outline

- Clinical Risk of Visible Particulates
- Quality Risks: Statutory and Regulatory Framework
- Regulatory Impact
- Particulate Matter Breakdown
- Compendial Requirements
- Additional Considerations of the Visual Inspection Program
- Visible Particulate Test/Common Misconceptions
- Life-Cycle Approach to Visible Particulate Control

Potential Clinical Effect and Risk Factors

Potential Clinical Effect

- Venous and arterial emboli, granulomas, occlusions, phlebitis, inflammation, and infection.

Clinical Risk Factors

- Route of administration,
- Patient population,
- Size and shape, number,
- Composition/type of particle.

Quality Risks

Statutory and Regulatory Framework

- **FD&C Act 501(a)(2)(A) –** "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"
- **FD&C Act 501(a)(2)(B): –** non-conformance to cGMPs
- **FD&C Act 501(b): –** drug "its strength differs from, or its quality or purity falls below, the standards set forth in such compendium"

- **21 CFR 211.94(a) –** container/closure -drug interaction
- **21 CFR 211.165(f) –** rejection of drugs failing to meet established standards or specifications

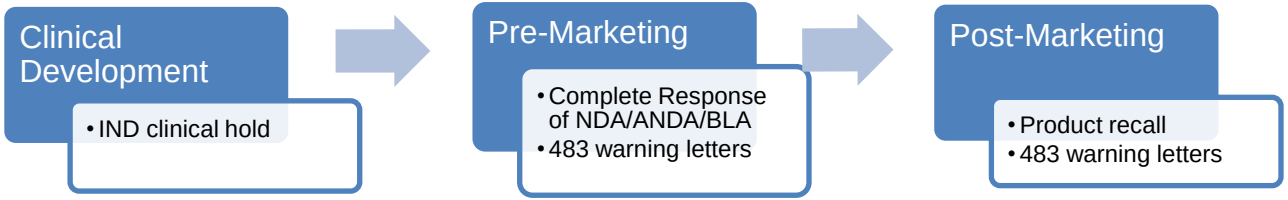
Quality Risks

ICH Q8 – Pharmaceutical Development

"The choice of materials for primary packaging should be justified… A possible interaction between product and container or label should be considered."

"The choice of primary packaging materials should consider…compatibility of the materials of construction with the dosage form"

Regulatory Impact



Example 483 Warning Letters

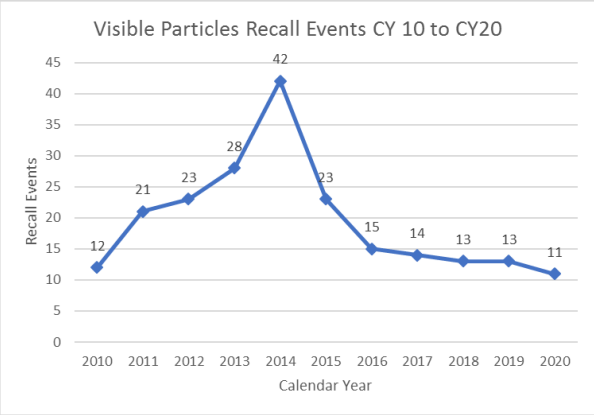
"…our inspection documented that your visual inspection program is unreliable. Your **qualification and re-qualification** of operators did not include determining the operator's ability to detect and identify known product defects for **(b)(4)** products or products filled in amber vials."…

…"Our investigator noted many complaints related to particulate matter in sterile injectable products manufactured at your facility, indicating that the **lack of defect limits** for visual inspections may have resulted in the release of products that otherwise would not have been distributed"….

"There is a **lack of assurance** of the quality of your drug products. For example, during one of your quality assurance audits following 100% visual inspection, additional particulate contamination was found that was not identified during a previous 100% visual inspection conducted for lot release. In addition, you repeatedly discarded contaminated ampules identified from visual inspection, sometimes **exceeding 10%** of a batch, and then distributed the remainder of the batch.

2010 - 2020 Recalls For Injectable Products

Rank	Recall Reason	# of Recall Events
1	Lack of Assurance of Sterility/Microbial Contamination/Non-Sterility	327
2	Presence of Foreign Particulate Matter/Crystallization	220
3	Failed Specifications	88
4	Labeling Related Errors	84
5	Subpotent Drug	45
5	CGMP Deviations	38

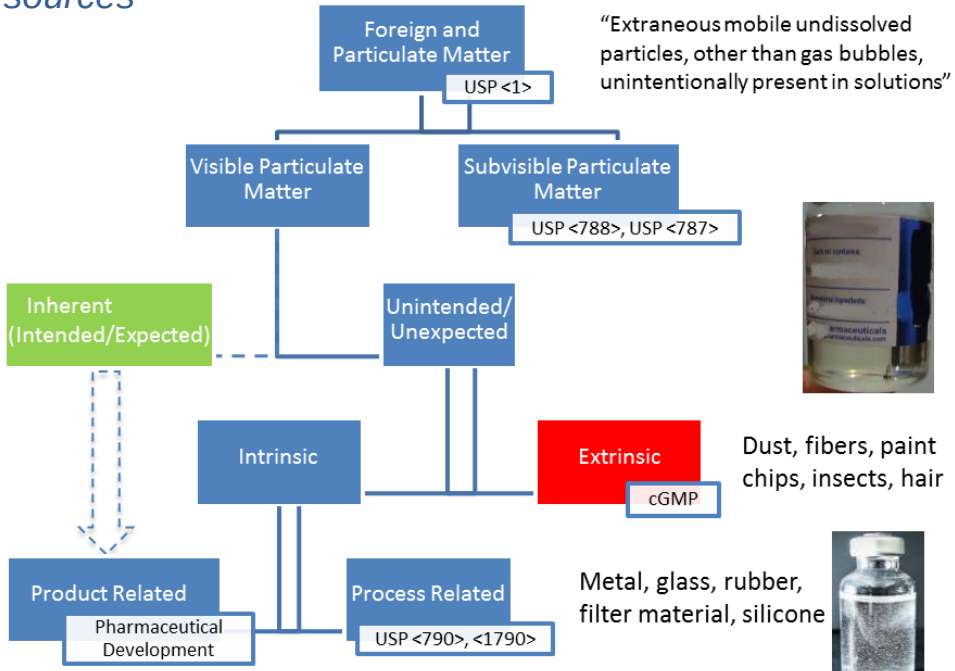


Common Types of Particulate Matter Identified During Recall:
Glass, API/formulation related, stainless steel/iron oxide/metal, hair, silicone, fiber, rubber

Particulate Matter Breakdown - Avoidable vs Unavoidable

Definitions, types and sources

Suspension, emulsion, liposome, proteinaceous particle



Dust, fibers, paint chips, insects, hair

Metal, glass, rubber, filter material, silicone

Precipitation of API, insoluble degradants, protein-silicone oil interaction, aggregation, agglomeration

Compendial Requirements and Scope

- USP <1> Injections and Implanted Drug Products (Parenteral):

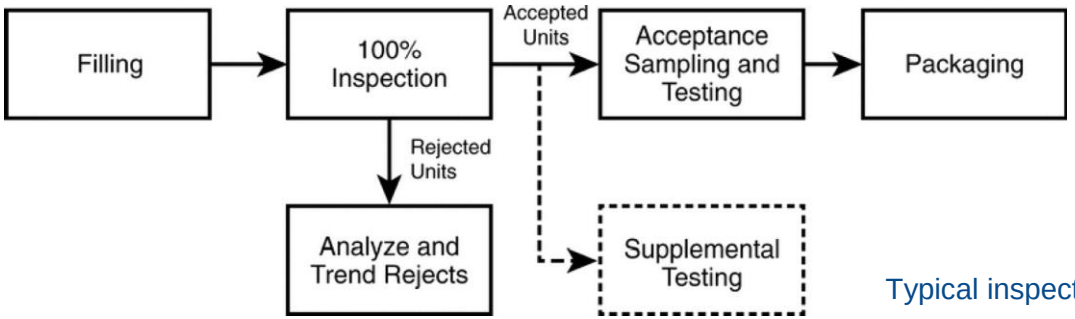
  "Each final container of all parenteral preparations should be inspected to the extent possible for the presence of observable foreign and particulate matter in its contents".

  "Every container in which the contents show evidence of visible particulates must be rejected".

- **Routes of administration**: intravenous, intraventricular, intra-arterial, intra-articular, subcutaneous, intramuscular, intrathecal, intracisternal, and intraocular

- **Dosage forms**: solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), implants (including microparticles), and products that consist of both a drug and a device such as drug-eluting stents.

Visible Particulate Test – USP <790>



Typical inspection process flow chart per USP <1790>

- 100% inspection (during examination of other defects), followed by acceptance sampling (AQL of 0.65% or more stringent plan for higher risk products);
- Probability of detection varies with differences in product formulation, particle characteristics, and package design;
- Zero defects is not feasible due to current process capability and probabilistic nature of the visual inspection process;
- Minimal requirement: lot is <u>essentially free</u> from visible particulates.

Additional Considerations for the Visual Inspection Program – USP <1790>

- **Inspection process qualification**: defect standards, inspector training, qualification and requalification; inspection equipment qualification and validation; automated inspection and new technology considerations.

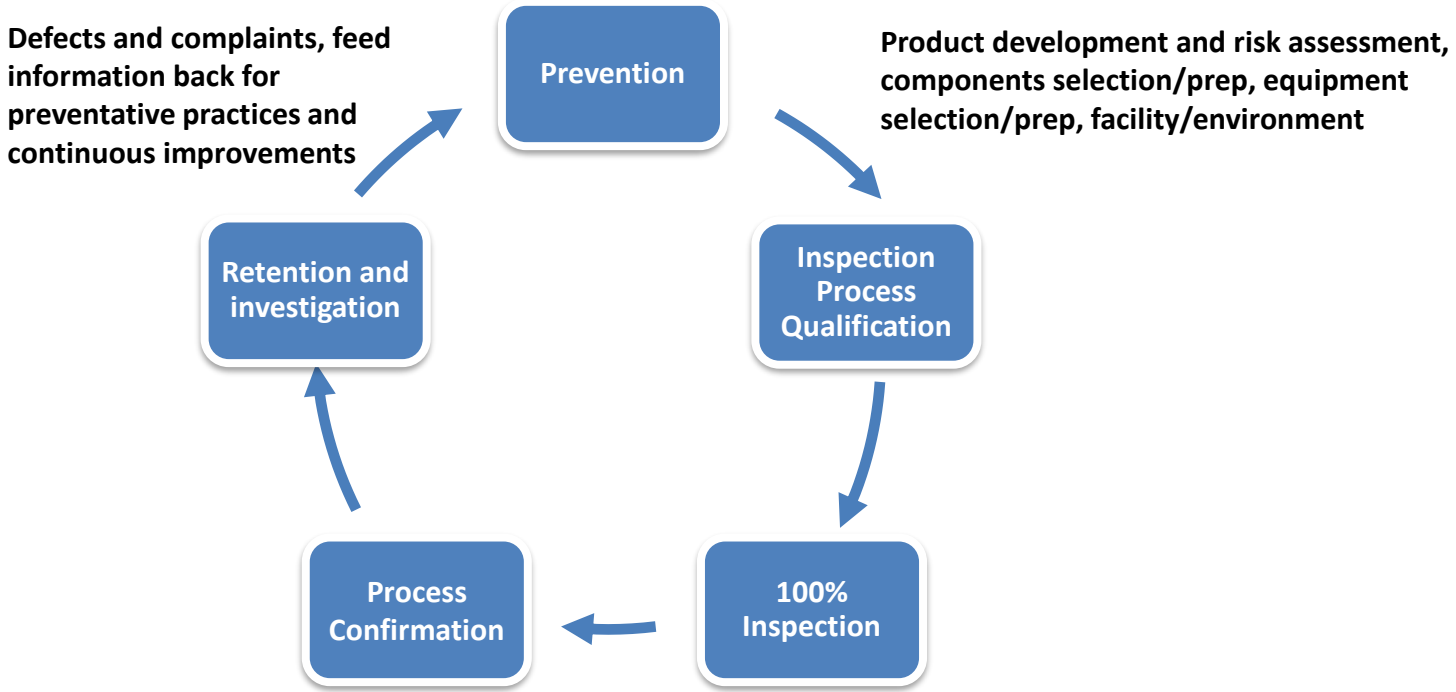
- **Inspection process**: written SOPs for the inspection process and defects removal, alert and action limits, actions for non-conformance, reject analysis, trending and analysis, reinspection (number and acceptance criteria);

- **Difficult-to-inspect products considerations**: AQL to support 100% inspection, plus supplemental/destructive testing (e.g. lyo products, suspensions, amber vials).

Common Misconceptions

- Essential free: Lot vs Vial
- <790> test is same as appearance test in the DP specification: release vs release & stability
- Product can be inspected into quality/compliance
- There is an acceptance level for extrinsic particles
- Meeting <790> is sufficient for meeting cGMP requirements

A Life Cycle Approach to Visible Particle Control of Injectable Products



Desired State

- Rigorous pharmaceutical development studies to prevent product related intrinsic particulates;
- Preventative measures to reduce process related intrinsic particulates;
- Robust visual inspection program to minimize process related intrinsic particulates in the final product;
- Implementation of cGMP requirements to prevent extrinsic particulates;
- Retain samples for stability testing and product complaints;
- Feedback loop for continuous improvement.

Thank You!

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