Inspection of Injectable Products for Visible Particulates

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Regulatory Framework

- Under section 501 of the FD&C Act, a drug product, including an injectable product, is deemed adulterated 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" (section 501(a)(2)(A)).
  - "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 to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess" (section 501(a)(2)(B)).
  - "It purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium" (section 501(b)).

Inspection of Injectable Products for Visual Particles

- USP General Chapter <1> states that "[t]he inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates" as defined in USP General Chapter <790>.
- Injectable products should be prepared in a manner designed to exclude visible particulates, and the inspection process should be designed and qualified to ensure that the products are essentially free of visible particulates.
- Each final container must be inspected using a qualified method to detect particles within the visible size range, and all units that are found to contain visible particulates must be rejected.

FDA Draft Guidance 2021: A Risk-based Approach

- Development and implementation of a holistic, risk-based approach to visible particulate control
  - Clinical and quality Risks
- Incorporates product development, manufacturing controls, visual inspection techniques, particulate identification, investigation, and CAPAs to assess and prevent the risk of visible particulate contamination.
- **Clarifies that meeting an applicable USP compendial standard alone is not generally sufficient for meeting the CGMP requirements for the manufacture of injectable products.**
  - Applying criteria outlined in USP is an important component of the overall visible particulate control program
  - Meeting these criteria alone is not sufficient to ensure compliance with the CGMP requirements
  - Full compliance with CGMP requirements is needed to ensure the continued pure, safe, and effective injectable products.

Clinical Risk Considerations

- The route of administration
  - Intravascular or intravisceral injections generally can cause more adverse events than those in subcutaneous or intramuscular injections.
- Patient population
  - Age (e.g., pediatric and elderly patients)
  - Personal or family history of high risk diseases
- Nature or class of the particulates
  - Physical size or shape, quantity, chemical reactivity to certain cells or tissues, immunogenicity, infectivity, carcinogenicity
- **Depending on the clinical risk profile associated with a specific product, FDA may expect that product to comply with stricter standards than those set forth in the compendia in order for those products to meet CGMP requirements.**

Quality Risk Assessment of Visual Particles

Risk considerations based on the category of particulates:

- Inherent particulates are particulates that are an innate product characteristic.
  - Consider as part of the quality target product profile if they are a property of the product and product release specifications are met
  - Monitor time-dependent changes during stability testing
- Intrinsic particulates are particulates that are derived from the manufacturing equipment, product formulation, or container system.
  - Establish process controls
  - Assess impact on manufacturing process, equipment and facilities
  - Evaluate trends to monitor and controls, time-dependent particle formation
- Extrinsic particulates are particulates that originate from the manufacturing environment and are foreign to the manufacturing process.
  - Negatively impact on process, product quality and sterility assurance

Visual Inspection Program: Essentially Free

- USP <790>: The term essentially free means that when injectable drug products are inspected, no more than the specified number of units may be observed to contain visible particulates.
- FDA Draft Guidance (2021): A visual inspection program should ensure that any visible particulates present in the batch at the time of release are only those that have a low probability of detection because they are of a size approaching the visible detection limit.
  - USP recommendation: a visual inspection program should ensure that any readily detectable particulates in the batch are removed upon visual inspection at the time of release.

Visual Inspection Program

- Establish procedures for inspecting the product (100% Visual Inspection)
- Statistical sampling plan (AQL testing)
- Acceptance/rejection criteria (Critical or Major)
- Training and Qualification (equipment and operators)
- Investigation/reinspection

Visual Inspection Program: Overview

- Part of a larger program to ensure that injectable products are essentially free of visible particulates.
- During development, manufacturers should establish procedures for inspecting the product, statistical sampling plan(s), acceptance/rejection criteria, and procedures for evaluating inspection results.
- Allow for appropriate adaptations based on knowledge gained throughout the product's life cycle.
  - the inspection procedures and/or analytical and statistical methods may need revision if the batch size, manufacturing process, or conditions change.
- A visible particulate control program should include the training and qualification of operators and investigation of discrepancies, including root cause analysis, corrective actions, and preventive actions.
- Inspection procedures carried over from another site or another product may not always be suitable for a new product.

Visual Inspection Program: Training and Qualification

- Train all operators with common procedures for 100% inspections and AQL
  - All inspection practices should be standardized and consistently executed across all inspection groups
- Qualification should be performed for each product type and package under normal operating conditions
  - Inspection timing and sequence, physical environment, and inspection duration per unit.
- Acceptance criteria for each defect class should be based on the probability of detection (POD).
  - A limit is also needed for false rejection, with a recommended target of <5% falsely rejected good units.
- Requalification should be performed annually or as needed based on performance
  - Define the worst case conditions
- If an operator fails the requalification test, a retraining process should be initiated to identify the root cause and allow the inspector to receive additional instruction.
  - Product quality impact assessment should be conducted

Visual Inspection Program: Training and Qualification

- Defect Standards
  - Samples collected throughout the product life cycle
    - Any new particulate matter defect is identified, it should be analyzed to determine its source and added to the training library.
  - Sample types likely to occur for the drug product and its manufacturing process
  - Examples from the lower limits of visual detection determined in the threshold studies
  - The percentage of defective units in a test set should not exceed 10–20 percent and sufficient quantities to provide an adequate degree of confidence in the test results
    - Identity of defective units should be masked to test subjects
- Established procedures:
  - Handling of the units (e.g., swirling, inversion, distance from light)
  - Maximum length of the inspection period without a rest break
    - 20 minutes of inspection followed by a break of at least 5 minutes
    - A total maximum duration not longer than 4 hours.

Visual Inspection Program: Automated Visual Inspection

- AVI offers advantages in the areas of throughput and consistency, compared with manual VI
- Machines should be validated to meet or surpass manual inspection capabilities
  - Higher false rejection rates?

- Define a "grey" channel/eject channel, for containers for which the inspection result is not clear.
  - Re-inspection of objects in the grey channel should only be done one time
- Re-inspection of rejected containers shall not be performed without justification based on a thorough investigation.
- Establish procedures and limits for particulate category evaluation and trending
  - Potential impact of Extrinsic particulates on product quality and sterility assurance

100% Visual Inspection

- Components and Container Closure Systems
  - Procedures for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and product containers
  - Components and containers and closures are tested or examined and approved, as appropriate, before use in manufacturing
- Facility and Equipment
  - For manual inspections, requirements for the inspection station background and the light intensity.
  - For semi- and fully-automated machines, equipment should be properly qualified and routinely maintained/calibrated to ensure proper performance.
  - The inspection environment should be free from distractions and extraneous light, and the inspection rate should be qualified and should allow for thorough visual inspection

100% Visual Inspection

- Process
  - Conduct inspection feasibility studies for visible particulate detectability, unit inspection duration, illumination, and fatigue timeframe.
  - Procedures on how to conduct 100% inspections (AQL), handling of the units (e.g., swirling, inversion, distance from light), maximum length of the inspection period without a rest break, and disposition and documentation of rejected units.
- Special Injectable Product Considerations
  - Supplemental destructive testing
    - Typical sampling plans for this type of test can be found in the special sampling plans S-3 and S-4 in ANSI/ASQ Z1.4
    - For most batch sizes between 3,201 and 150,000 suggest a sample size of 20 with an accept number of 0.

Statistical Sampling: AQL

- Typical sampling plans can be found in the ANSI/ASQ Z1.4 standard
  - For batch release, the sampling plans listed as Normal II are typically used
  - Tightened sampling plans may be appropriate when an atypical result is observed or re-inspection is performed.
- Extrinsic particulates identified during 100% inspection or AQL
  - The presence of filth, sterility assurance issues, or other CGMP violations may result in product that could be considered adulterated, even if the statistical sampling acceptance criteria are met
- All inspection practices should be standardized and consistently executed across all inspection groups

Quality Assurance Through a Life Cycle Approach

- Process performance and product quality monitoring systems
  - Measurements on the state of control during manufacturing
    - Deviations, in-process defect results, statistical process control reports, equipment and facility breakdowns
  - Product or process design issues
    - Trends of increased particulate contamination, identification of new types of particulates, or particulates that exceed alert or action limits
  - Particulates-related quality issues
    - Product quality indicators (e.g., stability test results, complaints, returned product)
    - Field alert reports and adverse event reports

Actions To Address Nonconformance

- Investigations should be conducted in situations such as the following:
  - Individual or total defect limits are exceeded
  - A batch fails to meet AQL limits
- Investigations should identify and categorize the particulates (intrinsic or extrinsic)
  - Understand their origin and identify potential CGMP issues or sterility failures
    - Impact on batch release
  - Improvements to the 100% inspection and/or AQL inspection program
- Re-inspection of product batches may be permissible with appropriate scientific justification with tightened acceptance criteria.
  - FDA does not recommend more than one re-inspection in an attempt to release a batch with atypical defect levels.
  - Samples failing the AQL reinspection should be counted along with rejects from any other inspection of the product in calculations to account for and reconcile all units of final product in the batch.

Case Study - 1

- Visual particulates classification
  - All particulates are classified as Major defects for 100% VI and AQL
- Observations
  - No identifications/investigations for unknown or extrinsic particulates found during 100% inspection if they are within the major defect limit
  - No investigations for particulates found during AQL if they are within the major defect limit
    - No particulate size limits

Case Study - 2

- Automated Visual Inspection machine for 100% Visual Inspection
  - Automated Visual Inspection machine was not qualified for particulate identification
- Observations
  - All visual particulates found during 100% VI were rejected without ID for particulate categories
    - Inherent, intrinsic, or extrinsic particulates
  - Potential impact on product quality and sterility assurance for all previously manufactured batches is unknown since all defect units were rejected and not available for re-inspection.

Case Study - 3

- Automated Visual Inspection machine for 100% Visual Inspection
  - Automated Visual Inspection machine was “qualified” with a higher rejection rate for visual particulates
  - Accepted units were released for packaging
- Observations
  - The VI procedure allows another 100% manual visual inspection of “rejected” units to recover “good” units as a routine process without investigation and justification
  - A CGMP concern: test into compliance

Case Study - 4

- A unit containing an extrinsic/unknown particulate was found during the 100% manual VI
  - The batch met the acceptance criteria (major defects) for 100% VI
  - The defect unit containing an extrinsic particulate was rejected
- Observations
  - The defect unit was rejected and the batch was release after it passed AQL without investigation.
  - There was no impact assessment on product quality and sterility assurance
- Batches containing extrinsic particulate(s) should be evaluated to determine potential impact on product quality and sterility assurance

Case Study - 5

- Automated Visual Inspection machine for 100% Visual Inspection
  - The automated Machine has been qualified for all existing defect categories
  - A new defect category for visual particulates was identified
  - The machine failed to reject units with the new defect category using the existing commercial recipe during re-qualification
- Observations
  - The existing machine recipes were found to be inadequate for VI.
  - There was no investigation to evaluate the impact on previously released batches that used the deficient visual inspection process.

Case Study - 6

- Visual inspection failure
  - A batch passed the 100% VI, but failed the AQL
- Observations
  - A 100% re-inspection was conducted without initiating an investigation. The batch was released after it passed 100% re-inspection and AQL
  - No investigations required after an AQL failure unless a critical defect was identified
- An investigation should be conducted to identify the root cause(s) before re-inspection.

Case Study - 7

- Inadequate training for VI operators
  - Operators failed annual requalification
  - Operators failed to identify defect units during 100% VI (AQL failure)
  - Training prior to requalification
- Observations
  - Failed to conduct product quality assessment for previous batches inspected by the operators
  - Inadequate operator qualification program

Thank You!