Quality (QA/QC) Methods

Trending and Monitoring of Particulate Matter

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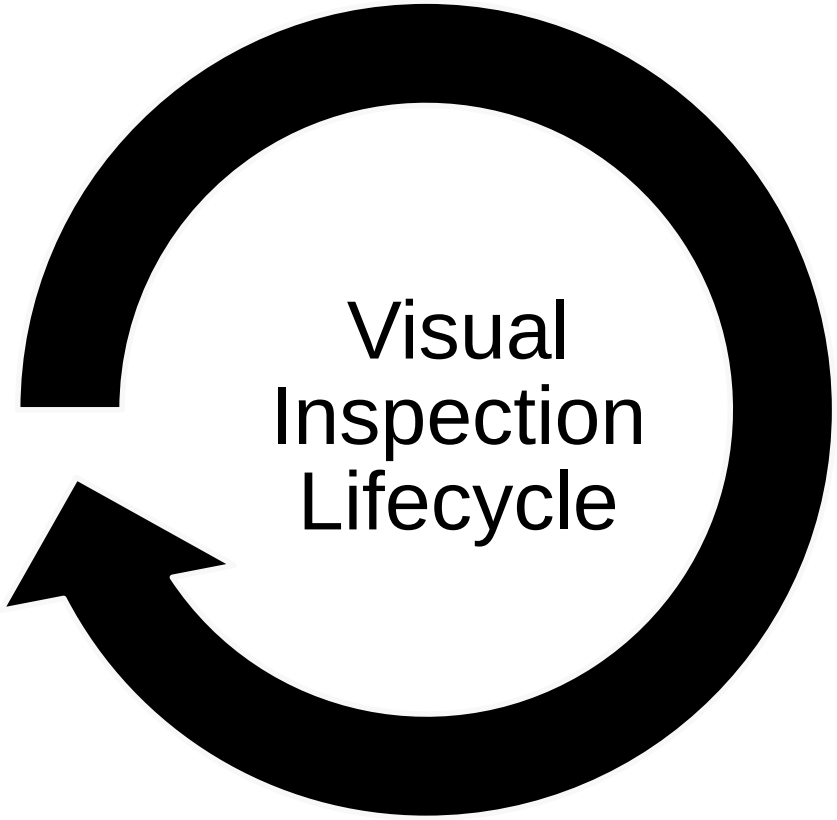
Quality (QA/QC) Foundations
Check List of the Ground Rules

- ❑ Lifecycle concept embraced and implemented to track and control defects in a phased approach
- ❑ Standardize Visible Particle Terminology
- ❑ Awareness of what is a visible particle
- ❑ Understand the Knapp Reject Zone Concept and Limitations
- ❑ Manual Particulate Inspection Prerequisites
  - ✓ Stabilized Inspection Parameters
  - ✓ Test Sets-Single Visible Particle per Unit
  - ✓ Trained & Qualified Inspectors
  - ✓ Method Sensitivity Demonstrated -Threshold Studies
  - ✓ Secure Reject Zone Knapp studies
- ❑ Establish Basic In-House microscopic particle characterization and investigative capabilities
  - ✓ Particle Characterization and Identification Levels
- ❑ Appropriate AQL Criticality applied to Particulates
- ❑ USP <1> Supplemental Inspection: Discussion on Various API forms
  - ✓ Solids, Suspensions, Emulsions, Non-Transparent Product or Containers
- ❑ Special Considerations for Characterizing Protein Formulations

Visual Inspection Lifecycle



- Supplier Quality Agreements
- Component Testing and Acceptance
- Component Preparation
- Bulk Preparation
- Filling
- 100% Inspection
- AQL Inspection
- Stability
- Retention
- Customer Complaints

Lifecycle of Visual Inspection presented by R. Cherris at the October 2011 PDA Visual Inspection Forum, Bethesda, MD

Particulate Terminology

- ***Inherent Particulate:*** Particulate made entirely of components of the formulated product, arising from the product itself. Indemic particulates are related to the product formulation (e.g. Distributions of API Proteins, API Solid Suspensions, Emulsions, adjuvant aluminum salts added to vaccines.)

Inherent particles must be well Characterized and Monitored over the product shelf-life

- ***Intrinsic Particulate:*** Intrinsic particles include product contact materials from the manufacturing process or primary packaging components (i.e. glass, stainless steel, rubber closure, polymer tubing, semi solid silicone lubricant, process related fibers, etc).
  - Also includes particulates found predominanly during development or stability studies (Formulation Degradents, Container Closure Interaction, Glass Delamination, etc.)

Intrinsic Particle Types Must be Monitored/Controlled and Minimized or Eliminated

- ***Extrinsic Particulate:*** Particulates which are introduced from foreign or external sources. Any particulate not sourced from the manufacturing process or product contact materials including particles of a biological source (i.e. external environmental fibers, hair, insect parts, paint chips, etc.)

Extrinsic Particle Types should be a Rare Occurrence and Eliminated

What is a Visible Particle?

Assumption: a consistant and reproducable manual inspection procedure as per compendia (EP and new USP-790) for a clear solution in a standard transparent glass vial (5-10ml):

- using at a **minimum** illumination at the point of inspection in the range between 2000-3750 lux
- Consistant aggitation to place particles in motion prior to inspection
- 5 sec. Inspection per black and white background (10 sec. Total Inspection time)

✓The detection process is probabilistic, with the probability of detection increasing with increasing particle size.

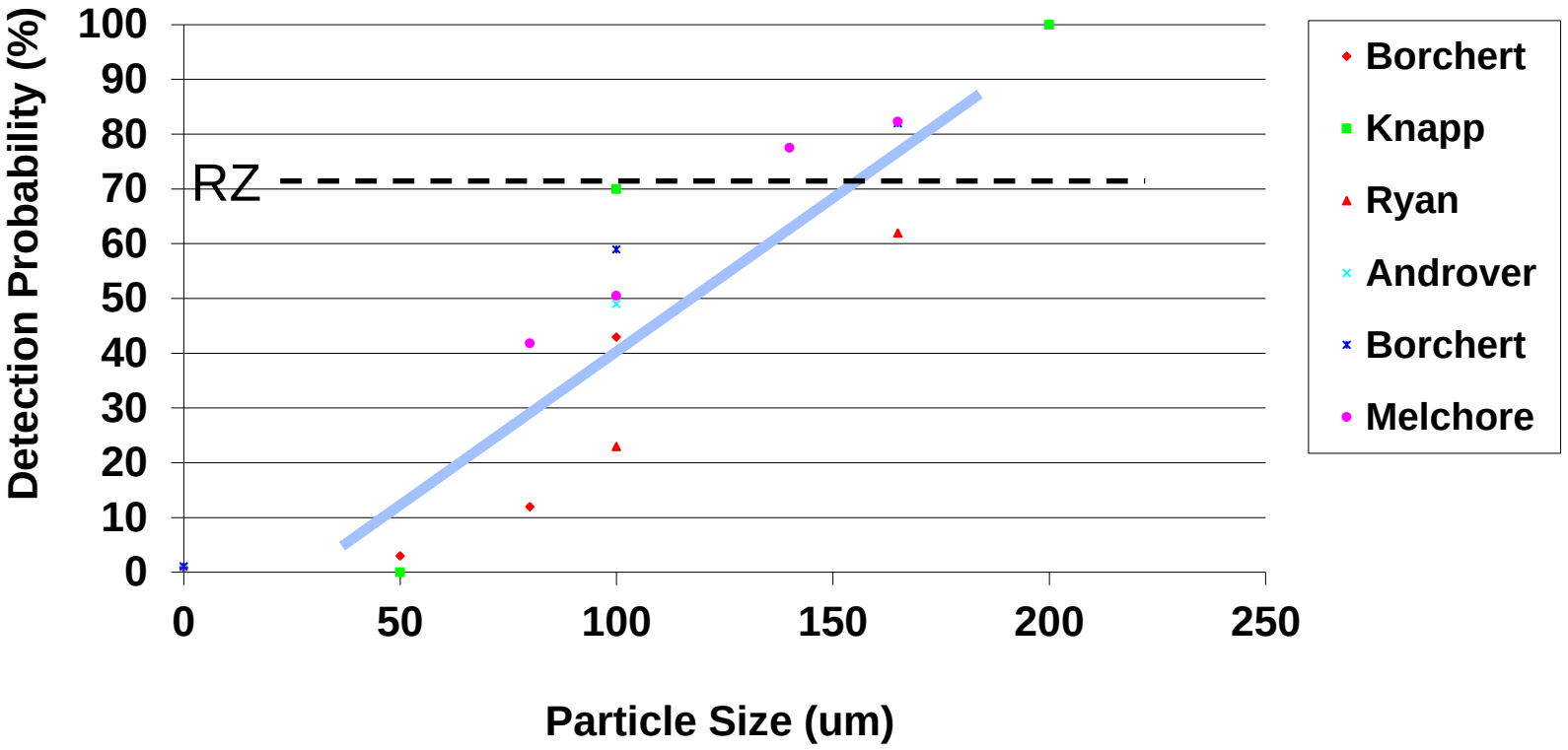
✓The lowest detectable size for 20/20 human vision under controlled inspection conditions is generally accepted to be 50 µm.

✓The probability of detection for a single 50 µm particle is slightly greater than 4%.

✓This probability of detection increases to approximately:

- 40% for a 100 µm particle
- 70% for a 150 um particle
- >80-90% for particles 200 µm and larger

A Very Well Known PDA Survey Slide
Human Inspection Performance (1995)



Studies in Clear Glass Vials
From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995
Published in the PDA Survey Summaries

Particle Size and Type Detection Threshold

- Manual Inspection Particulate Threshold Studies
  - ✓ Human visual particle size detection threshold studies confirm manual inspection method sensitivity (suitability)
  - ✓ Use **Intrinsic** particle types of various densities (stainless steel, glass, rubber, polymer tubing, process related fibers, etc.)
    - ✓ The particulate threshold test sets should include a graduated seeded or natural particle size range covering 100 um to 1000 um at a minimum
  - ✓ Particulate detection size threshold studies should show reproducible probability of detection of particles in the 150 to 250 um range
  - ✓ Fiber detection threshold 700 to 2000um due to length:width aspect ratio)
  - ✓ Demonstrates the inspection method can reliably detect visible particles at ≥70% Probability Of Detection (POD)

Knapp Zone Methodology

- ✓ **Knapp's Methodology** was developed specifically for use in particle detection focusing on a repeatable visible particle detection/rejection threshold at ≥70% Probability Of Detection (POD)

- ✓ **Reject Zone Containers** Non-Acceptable/Reject units containing visible particles starting at approximately 150 um and greater (≥70% POD). This reject zone must be maintained and secure in all methods of inspection (manual and fully automated)
  - The Knap methodology is based on the qualification of a defect rejection efficiency (≥70 % POD) demonstrated by using characterized production rejects or standards seeded with single particles

- ✓ **Gray Zone** (≥30% to <70% POD) and **Accept Zone Containers** (≥0% to <30% POD)**:**
  - Some portion of all rejects will contain units with Gray Zone particles based on variations of visual inspector acuity or inspection method
  - Finished product units with particles in the Gray Zone are acceptable units for market distribution and contain sub-visible particles evaluated by USP<788> methods

- ✓ The **Accept Zone Containers**(<30% POD) can be used as blanks in test sets or are analyzed during inspection studies to measure the effects of false rejects on the process

Knapp Inspection
Alternate Method Correlation

- ✓ Knapp Reject Zone Efficiency (RZE @ ≥70% POD)
  - Studies are also used to demonstrate that any alternate method is equivalent to or better than the baseline Manual Visual Inspection (EP and new USP 790)
  - The manual Visual Inspection is the method which is the basis used for the final AQL (essentially required as a Quality Control verification for batch release)
  - Test sets are used to show the equivalency of the average reject zone efficiency of the manual process (**mRZE)** in comparison with any alternate inspection method (**aRZE)**
  - This comparison is part of the qualification of any alternate inspection method

Knapp Zone Methodology Limitations

- ✓ **Knapp's Methodology** at ≥70% Probability Of Detection (POD) is the Parenteral Industry Gold Standard for inspection qualification however there are limitations
  - There is a possibility that up to 30% of the particles at the demonstrated threshold of detection will not be observed (missed)
  - Therefore assuming that the 70% POD threshold is approximately 150 um for particles and >500 um for fibers, We can expect to find these undetected particles in the threshold range in subsequent Stability and Retention sample inspections
  - Inspection of Stability and Retention samples are defined by CFR to evaluate product or container/closure degradation
  - Intrinsic process related particles (SS, glass, plastic, do not spontaneously generate in Stability and Retains samples so finding low frequency of these particles should not create a panic or field alerts
  - Again characterization and sizing of recovered particles is essential

Quality (QA/QC) Methods
Foundations or Ground Rules

- ✓ Manual Particulate Inspection Prerequisites
  - Stabilized Inspection Parameters
  - Test Sets with a Single Visible Particle per Unit containing Intrinsic particle types and a range of sizes
  - Trained & Qualified Inspectors
  - Manual Method Sensitivity Demonstrated -Threshold Studies
  - Alternate Inspection Methods shown to be secure by Knapp Reject Zone studies
- ✓ Establish Basic In-House Microscopic particle handling and characterization capabilities
  - Allows initial triage of recovered visible particles for photographic documentation and the first steps toward investigation
  - Defines specific particles of interest for further ID or analysis at contract laboratories

Quality (QA/QC) Methods
Particulate Characterization/ID Levels

- ✓ Microscopy Lab – An Essential Requirement
  - Trained personnel to separate rejected units into basic groups (Level 1- In Situ)
  - Basic capabilities in-house to microscopically characterize the visible particulate (Level 2 - Characterization/ID)
  - Internal or External Support for Spectroscopic (level 3 – Fingerprint ID)
- ✓ Level One: Visual Observation (in-Situ)
  - Nondestructive, as seen during manual inspection
  - Light, dark, sinking, floating, color, shape, etc.
- ✓ Level Two: Macroscopic and Microscopic
  - Rapid characterization to specific material categories
  - Metallic, glass, rubber, plastic, fiber (natural or synthetic), silicone lubricant, inherent particles, etc.
- ✓ Level Three: Spectroscopic or other fingerprint ID
  - FTIR, Raman, LIBS, SEM/EDX, Mass Spec, etc.

No Parenteral batch is Free from Visible Particles!!

PF 38-6 USP <790> Briefing Statement:

- The detection of visible particles is probabilistic; i.e., the probability of detection increases with increasing particle size
- **Although zero defects is the desired goal and should drive continuous process improvement, it is not a workable acceptance criterion for visible particulate matter because of current packaging components and processing capability**
- USP has adopted the terminology of **"essentially free"** to recognize this current state; however, a more precise definition of "essentially free" is established in USP <790>
- Utilizing a Lifecycle approach "Essentially Free" is defined by passing an AQL at ≤0.65 following a qualified 100% inspection procedure

Quality (QA/QC) Methods
AQL Levels

- Defect Criticality Categories: Representing Orders of Magnitude

  - ✓ **Critical** range is the lowest order of magnitude, between 0.01 to 0.065
    - Is Zero tolerance to Visible Particle Defects practical?
    - USP 788 allows up to 600 particles >25 um per container
    - Visible particles >150 um will be recovered routinely in each product lot so they don't really fit in the "zero tolerance" or critical category

  - ✓ **Major** Defect range typically applied to an AQL of 0.1 to 0.65
    - USP<790> Minimum acceptance of "Essentially Free" ≤0.65 AQL

  - ✓ **Minor** defects typically applied to an AQL of 1.0 to 4.0
    - More conservative approach for Minor Primary Component defects yields an AQL of 1.0 to 2.5

Quality (QA/QC) Methods and Particulate Criticality

- ✓ Particulate AQL Acceptance Values - Major or Critical?
- ✓ AQLs Critical and Major are differentiated by orders of magnitude (previous slide)
  - Particulate matter was originally specified as a **Major A** defect in Fed. Std. 142A
  - USP <790> promotes a ≤0.65 AQL (**Major** defect level) for all particle types as the minimum acceptable standard
  - PDA Industry Benchmarking survey roughly split between categorizing particles as Critical or Major however the median value reported as the AQL used for batch acceptance was 0.65 (a **Major** defect level)
- ✓ Differences of individual industry and regulatory opinion adds to the confusion
  - The term Critical is being applied inconsistently and inappropriately with regard to AQLs used in current industry standard practice for visible particles
  - Currently industry AQL values for Intrinsic particles are being applied variably in ranges between 0.1 to 0.65 (This range is typically applied to the **Major** defect category)
  - True Critical range would be between 0.01 to 0.065 of which the lower AQLs represent a Zero Tolerance for particulates which is not currently attainable by current industry standard manufacturing

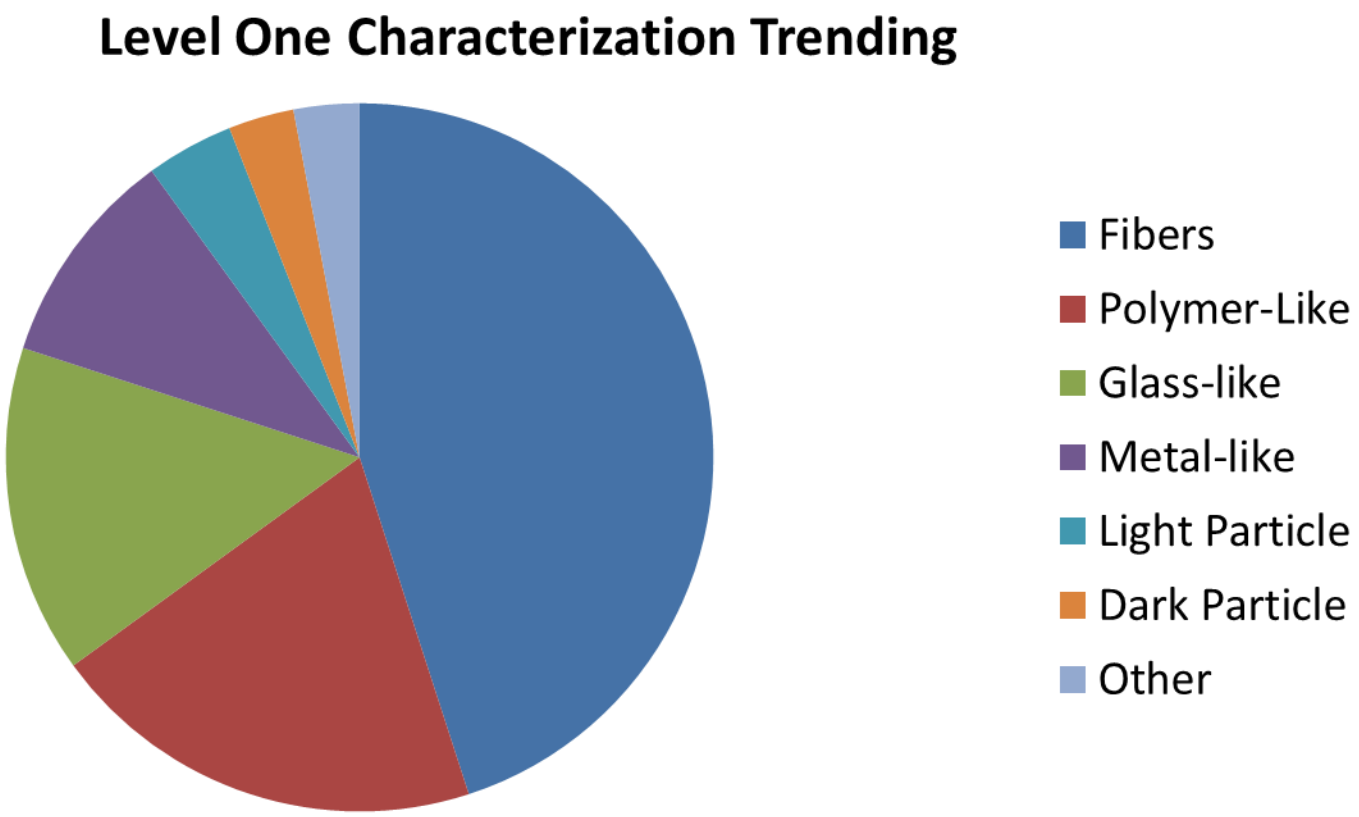
Quality (QA/QC) Methods
Particulate Criticality (continued)

- ✓ **Reality:** visible particles classified to Critical (zero tolerance) is clearly a future goal but as an industry we are collectively controlling particulate matter predominantly in the Major defect AQL ranges (remember up to 30% of threshold particles can be missed)
- ✓ Particle control levels should be Process Capability Derived (Historical Data). Rejected product holds the answer!!
- ✓ Repeated cycles of trending and particle source mitigation followed by continued trending leads to true process monitoring and control
- ✓ Rejected Product Characterization is similar in concept to Environmental Monitoring for microbial control
  - Routine collection of samples to determine contamination frequency
  - Characterization and Identification of contaminant to segregate them into populations
  - Based on the contaminant identity we would investigate and apply mitigation procedures to maintain contamination at controllable levels
  - This cycle is repeated on every lot of product manufactured

Quality (QA/QC) Methods
100% Inspection - Reject Classification and Trending

- ✓ 100% inspection rejects are examined from each batch
  - Level 1 characterization (In-Situ) of all particulate rejects initially from batches fractional sampling and classification can be justified after developing the historical profile
  - Trend primary populations: Glass-like, Metal-like, Fiber, Polymer-like, Light Particle, Dark Particle, Other (add groups as appropriate)
  - Statistical fractions of each group above taken to Level 2 ID (Microscopic): based on optical properties these are confirmed in known groups Glass, SS, Fibers (natural or synthetic), Polymer Tubing, Rubber Closure, Semi-Solid Silicone, etc.
  - Build a visible particulate reference library based on Level 2 (Microscopic) and where necessary Level 3 (Spectroscopic)
- ✓ Institute Action and Alert Levels where feasible

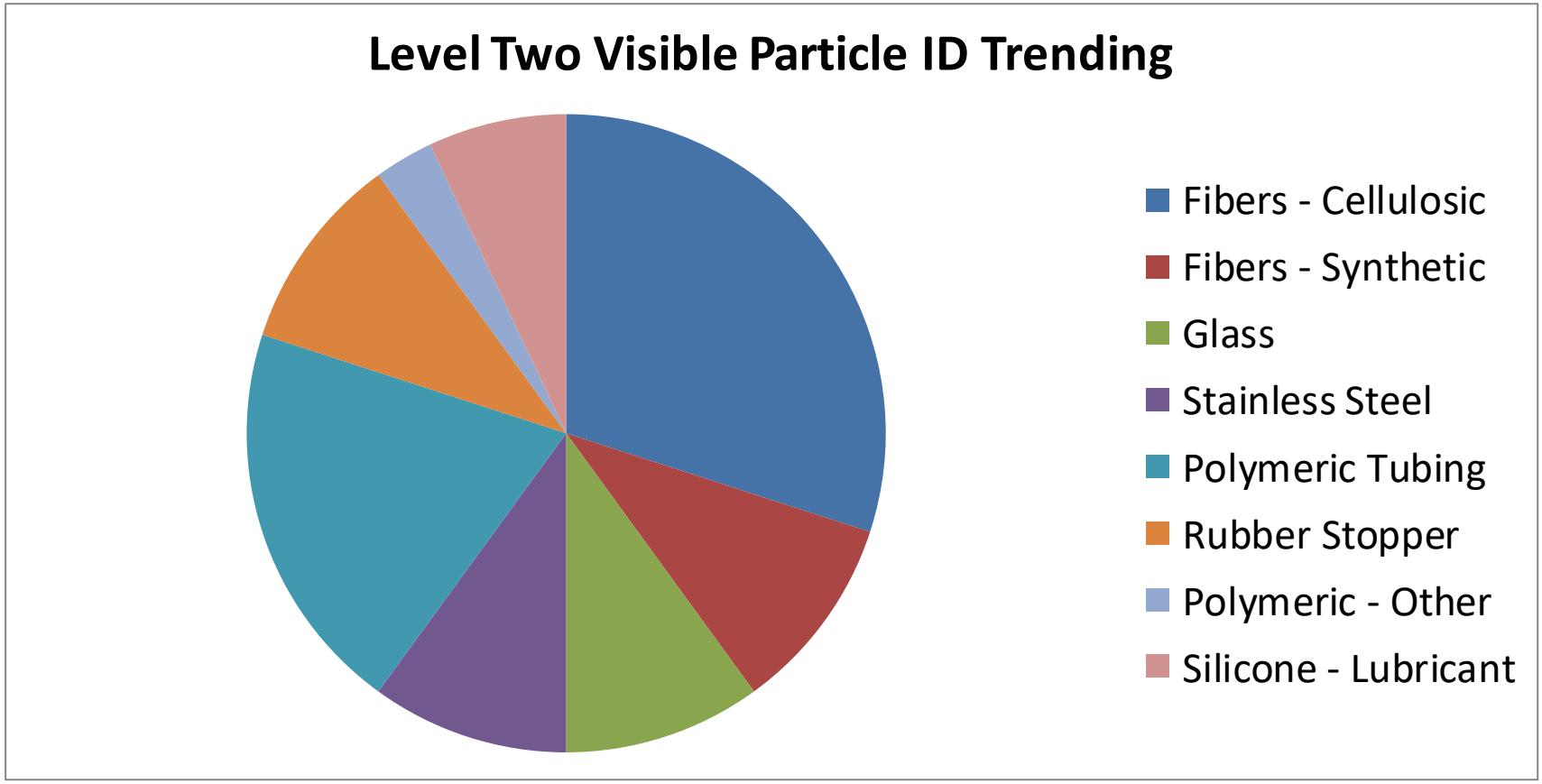
Trending After 100% In-Process Inspection



Quality (QA/QC) Methods
AQL Inspection - Reject Classification and Trending

- ✓ Particle type characterization or Identification of all AQL rejects is needed to determine Intrinsic or Extrinsic particles
- ✓ All Intrinsic product contact particles should remain a Major defect with AQL ranging from 0.1 to 0.65
- ✓ Question: Glass or Stainless Steel are they really a different risk than other particle types?
  - Physiological risk specifically for glass and SS is not demonstrated in studies or literature
  - Evaluate process risk and detectability by inspection method
  - Based on risk, apply additional controls where indicated (Trigger Investigations or use tightened AQL for specific particle types if deemed appropriate)
- ✓ Extrinsic particles a heightened concern may be considered in the Critical category
  - Recommend applying an AQL of 0.065 for Extrinsic particles
- ✓ Database particulates & container/closure defects found in AQL
  - Routinely trend data and periodically re-evaluate control levels
- ✓ AQL Reminders
  - AQL Inspections should be identical to manual in-process 100% inspection used to initially qualify the inspection method. Maintain strict adherence to pacing and sequence
- ✓ Formal re-inspection policy should be in-place followed by tightened AQL acceptance

Trending After AQL Inspection



Quality (QA/QC) Methods
Defect Mitigation

- ✓ **Particulate Risk Management by Optimization of the Process**
  - Use the Trending Data from Reject Characterization and Monitoring
  - Review the various particulate sources for Process Improvement opportunities
  - Focus, as with any reoccurring phenomenon, should be on the most predominant particle types, those that may often delay release decisions or those that most often place the product or process in jeopardy
  - Rationalization of those that can be eliminated or further minimized
  - Repeat the Cycle of Monitoring, Trending, Corrective actions and follow-up Monitoring

Quality (QA/QC) Methods
Supplemental Inspection

- ✓ Required by current USP Chapter <1> Particulate Matter
  - Where the nature of the contents or the container-closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot **shall be supplemented with the inspection of constituted** (e.g., dried) **or withdrawn** (e.g., dark amber container) **contents of a sample of containers from the lot**

- ✓ Appropriate for Lyophilized, Powder, Suspensions, Emulsions, Protein Formulas or Products in Opaque Containers

Quality (QA/QC) Methods
Supplemental Inspection

- ✓ Lyophilized products or Powder products that form a clear solution when reconstituted
  - Extreme care is required to protect the samples from laboratory introduced artifacts such as particulates (reconstitute under grade A (class 100) LF conditions use terminally pre-filtered diluents)
  - Define reconstitution method timing and degassing period
  - Reconstituted sample AQL Visual Inspections should be identical to manual inspection method used to initially qualify the liquid AQL inspection method
  - Use a statistically valid sampling Plan ANSI/ASQ Z1.4 or ISO 2859-1 and an S-4 Inspection Level (S-4 has the highest statistical security of all the special sample levels typically used for destructive testing)
  - Visible particles recovered should be characterized to Level 2 (Microscopic ID) at a minimum
  - Historical databases with trending of particle types and frequency will lead to establishing appropriate AQL or Action levels
  - Some products will require a routine membrane filtration to examine the typical background particulate profile
  - For Powders look at the bulk API background visible particulate profile for control prior to filling

Quality (QA/QC) Methods
Suspensions, Emulsions, etc.

- ✓ Foreign Particle characterization of the bulk API or Suspension is Essential
  - As an incoming Raw Material the bulk API may contain 50% or more of the visible and sub-visible particle load
  - Powders and Suspensions do not have terminal filtration prior to filling

- ✓ Method development is the first step to foreign particulate determination
  - EP and USP790 is reserved for foreign (intrinsic/extrinsic) particles not Inherent particles
  - Methods need to be able to separate, clear or remove the suspended API or excipient so Intrinsic or extrinsic particles can be detected, sized and enumerated

- ✓ Membrane Filtration
  - In order to assess the identity of any non-inherent background foreign (intrinsic/extrinsic) particle profile in the uninspected portion of the product it may be necessary to employ variations of Membrane Filtration and Microscopy
  - This method is similar to the USP 788 Method 2 which allows the quantification and profiling of the foreign particle burden
  - This method can also be used to separate suspended API or visible protein aggregates from foreign particulate matter

Quality (QA/QC) Methods
Protein Based Products

- ✓ Challenge for Therapeutic Protein products
  - Determine the particle size distribution profile of the Inherent API particles over the shelf life of the product
  - Determine the background presence of Intrinsic and Extrinsic foreign particles
- ✓ Inherent protein API particles are unique and their shape or habit can be variable from one product formulation to another
- ✓ Each new product formulation must be characterized by several methods to determine the best long term monitoring system

Quality (QA/QC) Methods
Protein Based Products

- ✓ Opalescence or Turbidity
  - Develop an analytical method Nepholometry or Photometric (Quantitative)
  - Gradation using Visual Standards (Qualitative)
- ✓ Characterize the particle size distribution of inherent proteins from sub micron to 10 um range (immunogenic Response)
- ✓ USP 788 Light Obscuration (LO) Data is collected on each batch at >10 um and >25 um
  - Begin collecting more differential particle size data to determine if LO data could indicate the aggregation of proteins from smaller particles over the stability interval testing
  - The typical LO particle counter can be separated into additional channels to collect this differential data. (i.e. >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um)

Quality (QA/QC) Methods
Protein Based Products

- ✓ Microscopic Flow Image Analysis data is typically collected at >1 um, >2 um , >5 um, >10 um, > 25 um. (examples Flow-Cam, Protein Simple, MFI)

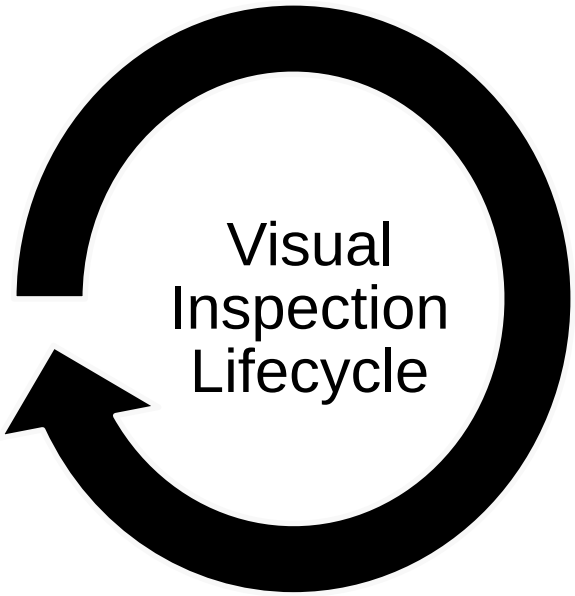
  - Microscopic Flow Imaging data should also be separated into additional channels to collect this differential data. (i.e. >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um) looking into the visible particle ranges

  - Consider re-analyzing existing Microscopic Flow Imaging stability data. If it has been stored electronically it may be it feasible to reprocess the data into these expanded visible size ranges

Quality (QA/QC) Methods
Protein Based Products

- ✓ Combine several sizing technologies (example: PSS Accusizer)
  - Dynamic Light Scattering Particle size distribution for particles 1um to 10um
  - Laser light obscuration Particle size distribution for particles >10um & >25 um
  - Add differential size channels (i.e. >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um) subtle changes in aggregation data toward the visible range can be observed
- ✓ Characterization methods that also look at the much smaller particle sizes <10 um.
  - Size Exclusion Chromatography (SEC)
  - Resonant Mass Measurement (example: Archimedes)

Conclusion



- Particulate or Defect Quality Control is a Continual Process
- Assess each area in the Life Cycle
- Analyze the process rejects to understand your defect populations (Particulate and Physical Defects)
- Go through cycles of targeted foreign particle reduction and mitigation
- Conduct routine trending and periodic limits evaluation
- Develop Action and Alert levels were possible
- Adjust AQL levels as particle mitigation efforts are found effective
- Prioritize Action Plans for continual process Improvement in a manageable phased approach
- A Lifecycle Approach supports a product that is the definition of “Essentially Free” from Particulates and Defects forming the foundation of USP<790>