Visual Inspection Lifecycle

Particulate and Container/Closure Defects

Roy T. Cherris – Managing Partner

Bridge Associates International LLC

"Partners for Quality and Manufacturing Excellence"

Visual Inspection Lifecycle

Discussion Agenda

- Particulate Inspection History
- PDA Visual Inspection Task Force and Benchmarking
- Global Compendia requirements
- USP Chapters<790>, <1790>, <788>, <1788>both Current & In Revision
- Manual Visual Inspection Life Cycle
- Manual Inspection Station and Illumination
- Developing a Defect Library
- Defect Standards and Test Sets
- Developing, Optimizing and Qualifying the Inspection Sequence for Manual Inspection
- Inspector Training and Qualification Requirements
- Routine Manual Inspection in the Manufacturing unit
- Attribute Inspection (AQL) in the Quality unit
- Supplemental Solid or Lyophilized Product Inspection

Visual Inspection Lifecycle

Discussion Agenda

- Defect Characterization, Identification
- Trending and Control Levels
- Completing the Inspection Life Cycle (inspection sub-cycles)
  - Supplier Agreements
  - Incoming Materials Testing
  - Component Preparation
  - Filling
  - Stability/Retention
  - Customer Complaints

- Alternates to the Manual Inspection Method (Semi-Automated & Automated Inspection) Qualification and Validation requirements
- Re-Inspection Strategies
- Special Considerations for Characterizing Protein Formulations
- Discussion on Various API forms
- Case Studies

History of Visual Inspection

- 1905 USP 8 Diphtheria Antitoxin was described as a "transparent or slightly turbid liquid."
- 1936 NF VI "Clearness" was defined as " Aqueous Ampul Solutions are to be clear; i.e., when observed over a bright light, they shall be substantially free from precipitate, cloudiness or turbidity, specks or fibers, or cotton hairs, or any undissolved material."
- 1942 NF VII Provided a definition for "substantially free.“
  - Substantially free shall be construed to mean a preparation which is free from foreign bodies that would be readily discernible by the unaided eye when viewed through a light reflected from a 100-watt mazda lamp (standard incandescent bulb) using as a medium a ground glass and a background of black and white."
- 1945 USP 12 First particulate matter standard: "Appearance of Solutions or Suspensions - Injections which are solutions of soluble medicaments must be clear, and free of any turbidity or undissolved material which can be detected readily without magnification when the solution is examined against black and white backgrounds with a bright light reflected from a 100 watt mazda lamp or its equivalent." Note: the absence of "substantially."

History of Visual Inspection

- 1949 (early) FDA- Lost the Bristol Case. A prime example of inspection variability due to un-controlled inspection conditions. The key FDA inspector could not detect the “Problem Particles” during the court case.
- 1949 USP 13 - In revision.

  General Tests: Went into great detail in describing a "suitable device" (i,e,, a gooseneck desk lamp and a vertical screen) how the containers were to be held, rotated, etc., during an examination against a white and black background.

  General chapter on injections stated that "... medicaments, intended for parenteral administration, ... must be substantially free of any turbidity or undissolved material which can be detected readily ..." Note: reappearance of "substantially."
- 1949 (late) USP 13 - Deleted all except: "Every care should be exercised in the preparation of Injections to prevent contamination. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to visual inspection.“
- 1976 USP 21 Chapter <788> for Sub-visible Particles becomes official and includes the statement “Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, should be substantially free from particles that can be observed on visual inspection."

History of Visual Inspection

- 1980 USP 23 <1> General Requirements; Foreign matter: "Every care should be exercised in the preparation of all products intended for injection, to prevent contamination with microogranisms and foreign material. Good pharmaceutical practice requires that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents shows evidence of contamination with visible material be rejected."
- Also, in <788> PARTICULATE MATTER IN INJECTIONS, the following statement is given: "Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, should be essentially free from particles that can be observed on visual inspection."

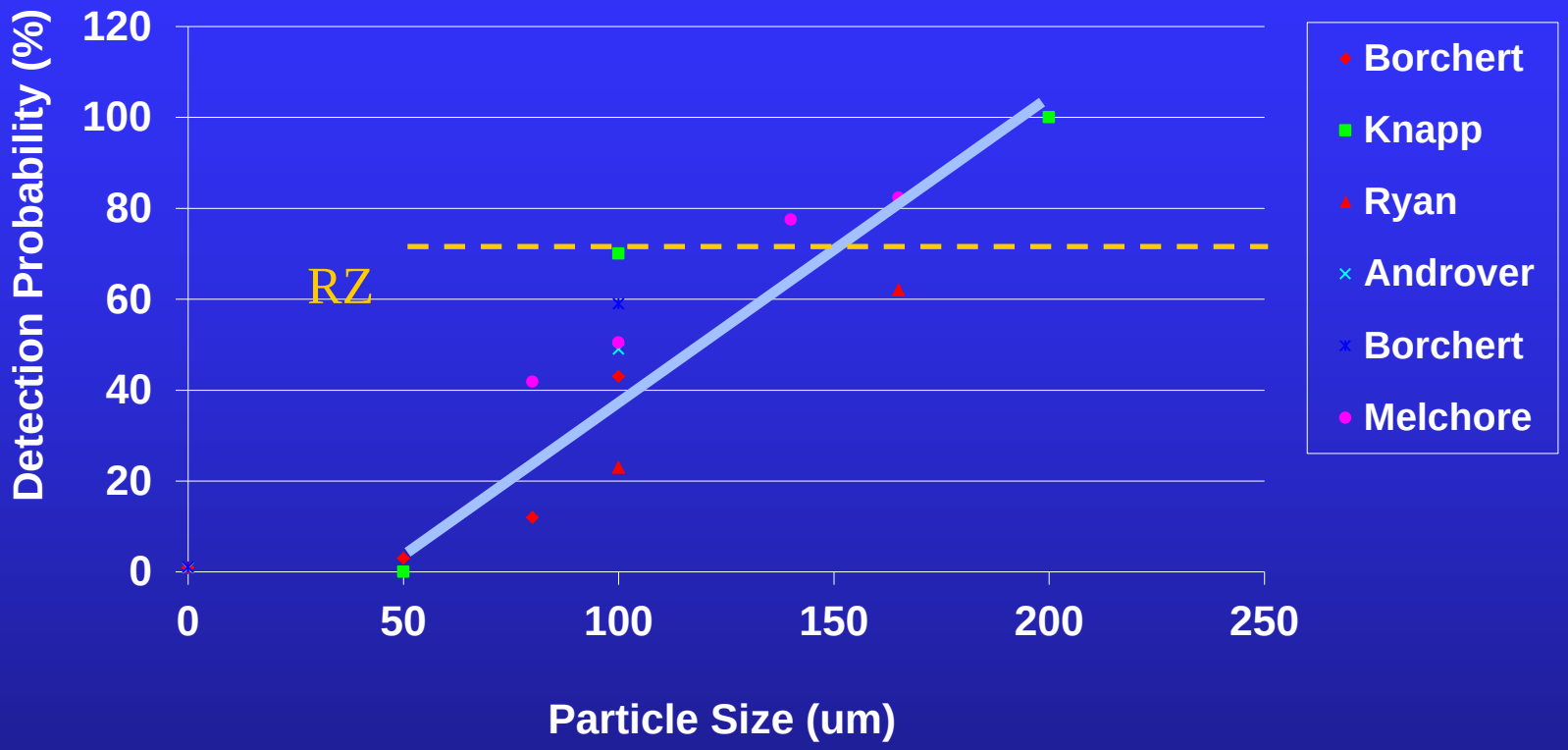
  (Note: substantially free changed to essentially free).
- 2006 USP 29 No significant changes. Still no definition of “Essentially Free”.

  Added the statement to Chapter <1> to require routine reconstitution studies for Lyophilized, Powder products or Liquids in amber containers.

Visual Inspection Guidance

- USP-PMA Particulate Task Force (1976-1986)
  - USP <788> for sub-visible particulate matter Represented by big pharma world wide
- PDA Visual Inspection Task Force (1998 to 2008)
  - Barber, Cherris, Knapp, Madsen, Shabushnig
  - PDA Industry Benchmark Surveys 1999-2009
    - (Three Industry surveys over a 10 year period)
  - In-depth review of the subject of Visual Inspection
  - PDA TR-37 Visual Inspection Practices
    - 80% Drafted but remains unpublished
    - Further work proposed after USP 790 and 1790

A Very Well Known Survey Slide
Human Inspection Performance



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

Manual Visual Inspection Sensitivity to Particle Size

Assuming a consistant and reproducable inspection procedure for a clear solution in a transparent 10 mL glass vial with diffuse illumination between 2000-3000 lux:

- ✓ 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
  - ✓ >90% for particles 200 µm and larger

USP <1>

Current Contents of General Chapter <1> Injections:

- Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter and other defects
- Inspection process designed and **qualified** to ensure that every lot of all parenteral preparations is “essentially free” from visible particulates
- Supplemental constitution or other exam required for dry or non-transparent products
- No inspection method is specified

European Pharmacopeia

- **Current contents of EP 2.9.20 Particulate Contamination: Visible Particles**
  - Solutions for injection, examined under suitable conditions of visibility, are clear and **practically free** from particles
  - 2,000 -3,750 lux diffuse illumination
  - Gently swirl or invert the container . . . and observe for about 5 seconds in front of the white panel; repeat the procedure in front of the black panel
  - Record the presence of any particles

Japanese Pharmacopeia

- **Current contents of JP 20. Foreign Insoluble Matter Test:**
  - Unless otherwise specified, Injections meet the requirements of the Foreign Insoluble Matter Test for Injections
  - Unaided eyes, light intensity of approximately 1,000 lux under an incandescent lamp
  - Up to one minute inspection per container
  - Clear and **free from readily detectable** foreign insoluble matter
  - Method 1 for solutions, Method 2 injections with constituted solution
  - Plastic containers, unaided eyes, light intensity approximately 8,000 to 10,000 lux

Change USP <1> (PF 35-5)

- USP Visual Inspection of Parenterals Expert Panel
  - Scott Aldridge, Roy Cherris, Mike Groves, Russell Madsen, Steve Langille (FDA), John Shabushnig, Deborah Shnek
- USP <1> (PF 35-5) 2009 Stimuli to the Revision Process

•**Discussed Physiological Effects of particles**

–Emboli and granulomas (muscle, lungs, liver, other organs

–Route of administration

•Recent data suggest particulates in IM and SubQ products can have a potent immunogenic effect, generating blocking antibodies that neutralize the therapeutic effect of the drug

- Purpose of this Visual Inspection Standard
  - **Define "essentially free"**

–Inspection conditions (Lighting, Timing (Pacing), Contrast Backgrounds)

–Limits for visual particulate matter AQL $\leq$0.65 after 100% Inspection

–Definition of Essentially Free based on PDA Survey Benchmark

Origins of USP Proposal

- **Fed. Std. No. 142a (The first true regulatory guidance and established the AQL inspection)**
  - Based on Int. Fed. Std. No. 00142, Parenteral Preparations (Aug. 1, 1959)
  - Mandatory on all Federal agencies
  - Applicable to human sterile parenterals in final containers
  - Clarity of solutions and limits for visual particulate matter
  - Black/white background, 100-350 ft. candles, 10 in. from source
  - Major A, Level II, AQL=1.0%
  - Exception for some biological products for “characteristic” turbidity
  - Abandoned by the federal government by 1980

USP <790> (PF 38-6)

- USP Chapter <1> to be completely reorganized
- USP<790> commissioned after Expert Panel Discussions with FDA Center to clarify USP intentions for defining “Essentially Free”
- FDA agreed with the promotion of a “Life Cycle Approach” in a supporting Informational Chapter
- Key Points:
  - Visual inspection of injectable products is driven by the need to minimize the introduction of unintended particulate matter into patients
  - Also to reject nonconforming units, such as those with cracks or incomplete seals that pose a risk to the sterility of the product
  - Even though defects occur infrequently and many times are random events, there is still the expectation that each finished unit be inspected (100% in-process)
  - Human visual performance is critical to the assessment of visible particles and the development of alternate methods. Therefore fixed inspection conditions and specifically trained inspectors qualified with particle standards is essential
  - The use of automated inspection systems is encouraged if it is equal to or better than the manual inspection baseline.

USP <790> (PF 38-6)

- Particulate matter is defined in *Particulate Matter in Injections* 788 extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in solutions. Examples of such particulate matter include, but are not limited to, fibers, glass, metal, elastomeric materials, and precipitates.
- However, some products, such as those derived from proteins, may contain inherent particles or agglomerates; in such cases, requirements for visible particulates are specified in the individual monograph or in the approved regulatory application.
- “Essentially Free” Acceptance Criteria
  - Stable and reproducible manual Inspection parameters 5 seconds in-front of each background using a **minimum** illumination of 2000 to 3750 Lux at the lowest point of routine inspection
  - Life-Cycle Approach to particle and defect control expected
  - AQL of 0.65 or lower for particulates (Represents Major Defect AQL)
  - AQL in place for other Critical, Major and Minor defects

Updated USP <790> (PF 38-6)

PF Comments Addressed and USP <790> Briefing Statement added:

- 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>
- USP<1790> Best Practices Informational Chapter to be introduced ASAP
  - Holistic - Life-Cycle Approach to particle and defect control expected
- <790> Used as a final Release Test “Essentially Free” Acceptance Criteria:
  - AQL of 0.65 or lower (Represents Major Defect AQL)
  - AQL should be applied for other Critical, Major and Minor defects
- Evaluation of Product in the Field: 20 units examined - no visible particles
  - Additional statistical testing if one or more units contain visible particles as part of an investigation and product quality decision

USP <1790> General (draft)

- Best practices in the area of particulate and container/closure defect monitoring and control
- This informational chapter will provide an overview of the elements of a life cycle approach to support continual process improvement extending from inspection of incoming primary packaging to filled product release.
- Focus areas will cover the development of a stabilized manual inspection and how this baseline can be used to qualify semi-automated manual and fully automated inspection
- Inspector training/qualification, defect libraries, inspection standards development, particulate and container/closure defect characterization, data trending, stability, retention, and other supporting systems
- The proposed chapter will appear in *PF* late in 2013

USP <1790> General (draft)

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, aluminum 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, silicone, etc). Also includes particulates found during stability studies (Degradents, Container Closure Interaction, Glass Delamination) Intrinsic Particle Types Must be Controlled/Minimized/Eliminated

Extrinsic Particulate: Particulates which are introduced from foreign or external sources. Any particulate not sourced from product contact materials and/or particles of a biological source (e.g. environmental natural and synthetic fibers, hair, insect part, etc.) Extrinsic Particle Types should be Eliminated

Inspection Lifecycle Model

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

Information Silos
Need connections

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

Lifecycle Elements
100% Inspection

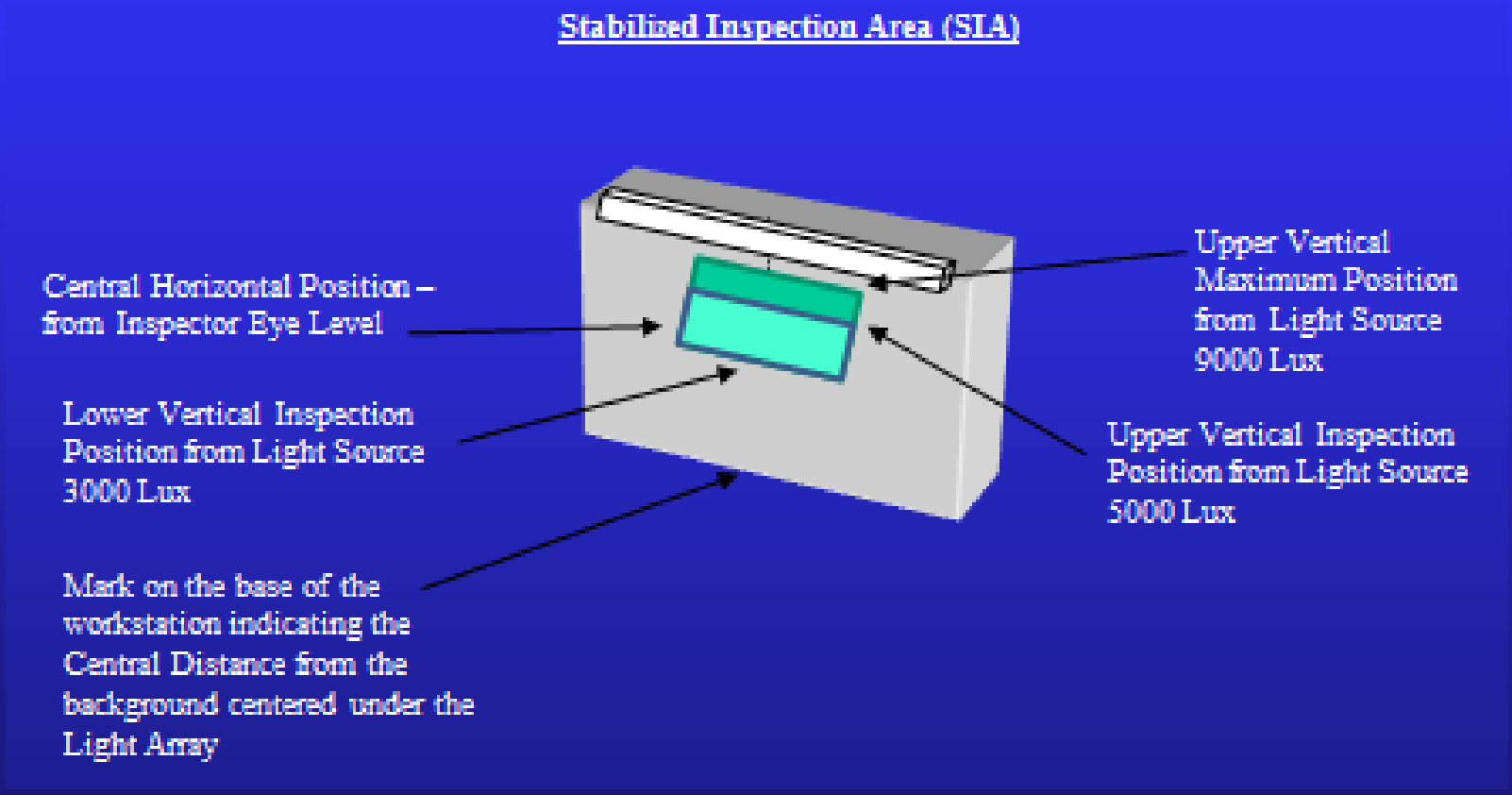
- Supplier Quality
- Component Testing and Acceptance
- Component Preparation
- Bulk Preparation
- Filling
- **100% Inspection**
- AQL Inspection
- Stability
- Retention
- Customer Complaints

100% Inspection Sub-Cycle
Manual Inspection Station

- Manual inspection booth considerations
  - ✓ Flicker free Florescent lighting or LED (adjustable intensity if possible)
  - ✓ Black and White Backgrounds for particle contrast
  - ✓ Pharmacopeial Minimum Point of Inspection illumination range 2000 to 3750 LUX
  - ✓ For clear glass containers recommend selecting a target illumination at the Point of Inspection (3000 LUX)
  - ✓ Higher illumination values needed for amber, plastic and other container types
  - ✓ Develop a Stabilized Inspection Area “SIA” (lighting and location)
  - ✓ Delineate the 3 dimensions of the “SIA” on the backgrounds
  - ✓ Ergonomic Seating required to adjust the human to the booth
  - ✓ Elbow or arm rests for comfort as needed
  - ✓ Standardize room lighting, temperature, sounds and distractions

100% Inspection Sub-Cycle

Manual Inspection Station



100% Inspection Sub-Cycle

Manual Inspection Station

VISUAL TASK	RECOMMENDED RANGE OF ILLUMINANCE, FOOT-CANDLES		
	MIN	MID	HIGH
HIGH CONTRAST OR LARGE SIZE	20	30	50
MEDIUM CONTRAST OR SMALL SIZE	50	75	100
LOW CONTRAST OR VERY SMALL SIZE	100	150	200
LOW CONTRAST AND VERY SMALL SIZE OVER PROLONGED PERIOD	200	300	500
EXACTING TASK OVER VERY PROLONGED PERIOD	500	750	1000
VERY SPECIAL VISUAL TASK OF EXTREMELY LOW CONTRAST AND SMALL SIZE	1000	1500	2000

Extract: IES Lighting Handbook 1981 Reference Volume
Section A-3, Table 1

Figure 26 An extract from the Illumination Engineering Society recommendations for illuminance ranges for visual tasks in the parenteral container inspection range.

100% Inspection Sub-Cycle
Defect Standards

- ✓ The lowest detectable size for 20/20 human vision under controlled inspection conditions is generally accepted to be 50 µm.
- ✓ The detection process is probabilistic, with the probability of detection increasing with increasing particle size.
- ✓ Analysis of inspection results pooled from several studies involving different groups of inspectors demonstrate that the probability of detection for a single 50 µm particle in clear solution in a 10 mL vial with diffuse illumination between 2000-3000 lux is slightly greater than 4%.
- ✓ This probability of detection increases to approximately 40% for a 100 µm particle and becomes greater than 90% for particles 200 µm and larger

100% Inspection Sub-Cycle
Defect Standards (Continued)

- ✓ **Knapp Methodology** was developed for use in particle detection
- ✓ **Reject Zone** security (≥70% detection probability) must be maintained in all methods (manual, semi-auto manual and fully automated) of inspection
  - ✓ The Knap methodology is based on the maintenance of a true defect rejection efficiency (≥70 % detection) which can remain secure even with automated (blind) methods that do not have the same capability of discrimination as human inspectors.
- ✓ The **Gray Zone** standards (≥30% to <70% detection) are utilized only to illustrate the subtle improvement or differences between the human detection and the "tuned" automated sensitivity.
  - ✓ The real utility of the gray zone is in the comparisons in the high end of the probability (>50% or >60%) of detection to show increased performance of Automated Inspection over Manual visual inspection.
- ✓ The **Accept zone** (<30% detectability) is utilized as the measure of the effects of false rejects on the process

100% Inspection Sub-Cycle
Defect Standards (Continued)

- Particulate Defect Standard Development
  - ✓ Should include a blend of seeded Intrinsic particles including NIST traceable spheres of various densities as well as simulated or naturally occurring particulates
  - ✓ Use spherical particles in smaller size ranges only (near the visual detection threshold 100 um to 200um)
    - Dense (Metal and Glass) spherical particles >300 um will not suspend properly during inspection
  - ✓ Use Production Rejects or naturally occurring particle rejects especially in the mid to larger size ranges that are anticipated from the process or environment. These Rejects must be characterized In-Situ (Size and Type)

100% Inspection Sub-Cycle
Defect Standards (Continued)

- Particulate Defect Standards
  - ✓ Prepare particle standards incorporating glass, stainless steel, rubber, neutral density (plastic or polystyrene) and fibers
  - ✓ The manual inspection method should be capable of repeatedly detecting particles of various densities and types between 150 um to 250 (700-1500 for fibers)
    - Utilize well trained staff, stabilized lighting, fixed method
    - Supports the sensitivity and qualification of the method
  - ✓ Applied to manual inspection then to semi-auto or automated inspection training and or qualification

100% Inspection Sub-Cycle
Defect Standards (Continued)

- Container/Closure (Physical) Defect Standards
  - ✓ All defect categories should be represented (Critical, Major and minor)
  - ✓ Use Production Rejects or naturally occurring rejects to cover the defect size ranges that are routinely recovered or anticipated
  - ✓ Manually create physical defects when necessary
  - ✓ Characterize the defect and write specifications for creating the physical defect
  - ✓ Develop written procedures to create, qualify, maintain, replace and re-qualify standards

100% Inspection Sub-Cycle
Defect Standards (Continued)

- ✓ Label containers with UV visible Markers for (blinded) identification
- ✓ Use adaptations of the "Knapp" model studies for demonstrating the probability of detection (rejection) for each container (≤30% blanks, ≥70% Reject probability)
  - Sound statistics (probability of detection) can be obtained for particulates with approx. 50 inspection cycles for particle standards. (Not more than 10% rejects due to Hawthorn Effect)
  - Container/Closure defect standards may use a reduced number of inspection cycles (approx. 25 inspections) to generate appropriate detection data
- ✓ Database the defect types, sizes, detailed description and detection frequency

100% Inspection Sub-Cycle
Manual Method Development

- Full Inspection Sequence - Utilizes two different human mental processes
  1. Smaller particles must be in Motion
     - Probability of detection of smaller particles near the visual threshold is improved when they are moving in the fluid.
  2. Container/Closure defects are stationary
     - Consistent slow rotation with visual scan of the container surface and closure – seal area
- ✓ Don't confuse the Inspectors by mixing the two sequences
- ✓ Maintain strict requirements for pacing and sequence

100% Inspection Sub-Cycle
Manual Method Development

- Particulate Detection Sequence is the most difficult
  - ✓ Preposition the tray of containers at an angle which allows particles to concentrate in the lower heal area Inspectors look there first before inversion or swirling
  - ✓ Inspect in the pre-defined Stabilized Inspection Area
  - ✓ Consistent inversion and of swirling of the solution in each container
  - ✓ Examine solution 5 seconds per background (approx. 10 sec total)
  - ✓ Re-swirl each time between backgrounds (motion decays)

100% Inspection Sub-Cycle
Manual Method Development

- Container/Closure (Physical Defect) Detection Sequence
  - ✓Maintain a consistent inspection approach to cover all areas of the container
  - ✓The inspection sequence should be well defined and written step by step in a procedure
  - ✓Can be a little more variable with timing on physical defects
  - ✓Can be a single background not as much need for contrast
  - ✓Approximately 5-10 seconds total
  - ✓All inspectors should follow the same procedural sequence

100% Inspection Sub-Cycle
Manual Method Verification

- Particulate Threshold Studies
  - ✓ Human visual particle size detection threshold studies confirms manual inspection method viability (suitability)
  - ✓ The particulate thresholding sets should include a graduated particle size range covering 100 um to 500 um at a minimum
  - ✓ Particulate detection size threshold studies should show reproducibility in the 150 to 250 um range
  - ✓ Use particle types of various densities (stainless steel, glass, rubber, plastic, fibers, etc.)
  - ✓ Supports inspection method having the appropriate sensitivity
  - ✓ Needed to show correlation to semi-auto manual or Automated procedures

100% Inspection Sub-Cycle
Manual Method Verification

- Particulate Threshold Studies
  - The calibration curve sets the standard for the inspection staff
  - Used as a measure for detecting specific particle defects during inspection method development
  - Provides data to compare human inspector performance as a group or by individual
  - Can be used as an inspector candidate training and qualification tool
  - A subset of these standards can be used to “tune” and qualify other inspection methods

100% Inspection Sub-Cycle
Inspector Qualification

- Inspector Vision Qualification

- ✓ The yearly vision testing requirement should state that you require for inspection staff an optical vision check at 20/20 vision (Snellen chart or equivalent) and near vision acuity (Jaeger 1+ at a reading distance approx. 40 cm) corrected with lenses where indicated.
- ✓ In addition recommend also performing color blindness testing.
- Near Distance Acuity Description: Many jobs require good near vision and so a near visual acuity standard is imposed. Near visual acuity can be measured using a miniature test chart scaled for a typical reading distance (40cm) or by using a near-test-type card. These have paragraphs of text printed in different font sizes and the patient is required to read the smallest text that they can from a normal reading distance. The corresponding font size in points is recorded. The point size refers to the height of the body of the letter in units of 1/72 of an inch and does not relate to the Snellen acuity chart. It is equivalent to the Jeager 1+ reading chart.
- A number of apps for assessing near vision are also available for tablet devices, which offer a range of near-vision tests and greater versatility than printed cards.

100% Inspection Sub-Cycle
Inspector Qualification

- Inspector Qualification
  - ✓ Train with defect photographs and clear written descriptions utilize a defect library
  - ✓ Hands on with defect standards using the specified method
  - ✓ Reinforce mental counting and follow the paced sequence
  - ✓ For particulates use a range of types (densities) and sizes from visual detection threshold range to largest routinely observed in your pool of rejects removed from product
  - ✓ Expect $\geq$ 80 % detection

100% Inspection Sub-Cycle
Inspector Qualification (Continued)

- ✓ Use a range of container /closure defect types from the routine pool of rejects found in the product
  - ✓ These rejects must be characterized In-Situ for approximate size and where ever possible also to particle type
- ✓ Supplement with characterized manually created defects
- ✓ Use individual acceptance criteria for each category Critical >90% (95-100% is best), Major >80-90%
  - ✓ Minor (cosmetic) defects you can set by company preference or specific supplier agreements
- ✓ Consider incorporating parts of the human inspector qualification at worst case fatigue conditions (end of shift)

100% Inspection Sub-Cycle
Inspector Qualification (Continued)

- **Heightened Awareness Philosophy**
  - The focused inspection for a specific defect attribute is not the standard inspection.
  - When conducting focused inspections a basic fact to consider is that you have changed the routine inspection process and the controlled timing/sequence.
  - Also the examination for a specific defect reinforces the detectability of that defect by the inspector.
  - Therefore the data generated during these special inspections generally will not be directly comparable to routine inspection data.
  - The focused inspection is affected by “heightened awareness” of specific defect types and these specialized inspections should be proceduralized or have a protocol as to how it is paced, timed and sequenced as well as have specific documented personnel training.

100% Inspection Sub-Cycle
Routine Operations

- Documented fatigue breaks for each inspectors are a must (NLT 5-10min/hr or by company policy)
- Inspection Supervision Recommended: Maintain strict adherence to the procedure to minimize controllable variables.
- Re-inspection policy should be defined in written procedures
- How many re-inspections? Typically NMT 2)
- Periodically trend data and evaluate control levels

100 % Inspection Sub-Cycle
Routine Operations

- Classification of Defects from Rejected Product (Essential for Process Monitoring)
  - ✓ Analysis of rejects as a process monitoring tool
  - ✓ Essential to support automated inspection
  - ✓ Similar to Microbial Environmental Monitoring Programs
  - ✓ Full classification of all Particulate and Physical rejects initially from batches
  - ✓ Develop a defect database to maintain the defect statistics
  - ✓ Fractional sampling and classification can be justified after developing the historical profile
  - ✓ Periodic Trending
  - ✓ Institute Action and Alert Levels where feasible

100 % Inspection Sub-Cycle
Routine Operations

- Classification of Rejected Product
  - ✓ Following 100% inspection In-Situ (Level 1)
    - Basic Particle Categories: Glass-like, SS-like, Fiber-like Rubber-like, Polymeric-like, Light Particle, Dark (or Color) Particle, Other
      - Representative samples of each of these groups can be verified by microscopic examination and characterization (level 2)
      - Useful for building a particulate defect reference library
    - Basic Physical Defect Categories: Critical, Major & minor
      - Further break down Critical and Major defects for granularity in defect mitigation efforts
      - Useful for building a physical defect reference library

Lifecycle Elements
AQL Inspection

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

AQL Inspection Sub-Cycle

- 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
- Particle type characterization or Identification of all AQL rejects an expectation
- Glass or Stainless Steel Potentially objectionable to regulators
- Extrinsic particulates a heightened concern
- Database particulates & container/closure defects found in AQL
- Periodically trend data and re-evaluate control levels
- Formal tightened AQL (level III) re-inspection policy should be in-place

AQL Inspection Sub-Cycle

- Inherent particles must be characterized throughout the product shelf life
- Defect Categories: Orders of Magnitude
- ✓ **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
- ✓ **Major** Defects typically applied to an AQL of 0.1 to 0.65
  - USP<790> Minimum acceptance of “Essentially Free”) 0.65
- ✓ **Critical** range is an order of magnitude lower, between 0.01 to 0.065
  - Is Zero tolerance to Particle Defects practical?

AQL Inspection Sub-Cycle

- Particulate AQL Acceptance Values Major or Critical?
- USP <790> promotes a ≤0.65 AQL (Major defect) for all particle types as the minimum standard
- Should be Process Capability Derived (Historical Data)
- Differences of individual FDA field inspectors & Debated in the FDA between CEDER and CEBER
  - All Intrinsic product contact particles should remain a Major defect 0.1 to 0.65
  - Some Regulators encouraging individual manufacturers to designate Extrinsic particles in the Critical category
  - Often see AQL values for Extrinsic particles being applied variably applied in ranges between 0.25 to 0.65 (Typically applied to Major Defects)
  - True Critical range would be between 0.01 to 0.065 of which the lower AQLs represent a Zero Tolerance for particulates not currently attainable by current industry standard manufacturing
  - Recommend applying an AQL of 0.065 (at the lowest) for Extrinsic particles

AQL Inspection
Sub-Cycle (Continued)

- Lyophilized, Powder, Suspensions, Emulsions or Products in Opaque Container
- 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**
  - ✓ Some products will require a routine membrane filtration to examine the typical background particulate profile
  - ✓ Extreme care is required to protect the samples from laboratory introduced artifacts such as particulates
  - ✓ Reconstituted sample AQL Inspections should be identical to manual inspection method used to initially qualify the liquid AQL inspection method

AQL Inspection
Sub-Cycle (Continued)

- Lyophilized or Reconstituted Product
- **Sampling Sources**
  - Most companies sample randomly across the batch from finished containers (prior to labeling)
  - This is the most straight forward method of obtaining samples and the simplest for reconciliation
  - What can companies do if the product is extremely expensive?
  - How can they cut down on the expense of destructive testing for visual particulate matter inspection?

AQL Inspection
Sub-Cycle (Continued)

- Lyophilized (Reconstituted) or High Value Product
  - **Alternative Sampling Sources – Rejects**
    - Consider sampling from Visual Inspection rejects (cosmetic, minor or container defect categories which would have no impact on particulate matter generation
    - Once the original defect inspection is recorded, proper chain of custody documentation would allow these samples to be utilized for reconstituted inspection for visible particulates

AQL Inspection
Sub-Cycle (Continued)

- Lyophilized or Reconstituted Product
- **Alternative Sampling Sources – In Process**
  - Consider sampling containers from the filling line prior to Lyophilization (Aseptic Handling Caution)
  - Partially stoppered containers would need to have the stopper seated
  - Samples are still liquid, rehydration not required
  - OR use periodic WFI fills to demonstrate particle control
  - Primary sources of visible particulates occur prior to lyophilizer cycle (except glass breakage which should be handled by Lyophilizer Clearance Procedure)

AQL Inspection
Sub-Cycle (Continued)

- Lyophilized or Reconstituted Product
- **Supplemental Sampling Sources**
  Microbiological Media Fills
  - Consider generating supporting documentation from routine microbiological media fill challenge containers
  - Conducted after media fill is fully completed
  - Media Fills are generally statistically significant sample populations
  - No additional preparation costs
  - Provides an extra return on expenses associated with routine media fills

Particulate Characterization
Particulate Risk Management Life Cycle

Sampling and Initial Monitoring

↓

Develop Short-Term Historical Profile

↓

Identify Particulate Sources

↓

Develop Initial Alert Levels

↓

Optimize Process Relating to Particle Generation Sources

↓

Continued Monitoring / Trending

↓

Evaluate Alert Levels and Establish Action Levels Related to Optimized Process Capability

↓

Continued Monitoring / Trending and Long Term Historical Profile

Particulate Characterization

Particles originate from specific sources:

- Bulk drug substance
- Container / closure components as supplied by manufacturers
- Stopper washing and silicone process
- Vial / container washing process
- Depyrogenation oven and tunnels
- Equipment preparation and wrapping
- Filling area equipment (filter, pumps, and needles)
- Stopper feed bowl / hopper
- Clean Room Environment
- Personnel gowning or movement
- Filling area cleaning process or supplies
- Utilities, Water, HVAC, Gasses
- Glass breakage throughout the process

Particulate Characterization

- Level One: Visual Observation
  - 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: Spectral or other fingerprint ID
  - FTIR, Raman, Elemental, Mass Spec, etc.

Particulate Characterization

- **Developing Microscopy Tools**
  - Polarizing Light Microscope (PLM)
  - Relatively inexpensive
  - Minimal calibration
  - Can be applied in-situ utilizing an inverted or stereo microscope
  - Dedicated investment in training and practical application in basically comparative science
  - Photomicrographic Documentation is essential

Particulate Characterization

- **Rapid Microscopic Characterization**
  - Shape and size
  - Color and Transparency
  - Surface texture
  - Birefringence and refractive indexes
  - Homogeneity
  - Physical: Resilience, Hardness, etc.
  - Micro-Chemical spot tests
  - Comparison to known materials (exposure to simulated conditions, heating, charring etc.)

Particulate Characterization

- **Particulate Risk Management by Optimization of the Process**
  - Review the various particulate sources
  - Rationalization of those that can be eliminated or further minimized
  - 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.

Trending and Information Feedback Loops

- Supplier Quality
- Component Testing and Acceptance
- Component Preparation
- Bulk Preparation
- Filling and in-process testing
- 100% Inspection
- AQL Inspection
- Stability
- Retention
- Customer Complaints
- Use Electronic (21 CFR compliant) Databases

Lifecycle Elements
Supplier Quality

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

Supplier Quality Sub-Cycle

- Supplier Quality Agreements
  - ✓ Determine the attributes of the component that are important to the process in your facility
  - ✓ Conduct (SME) Workshop with appropriate departments
  - ✓ Understand the supplier's internal defect monitoring for in-process manual inspection (ANSI/ISO S4-Level AQL)
    - Supplier's List of component attributes that are controlled and monitored at their facility
    - Review defect criticality designation, control levels
    - Reference USP for components also PDA TR-43 for Glass
    - Evaluate suppliers supplemental automated inspection systems

Supplier Quality Sub-Cycle
(Continued)

- ✓ Incoming quality must be aligned with finished product expectations (AQLs)
- ✓ Develop Meaningful Specifications
- ✓ Supplier Certificate of Conformance

➢ Supplier Auditing

- ✓ Not just quality systems
- ✓ Each visit should assess component specific attributes and in-process controls

➢ Supplier feedback and communications

Lifecycle Elements
Component Acceptance

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

Component Acceptance Sub-Cycle

- Master Defect Library and Descriptions
- Training program for inspectors
- Focus on Critical and Major defects
- Meaningful in-house testing to supplement supplier controls
- Review of supplier certificate of conformance
- Maintain a component testing trending database

Lifecycle Elements
Component Preparation

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

Component Preparation Sub-Cycle

➢ Glassware Washing

- Determine Particle Burden and challenge with seeded particle loads
  - ✓ Smaller Finish Opening (ie. 13mm vs 20mm, etc.) harder to clean
  - ✓ Periodic Visual Checks
  - ✓ In-house check for container rinse drainage
  - ✓ Handling procedures
  - ✓ Glass breakage events and line clearance
  - ✓ Feedback of deviations and investigations
  - ✓ Operator training and enforcement

Component Preparation Sub-Cycle (Continued)

- Glassware Depyrogenation
  - ✓Periodic Visual Checks
    - Handling procedures
    - Glass breakage events and line clearance
  - ✓Periodic tunnel or oven vacuuming, cleaning and evaluation (wiring, filters, seals, doors, surfaces)
  - ✓Maintenance program for SS trays or racks
    - ✓Resurface or Replace scored or scratched surfaces

Component Preparation Sub-Cycle (Continued)

- Stopper Washing in-house or Ready to Use (RTU) or Ready to Sterilize (RTS)
  - ✓ Proper environments (handling, sterilization transfer and holding)
  - ✓ Evaluate stopper particle burden
  - ✓ Request particle data from component suppliers
- Control of Siliconization Levels
  - ✓ Minimized silicone while maintaining machinability
  - ✓ Improved application by diving nozzles
  - ✓ Determined by sub-visible particle count reduction studies

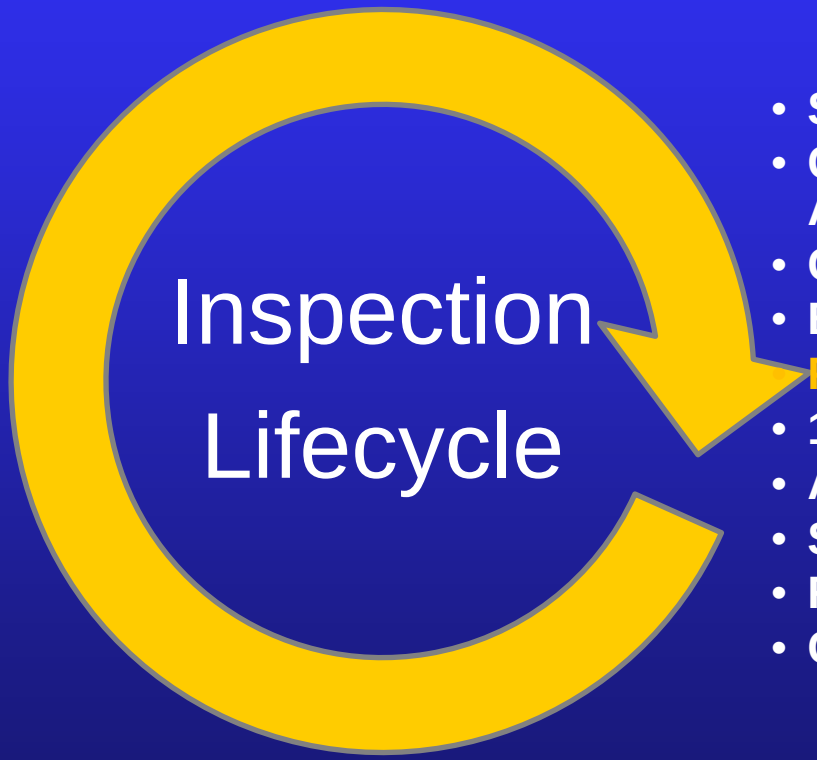
Lifecycle Elements
Bulk Preparation

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

Bulk Preparation Sub-Cycle

- Periodic Inspection tank or vessel
  - ✓ Look for mechanical abrasion or wear
  - ✓ Resurface or polish
  - ✓ Evaluate Particulate collection or entrapment points
- Bulk Prep Environment
- Gowning Materials
- Cleaning Materials
- Personnel Positioning and Training
- Tubing and connectors
- Filters and Filter Housing
- Sample Vessels for routine testing and stability

Lifecycle Elements Filling



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

Filling Sub-Cycle

- Filling Environment
- Gowning Materials
- Cleaning Materials
- Personnel positioning and training
- Equipment alignment and maintenance
- Pump design and Maintenance
- Tubing and connectors
- Filters and filter housing

Filling Sub-Cycle (Continued)

- Needle strikes and proper alignment (glass or SS particle generation)
- In-Process Checks (Documented)
  - ✓ Fill volume monitoring
  - ✓ Stopper Placement
  - ✓ Check for known Filling Related Defects
- Glass breakage events and specifically related written Area Clearance procedures

Lifecycle Elements
Stability and Retention

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

Stability Inspection Sub-Cycle

- Perform 100% inspection for particulate and physical defects prior to placement on stability
  - ✓ Stability Goal is to detect product change or a change in the container/closure system over product shelf life
  - ✓ Check for Generation of glass lamellae At R&D Stages (especially aggressive solutions, High or Low pH)
  - ✓ Stopper and/or silicone interaction with the product
    - Transient or Measurable Particulate (visible and sub-visible)
    - Characterization of protein aggregation (imaging or other)
- Training for inspectors of Stability Program samples
- Database visual inspection data and USP <788> sub-visible data

Retention Inspection Sub-Cycle

- Retention Samples Program Goal is to maintain a reserve testing stock to aid in future product quality investigations.
- Training for inspectors of Retention Program samples
- Inspection of retention samples for particulates can use the model for product in the field covered in Pharm Forum draft of USP<790> Visible Particulate Matter

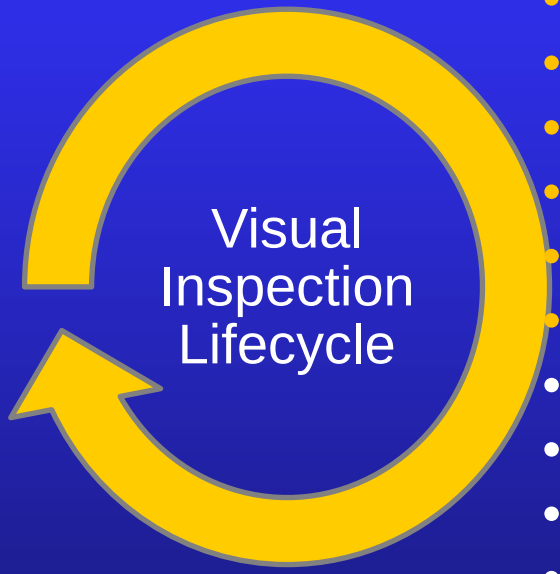
Lifecycle Elements
Customer Complaints

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

Customer Complaint Sub-Cycle

- Develop a clear description for all complaint particulate or physical (container/closure) defects
- Assure that the defect list is aligned with the defects recovered from Incoming Components, Manufacturing and Quality areas
- The defect classification (C, M, m) and AQL criteria should be harmonized across the organization
- Customer complaint database of physical and particulate defects is essential
- Must be shared with the departments in the Lifecycle

Conclusion



- Assess each area in the Lifecycle and the elements of each sub-cycle
- Component Testing and Acceptance
- Processing
- 100% Inspection
- AQL Inspection
- Stability
- Retention
- Customer Complaints
- Utilize information sharing Databases
- Conduct periodic trending and reporting
- Develop Action and Alert levels
- Prioritize plans for continual process Improvement
- Lifecycle Approach supports a product that is the definition of “Essentially Free” from Particulates and Defects forming the foundation of USP<790>

The Visual Inspection Life Cycle Keeps Functional Information Silos Connected

Alternate Methods to Manual Inspection

- Semi Automated Manual
  - ✓ Not typically appropriate for Particle Defects at very fast line speeds
  - ✓ Can be successfully used for Physical Container Closure Critical, Major Defects and Minor Physical Defects “Cosmetic”
- Fully Automated Particulates
- Fully Automated Particles and Physical Defects
- All alternate methods must be equivalent or better than manual (Compendial black and White Box)

Re-inspection Strategy

- Regulatory expectation to have a written Policy
- Following 100% inspection exceeding Action Levels
- Following Non-Conformance to AQL
- After initiating an Investigation:
  - ✓ 100% Inspection
  - ✓ Tightened AQL Inspection for added security
  - ✓ Repeat of Inspection Cycle, Not more than Two Times based on the specific defect and the ability to cull out the route cause defect

Protein Product Characterization

- Challenge for Therapeutic Protein products
  - Determine the particle size distribution profile of the Inherent API particles
  - Determine the background presence of Intrinsic and Extrinsic foreign particles
- Inherent 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

Protein Product Characterization

- 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. >10 um , >25 um, >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um).

Protein Product Characterization

- Micro Flow Imaging (MFI) Data is typically collected at >1 um, >2 um , >5 um, >10 um, > 25 um.
  - ✓ MFI data can be separated into additional channels to collect this differential data. (i.e. >10 um , >25 um, >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um).
  - ✓ If existing MFI data is stored electronically this may make it feasible to reprocess the data into expanded size ranges.

Protein Product Characterization

- PSS Accusizer – Combines two sizing technologies
  - ✓ Dynamic Light Scattering Particle size distribution for particles 1um to 10um
  - ✓ Laser light obscuration Particle size distribution for particles 10um
  - ✓ Separated into differential sizes (i.e. >10 um , >25 um, >50 um, > 75 um, >100 um, >200 um, > 300 um, > 400 um) subtle changes in aggregation data toward the visible range can be observed.

Protein Product Characterization

- Characterization methods that also look at the much smaller particle sizes <10 um.
  - ✓ Size Exclusion Chromatography (SEC),
  - ✓ Resonant Mass Measurement (Archimedes)

Protein Product Characterization

- In order to assess the identity of any non-inherent background intrinsic/extrinsic (foreign) particle profile in the lyophilized portion of the product it may be necessary to employ 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 visible protein aggregates from extraneous materials.

Protein Product Characterization

- Opalescence or Turbidity

  - ✓ Develop an analytical method Nepholometry or Photometric

  - ✓ Visual Standards (Gradation) Qualitative

Wrap-Up Discussions

- Thank you for your attention
- Questions and Answers
- Case Studies