Visual Inspection of Injectable Products:

More than Sorting Good from Bad …

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Agenda

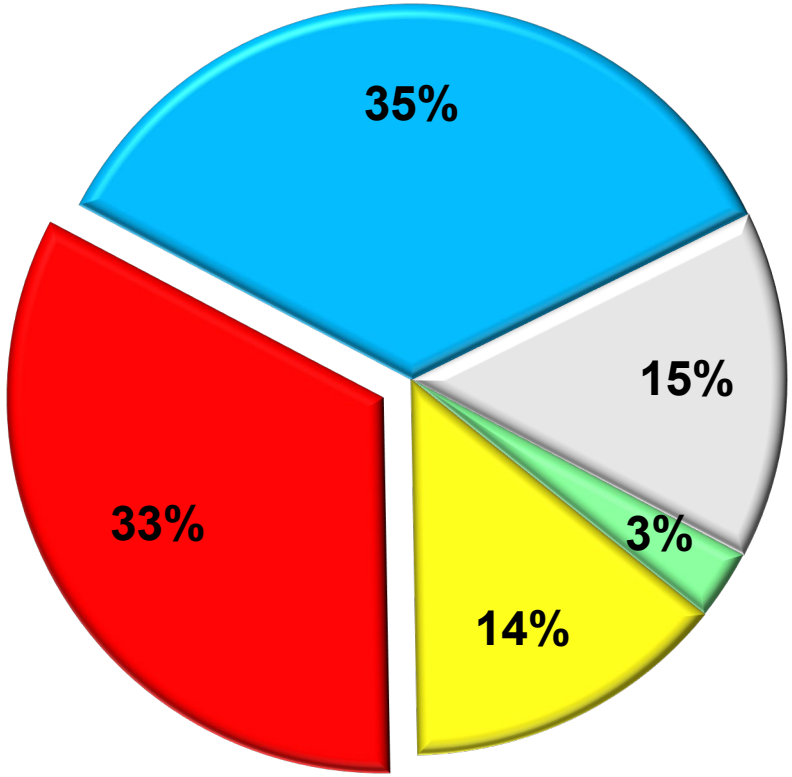
- Why inspect?
- What we are looking for
- How to inspect
- Acknowledgements
- References and resources

Why inspect?

Why Inspect?

- Patient Risk
  - Physiological Implications
    - Particles
  - Chemical and Microbiological Implications
    - Particles, Container Integrity
- Compendial Requirements
  - Pharmacopeias
- Regulatory Requirements
- Process Knowledge and Continuous Process Improvement

FDA Sterile Injectable Drug Recall Notices 2017-2021

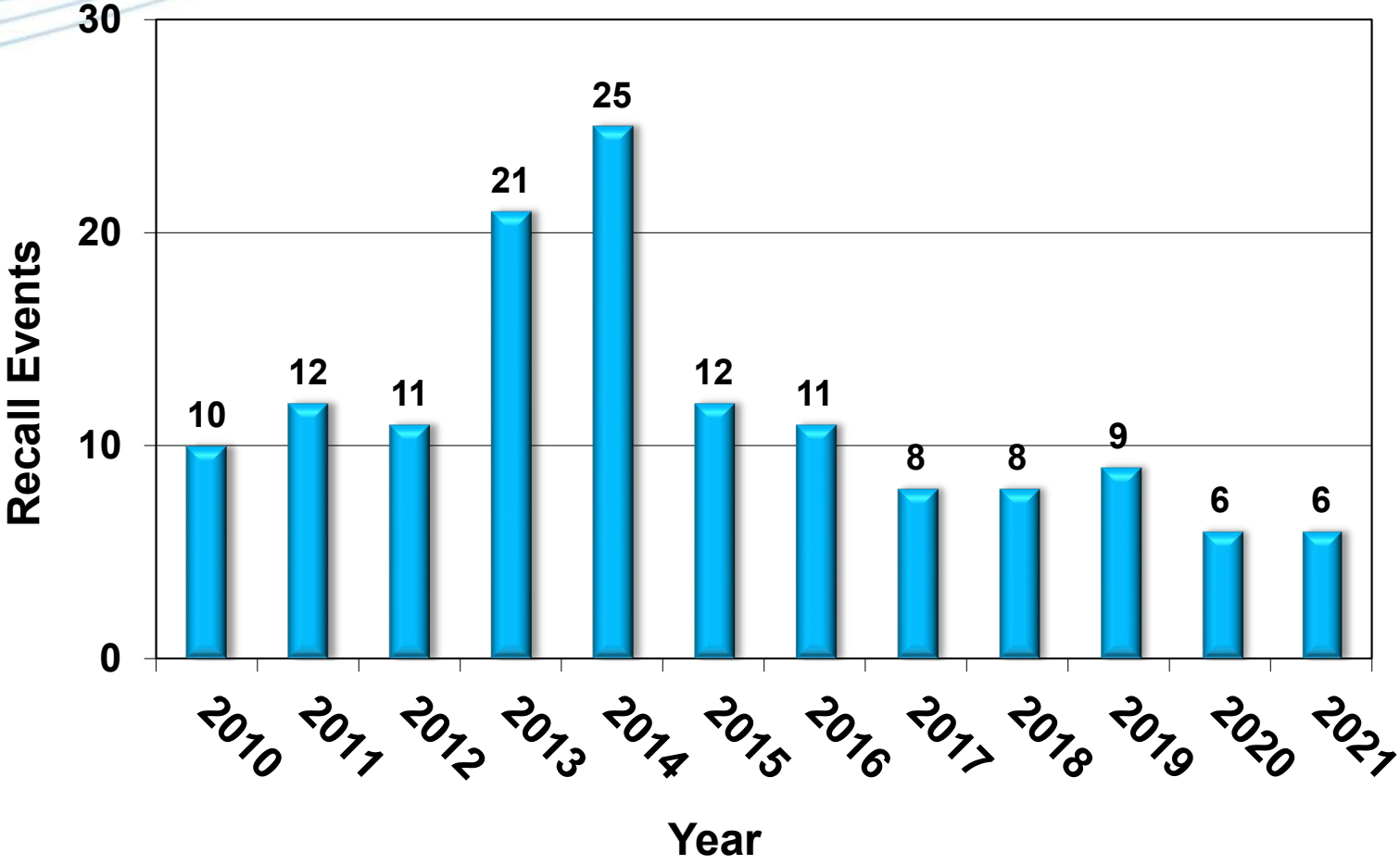


- Visible Particles
- Lack of Sterility Assurance
- Labeling
- Container
- Other*

* Incl. incorrect potency or dose, discoloration, impurities/degradation products and storage temp excursions.

Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

Visible Particulate Recall Notices



Data obtained from the FDA Recall and Safety Alerts Archive, https://www.fda.gov/Safety/Recalls/default.htm

Recent FDA Recalls

- 12-3-2021 Gilead Issues a Voluntary Nationwide Recall of Two Lots of Veklury® (Remdesivir) Due to Presence of Glass Particulates
  - Glass particles
- 9-3-2021 Hospira Issues a Voluntary Nationwide Recall of Aminosyn II 0.15%, an Amino Acid Injection, Sulfite Free IV Solution Due to the Presence of Particulate Matter
  - Fibers, hair and proteinaceous material
- 6-30-2021 Teva Initiates a Voluntary Nationwide Recall of One Lot of Topotecan Injection 4 mg/4 mL (1 mg/mL) Due to Presence of Particulate Matter
  - Grey silicone particle, cotton fiber
- 5-8-2021 ICU Medical Issues a Voluntary Nationwide Recall of Lactated Ringer's Injection, USP Due to the Presence of Particulate Matter
  - Iron oxide

US FDA 483 Themes

- Must establish a maximum allowable reject rate.
- Must control reinspection of product, including when appropriate, inspection conditions and number of reinspections permitted.
- Inspectors must be trained, and training documented.
- Inspectors must be periodically requalified.
- Training and qualification conditions must align with routine 100% inspection conditions.
- Address inspection fatigue during qualification.
- Must use statistically sound sampling plan(s) for AQL inspection.

Pharmacopeial Requirements

	USP <790>	EP 2.9.20	JP 6.06
Illumination Intensity (lux)	2,000-3,750	2,000-3,750	2,000-3,750 lux (8,000-10,000)*
Inspection Time (sec)	10 sec	10 sec	10 sec
Background	Black/White	Black/White	Black/White
Acceptance Criteria	"essentially free from visible particulates" ANSI/ASQ Z1.4 AQL=0.65%	"clear and practically particle-free"	"free of readily detectable foreign insoluble matter"

* Illumination intensity for plastic containers

United States Pharmacopoeia USP 43

- USP <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
  - Foreign and particulate matter: Articles intended for parenteral administration should be prepared in a manner designed to exclude particulate matter … Each final container of all parenteral preparations should be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed visible particulates) in its contents. The inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates …

United States Pharmacopoeia USP 43

- USP <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
  - Qualification of the inspection process should be performed with reference to particulates in the visible range and those particulates that might emanate from the manufacturing or filling process. Every container in which the contents show evidence of visible particulates must be rejected. The inspection for visible particulates may take place during examination for other critical defects such as cracked or defective containers or seals or when characterizing the appearance of a lyophilized product.

United States Pharmacopeia USP 43

- USP <790> *Visible Particulates in Injections*
  - Inspection conditions defined
    - Harmonized with EP
    - 2,000-3,750 lux
    - Black and white backgrounds
    - No magnification
    - 5 sec viewing against each background
    - Swirl and/or invert sample
  - Applies to *Extrinsic* and *Intrinsic* particles
  - *Inherent* particles addressed in individual monographs or approved regulatory filings

USP <790> Acceptance Criteria

- At Time of Batch Release
  - 100% inspection followed by acceptance sampling
  - ANSI/ASQ Z1.4 or ISO 2859
  - AQL= 0.65%, UQL= 2.3-3.3% typical
  - Alternate and equivalent plans acceptable
- For Product in Distribution
  - n = 20, a = 0
  - AQL= 0.26%, UQL= 10.9%

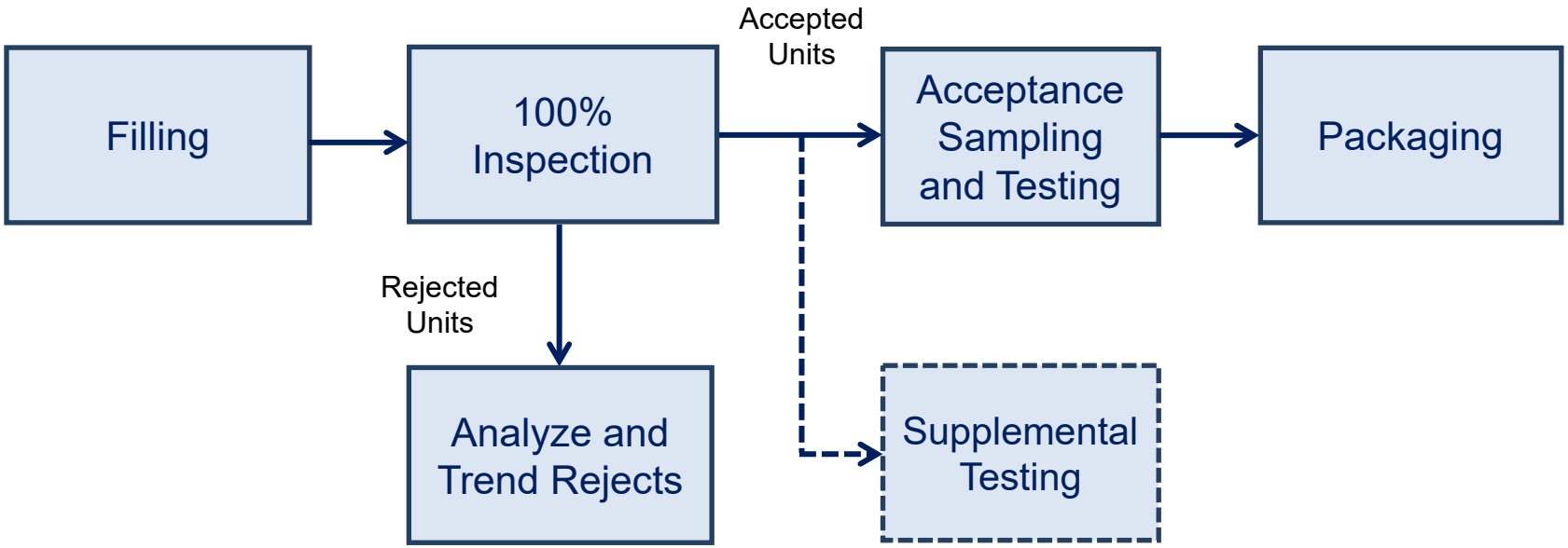
USP <790> Supplemental Inspection

- Supplemental Inspection
  - Where the nature of the contents or the container–closure system permits only limited capability for inspection of the total contents, the 100% inspection of a batch shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container, suspensions, highly colored liquids) contents of a sample of containers from the batch. The destructive nature of these tests requires the use of a sample smaller than those traditionally used for non-destructive acceptance sampling after 100% inspection.

USP <1790>

- <1790> *Visual Inspection of Injections*
  - Information Chapter
  - Key elements of an inspection process
    - Patient Risk
    - Elements of a good inspection process
    - Lifecycle / Continuous Improvement
    - Visible Defect Types
      - Extrinsic, Intrinsic and Inherent
    - Inspection Technologies
  - Published in USP 40 1st Supplement
    - Official Aug 2017, Updated May 2022

USP <1790>



Other International Standards

- EU
  - EMA Annex 1 *Manufacture of Sterile Products*
  - EP 2.9.20 *Particulate Contamination: Visible Particles*
  - EP 5.17.12 *Recommendations on Testing of Particulate Contamination : Visible Particles*
- Japan
  - JP 6.06 *Foreign Insoluble Matter Test for Injections*

What we are looking for.

Typical Defects found by Visual Inspection (Abbreviated List)

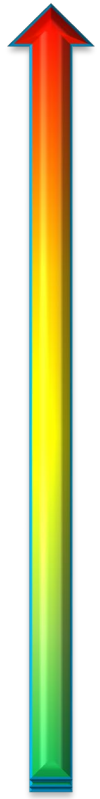
- Particles
- Product
  - Gross over- or under-fill
  - Cloudy or discolored (solution)
  - Melt or collapsed cake (lyo)
- Container (for vials)
  - Cracks
  - Chips
  - Scratches
  - Dirt on exterior

Typical Defects found by Visual Inspection (Brief List cont.)

- Closure (for vials)
  - Leaking
  - Missing or damaged stopper
  - Loose or torn overseal
  - Scratched or dented overseal
  - Missing overseal or flip-cap button
  - Incorrect flip-cap button color

Particulate Matter Definitions

- Extrinsic (from outside the process, uncontrolled)
  - Environmental Contaminants
    - insect parts, hair, fibers, paint, rust
- Intrinsic (from within the process, unplanned)
  - Processing Equipment, Primary Package
    - qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)
- Inherent (part of the formulation, controlled and expected)
  - Protein agglomerates



RISK

Particulate Size Ranges

<100 nm	100 - 1,000 nm	1 - 100 µm	>100 µm
Nanometer	Submicron	Subvisible	Visible

- SEC (Size Exclusion Chromatography)
- FFF (Field Flow Fractionation)
- SDS-Page Gels
- AUC (Analytical Ultra-Centrifugation)

- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter

- Manual / Human
- Semi-Automated
- Automated

Narhi, et al. J Pharm Sci, 2012

Defect Classifications

Critical Defect

Critical defects are those which make the product unfit for use. This defect may pose a risk to patient safety.

Major Defect

Major defects are those which may impair functionality, processing, or handling that may lead to a loss of performance.

Minor Defect

Minor defects are those which represent a general lowering of perceived quality (i.e. appearance) but do not limit the function of the product or make it unsafe.

How to inspect.

Common Visual Inspection Methods

- Manual Inspection (MVI)

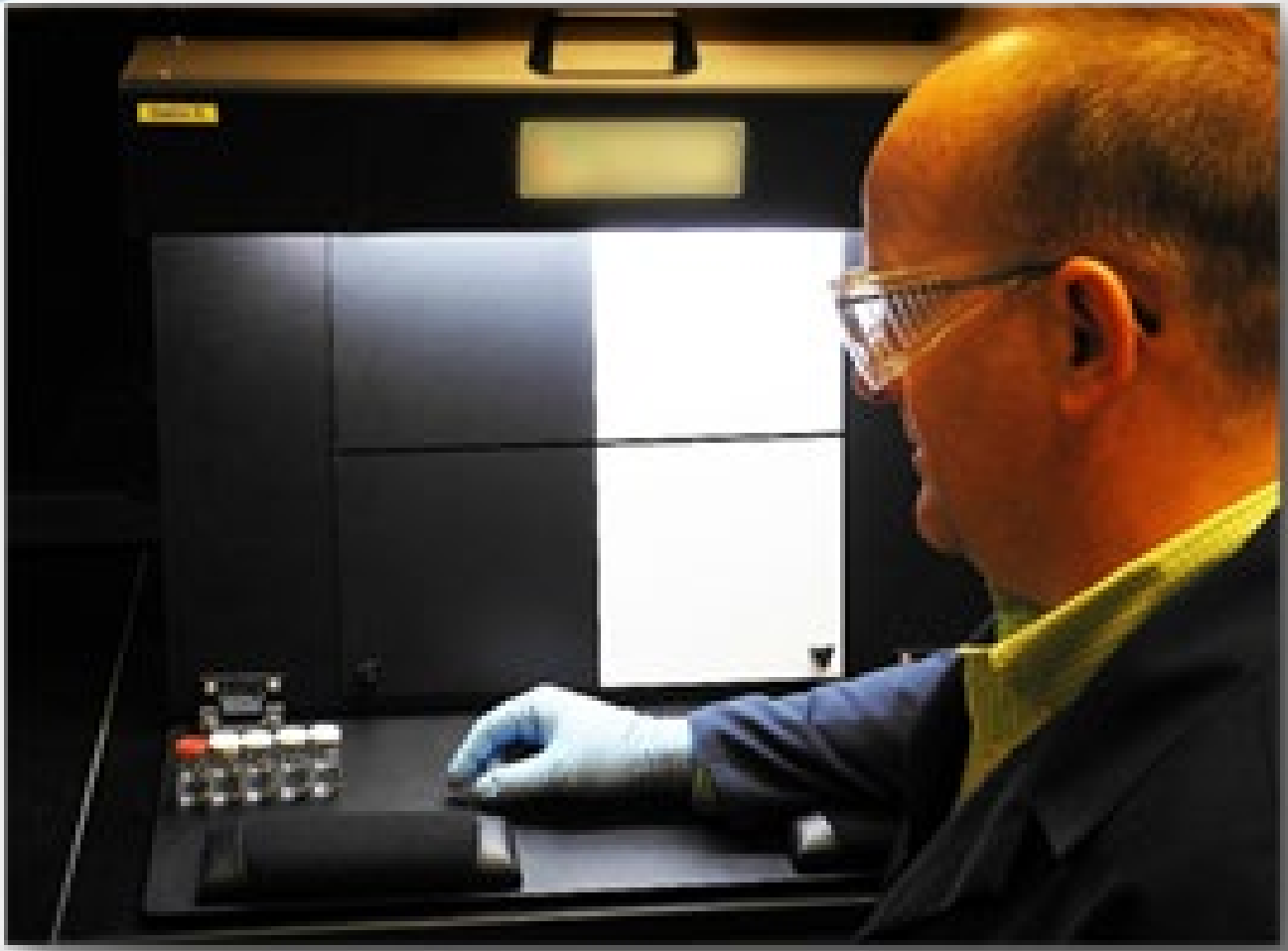
- Semi-Automated Inspection (SAVI)

- Automated Inspection (AVI)

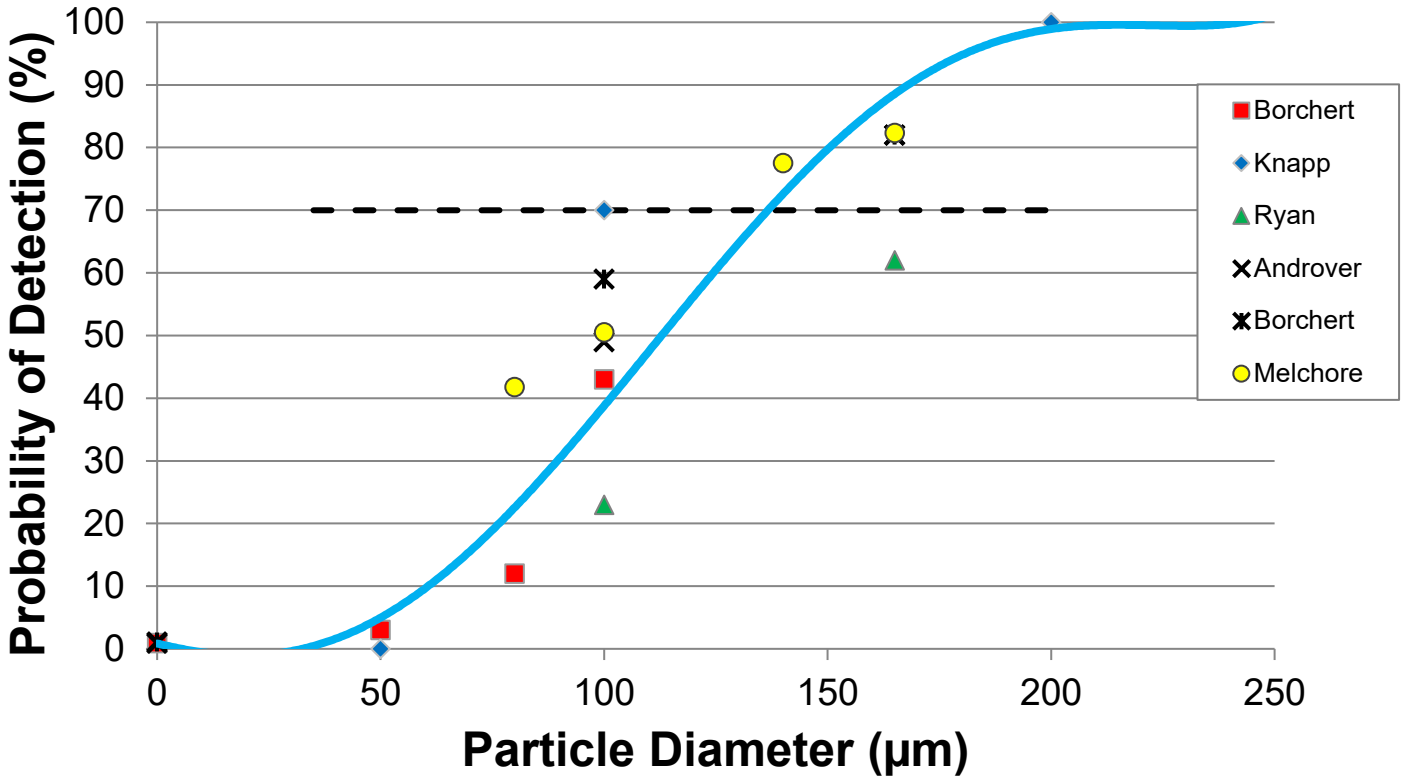
Critical Inspection Parameters

- Lighting
  - Illumination Intensity
  - Uniform, Flicker-free
    - Fluorescent, Incandescent, LED
  - Tyndall (dark-field)
- Background
  - Black / White
- Presentation and Manipulation
  - Swirl and/or invert
- Pace
  - 10 sec / container reference

Manual Inspection Booth



Human Inspection Sensitivity

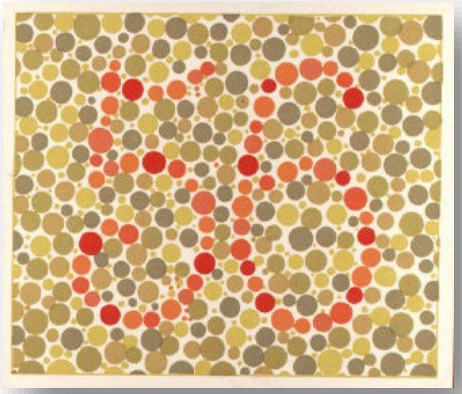


From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995

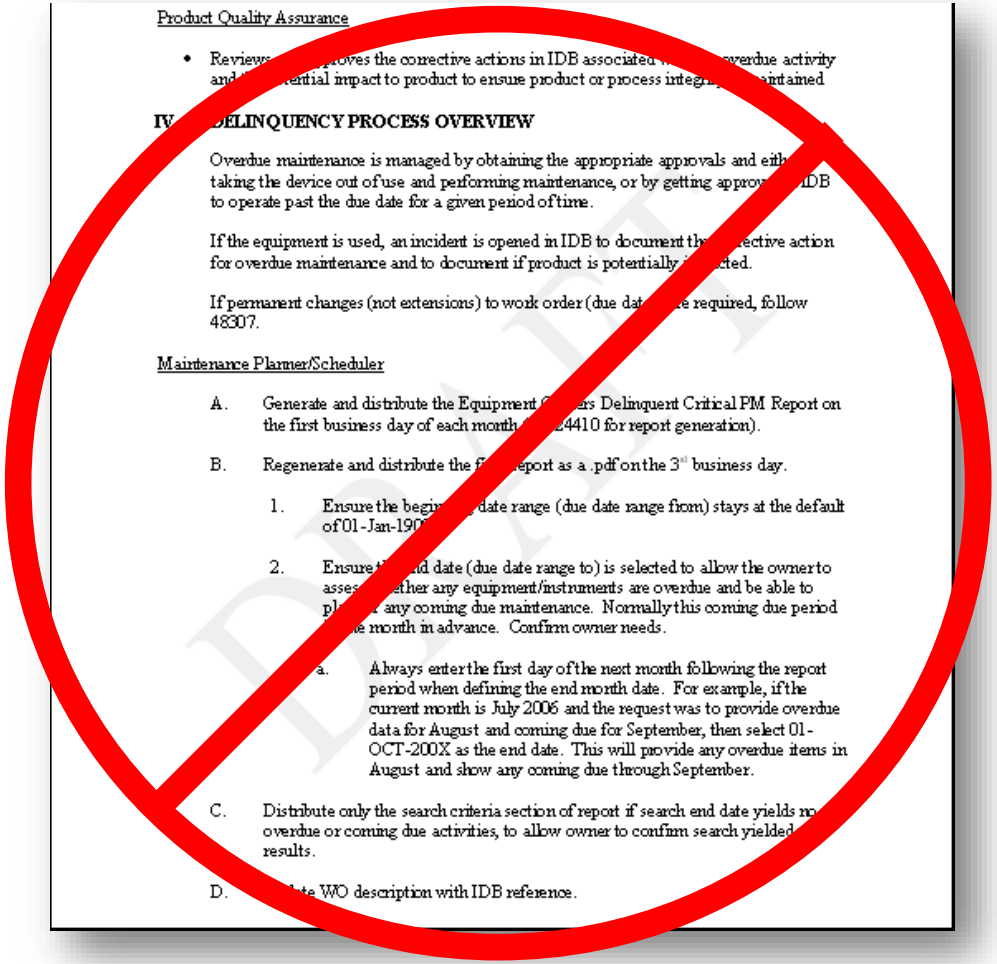
Inspector Selection

- Visual Acuity Testing
  - Must pass exam with 20/20 near vision
    - Vision may be corrected with prescription lenses or contacts
  - Tested annually

- Color Impairment Testing



Training



Product Quality Assurance

- Reviews ... proves the corrective actions in IDB associated ... overdue activity and ... ential impact to product to ensure product or process integ... aintained

IV. ... DELINQUENCY PROCESS OVERVIEW

Overdue maintenance is managed by obtaining the appropriate approvals and eith... taking the device out of use and performing maintenance, or by getting approv... IDB to operate past the due date for a given period of time.

If the equipment is used, an incident is opened in IDB to document th... rective action for overdue maintenance and to document if product is potentially i... cted.

If permanent changes (not extensions) to work order (due dat... e required, follow 48307.

Maintenance Planner/Scheduler

A. Generate and distribute the Equipment ... rs Delinquent Critical PM Report on the first business day of each month ... 4410 for report generation).

B. Regenerate and distribute the f... eport as a .pdf on the 3rd business day.

1. Ensure the begi... date range (due date range from) stays at the default of 01-Jan-190...

2. Ensure t... d date (due date range to) is selected to allow the owner to asse... ther any equipment/instruments are overdue and be able to pl... any coming due maintenance. Normally this coming due period ... month in advance. Confirm owner needs.

a. Always enter the first day of the next month following the report period when defining the end month date. For example, if the current month is July 2006 and the request was to provide overdue data for August and coming due for September, then select 01-OCT-200X as the end date. This will provide any overdue items in August and show any coming due through September.

C. Distribute only the search criteria section of report if search end date yields no overdue or coming due activities, to allow owner to confirm search yielded results.

D. ... te WO description with IDB reference.

Training

- Manual Inspection Training Process
  - Defect identification/categorization
    - Defect Reference Manual or Library
    - Defect Samples
  - Demo of inspection procedure by
  - Practice in non-production training environment
  - Inspect training set with good and defective units
- Typical training time two weeks

Qualification Test Kits

- Inspect Qualification Test Kit with representative defects
  - Typical test kit contains 300-500 units with 30-50 defect examples (≤10% defect rate).
  - Can be made with product or surrogate and contain production rejects or simulated defects.
  - Test kits may be prepared internally or purchased.
  - Test kits should have an expiration date (typically 1 year, does not need to match expiration of product) after which they can be critically inspected, and the expiration date extended (typically done annually).
  - They should be reviewed and approved by Quality.

Qualification Testing (1)

- Qualification Testing
  - Knapp RZE method based on probability of rejection (PoD) may be used to calibrate test kit and set acceptance criteria.
  - False reject rate (FRR) should be ≤5%.
  - Conduct tests at end of day/shift for maximum fatigue.
  - Set a time limit for completion of inspection of test kit to align with routine inspection rate (e.g., 3-4/min for MVI).
  - Initial qualification should require three (3) consecutive successful inspections of the test kit.

Qualification Testing (2)

- Separate qualifications should be performed for each family of products (e.g., clear solution, colored solutions, suspensions, lyophilized powders, etc.) and containers (e.g., clear, amber vials, syringes, cartridges, bags, etc.).

Requalification

- Requalification should be performed at least annually.
- It can be done with a single inspection of a representative test kit to demonstrate maintenance of proficiency.
- It is a good practice to requalify inspectors who have not done inspection for an extended period of time (e.g., 3-6 months).

Other MVI Considerations

- Various types of breaks help keep the inspector alert and focused.
  - Shift change and lunch breaks (2x/shift)
  - 5 minute ‘eye breaks’ (each hour)
  - Micro-breaks during the inspection process
  - Shift to non-inspection task (e.g., loading, unloading, documentation)
- Reduced ambient light recommended.

In Process Control

- Control alert and/or action limits should be established and applied to 100% inspection rejection rates to identify atypical lots.
  - Mean + 3σ (for critical, major, minor and particle defects) is often used for these action limits.
  - Limits are reviewed (and recalculated as needed) at least annually and when significant process (manufacturing and inspection) changes are made.
  - Typical actions when these limits are exceeded include investigation, tightened AQL, and reinspection.
- Inspection results should be trended and assessed for adverse trends.

Acceptance Sampling / AQL Inspection

- After 100% inspection, a sample of accepted units is sampled and reinspected.
  - Sampling plans and acceptance criteria follow ANSI/ASQ Z1.4 or ISO 2859.
  - Acceptable Quality Limits (AQL) are chosen for each defect category based on risk (critical, major and minor).
    - Industry mean values are 0.065%, 0.65% and 2.5%, respectively
    - These are used to determine the accept number or number of defects of each category permitted in the sample. Normally, no (0) critical defects are permitted.
  - If the number of defects found exceed the accept number, investigation and reinspection are required.

Important Points to Remember

- Inspection is probabilistic; it can not be relied upon to detect and remove all defects.
- Therefore, defect prevention through continuous process improvement should be part of your control strategy.
- While particles are most often associated with visual inspection, container and closure defects must also be detected and removed.
- Inspector training and qualification is critical to successful manual visual inspection.

Acknowledgements

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  - D. Scott Aldrich - Ultramikro
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  - John Shabushnig (Chair) - Insight Pharma Consulting
  - Deborah Shnek - Alder Biopharmaceuticals
  - Hailin Wang – FDA
  - Neal Zupec - Baxter

References and Resources (1)

- FDA Draft Guidance for Industry (2021): *Inspection of Injectable Products for Visible Particulates*
- USP <1> *Injections and Implanted Drug Products (Parenterals) – Product Quality Tests*
- USP <790> *Visible Particulates in Injections*
- USP <1790> *Visual Inspection of Injections*
- EMA Annex 1 *Manufacture of Sterile Products*
- EP 2.9.20 *Particulate Contamination: Visible Particles*
- EP 5.17.12 *Recommendations on Testing of Particulate Contamination : Visible Particles*
- JP 6.06 *Foreign Insoluble Matter Test for Injections*

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- Particulate Matter in Injectable Drug Products, Langille, PDA J Pharm Sci and Techn., 67 (3) (2013)
- PDA Survey – 2014 Visual Inspection, Shabushnig, Parenteral Drug Association, October 2015

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- Guide to Acceptance Sampling, Taylor, Taylor Enterprises, Lake Villa, IL, ©1992
- PDA Technical Report No. 43 (Revised 2013): Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing: Covering Ampoules, Bottles, Cartridges, Syringes and Vials
- PDA Technical Report No. 76 (2016): Identification and Classification of Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging
- PDA Technical Report 79 (2017): Particulate Matter Control in Difficult to Inspect Parenterals

Questions?