Hot Topics

in the Visual Inspection of Injectable Products

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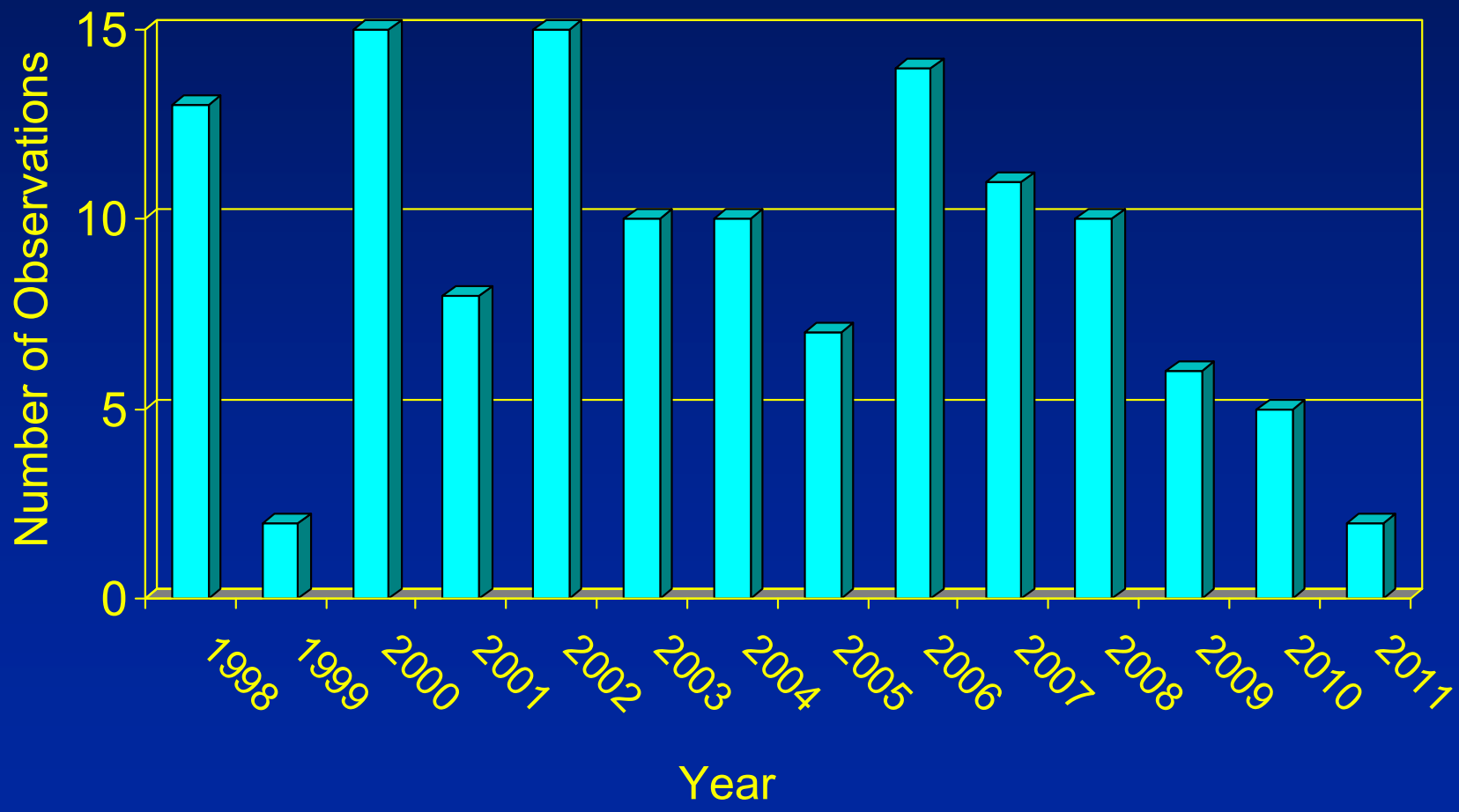
Hot Topics …

- What are the regulatory authorities saying about inspection?
- What does “essentially free” (USP) or “practically free” (EP) of visible particles mean?
- What is a “visible” particle?
- What about sub-visible particles?

More Hot Topics …

- How do we assess the risk that particles may pose to the patient?
- How do we use acceptance sampling in a visual inspection program?
- Is automated inspection better than manual inspection?
- What's new in automated inspection technology?
- Where can I get more information?

FDA 483 Observations



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 recertified.

FDA 483 Themes

- Identify particulate matter when performing Investigations
- Must use statistically sound sampling plan for AQL inspection.

Recent FDA Warning Letters

- 8-30-2010 … Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures …

  … The acceptance criteria is inadequate because your QCD approved the specification without adequate justification or a scientifically sound statistical analysis.

  … you fail to provide a sound scientific rationale for either establishing your acceptance criteria or classifying defects upon visual inspection of your lyophilized products. Typically, vials, with glass particles and cracks, are considered critical defects. However, you have classified these defects as major defects without justification.

Recent FDA Warning Letters

- 3-26-2010 … A self-check of validation batches … reported 19 and 6 trays respectively, with critical defects (particles) during your routine visual inspection evaluation. No investigation was conducted.

  … procedure … "Manual Visual Inspection of …" for visual inspection of product vials states that the inspection be conducted in … minute intervals, with … minutes for an eye-resting break. This procedure also states that each individual vial be inspected for … seconds (… seconds against a black background and … seconds against a white background. During the review of the marketed product …, the investigator observed that none of the … batches met the elapsed time requirement. …

Recent FDA Warning Letters

- 4-22-2009 … We have concerns related to your procedures for visual inspection of sterile drug products and the recurring incidents of particulate matter contamination. …

  … the instructions and acceptance criteria in the previous version of SOP# … "Acceptable Quality Level (AQL) Sampling of Filled Vials" were inadequate. You firm's acceptance criteria for this type of defect permitted … units of limited AQL sample to have visible matter, without rejection ... Lots … were released and shipped to the U.S. using this deficient acceptance criteria for AQL inspection. Based on your new AQL inspection acceptance criteria, as provided in your firm's response to FDA 483 … you would have rejected these lots.

Recent FDA Warning Letters

- 4-22-2009 cont. … Your response fails to provide information regarding your corrective actions related to the marketed lots … For example, your firm plans to conduct visual inspection in periods no longer than 30 minutes. Please include details on how your firm will document conformance to this standard.

  Additionally, based on information provided in your response, it appears that your "Visual Inspection Qualification Program" was inadequate. Prior to the revisions detailed in your response, the operators who conduct visual inspections were considered qualified if they detected only …. Therefore, your reliance on the sufficiency of the above described visual inspection process to assure that contaminated vials are excluded from batches is questionable.

Recent FDA Recalls

- 2-15-2011 … Johnson & Johnson recalls 70,000 Invega syringes
  - Cracks in syringes
- 2-3-2011 … American Regent Initiates Nationwide Voluntary Recall of Potassium Phosphates Injection, USP … Single Dose Vial, Lot #0048 Due to Translucent Visible Particles
  - Glass delamination
- 1-1-2011 … Acetadone (acetylcysteine) Injection: Recall – Particulate Matter Found in a Small Number of Vials
  - Glass particles
- 12-23-2010 … American Regent Initiates Nationwide Voluntary Recall of Sodium Bicarbonate Injection, USP … Single Dose Vials Due to Particulate Matter
  - Glass delamination

Recent FDA Recalls

- 12-20-2010 … American Regent Initiates Voluntary Recall of Dexamethasone Sodium Phosphate Injection, USP … Multiple Dose Vials
  - Glass delamination
- 10-27-2010 … Sandoz initiates voluntary recall in the US of … vials of Methotrexate Injection USP due to the presence of glass particulates
  - Glass delamination
- 9-24-2010 … Amgen Initiates Voluntary Nationwide Recall of Certain Lots of Epogen® and Procit®
  - Glass delamination

Recent FDA Recalls

- 8-2-2010 … Lundbeck Inc. Announces the Voluntary Nationwide Recall of Two Lots of NeoProfen® (ibuprofen lysine) Injection: Recall will Result in Temporary Product Shortage
  - Visible particles
- 6-3-2010 … Claris Lifesciences Initiates a Nationwide Voluntary Recall of All Lots of Ciprofloxine Inj. USP, Metronidazole Inj. USP and Ondansetron Inj.
  - Presence of floating matter
  - Also recalls by Sagent, West-Ward and Pfizer
- 5-17-2010 … Voluntary Recall of HYLENEX
  - Particulate matter, glass flakes

Recent FDA Recalls

- 3-17-2010 … The Medicines Company Expands a Nationwide Recall of Certain Lots of Cleviprex® That May Contain Particulate Matter
  - Visible and sub-visible stainless steel particles

FDA Safety Alerts

- 11-13-2009 FDA is warning healthcare professionals about potential for foreign particle contamination of several products manufactured by Genzyme that are used to treat rare, serious and life threatening disease. The foreign particles, believed to be found in less than 1% of product lots assessed to date include stainless steel fragments, non-latex rubber from vial stopper, and fiber-like material from the manufacturing process and could potentially cause serious adverse events in patients. This problem effects all lots Cerezyme, Fabrazyme, Myozyme, Aldurazyme, and Thyrogen.

FDA Consent Decree

- 7-31-2010 … There were various large- and small-volume parenterals … that should have been rejected but were not: one lot of … contained particles …

  An investigation into foreign material floating in a … lot should have extended to other drug products associated with the problem. Similarly, an investigation into high particulate counts for sterile water for injection did not extend to other batches of product.

  A number of product reserve samples had passed … visual exams even though FDA investigators saw that they contained particulates, while some … injectables including … had never been tested for particulates.

What does "essentially free" or "practically free" mean?

- The goal is the production of product free of visible particles.
  - This requires a well designed and run manufacturing and inspection processes.
  - Inspection should not be a sorting process used to remove high quantities of unacceptable product.
- 100% inspection (human or machine) is needed to detect small quantities of randomly sourced foreign material.
  - 100% inspection (man or machine) is not 100% effective.
  - Zero is not a practical limit.

USP Stimuli to the Revision Process

- Visible Particulates in Injections – A History and Proposal to Revise USP <1> Injections
  - *USP Pharmacopeial Forum* Vol. 35(5) Sept.-Oct. 2009, pgs 1383-1387
  - Russell Madsen, Roy Cherris, John Shabushnig and Desmond Hunt

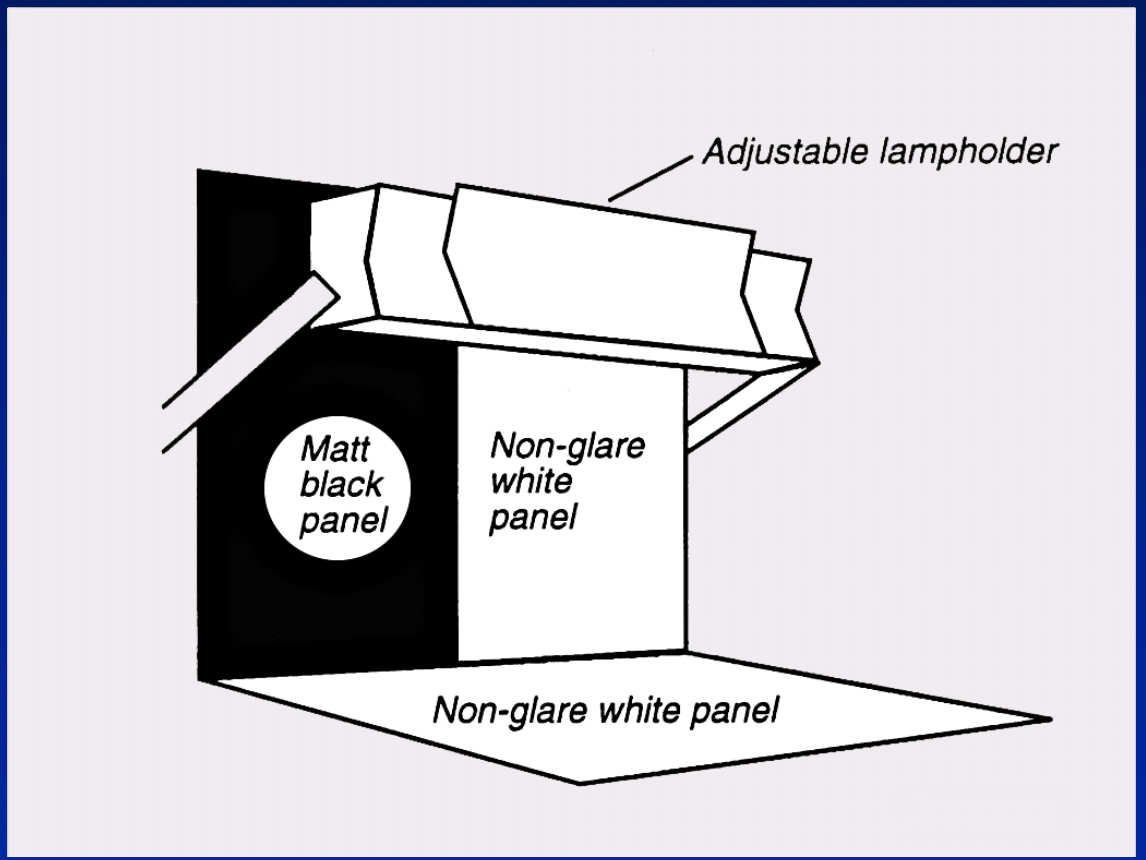
USP Stimuli to the Revision Process

- Visible Particulates in Injections – A History and Proposal to Revise USP <1> Injections
  - The Need to Inspect
  - History of Inspection Standards
  - Basis for Proposal
  - Draft Text for Consideration
  - References

Inspection Conditions

- Inspection conditions defined:
  - Harmonized with EP
  - 2,000-3,750 lux
  - Black and white backgrounds
  - 5 sec viewing against each background

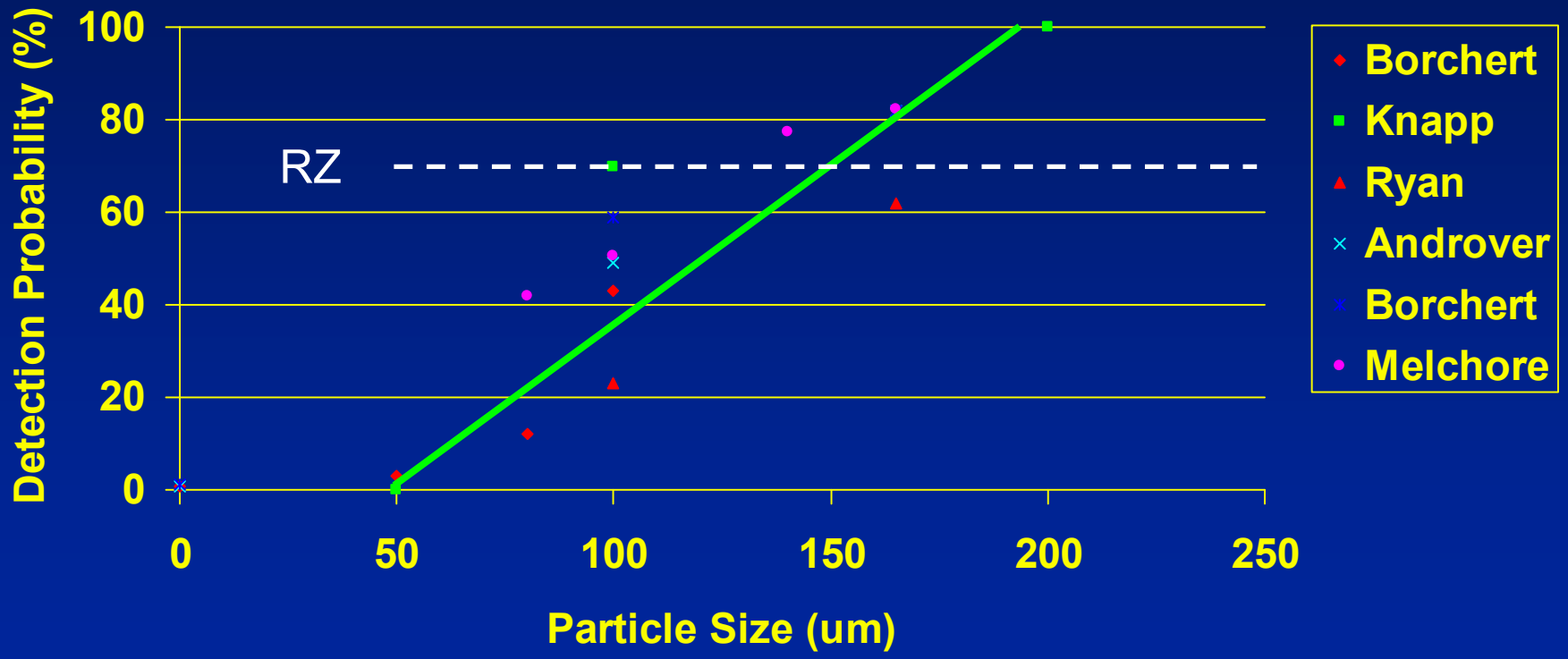
EP/WHO Inspection Workstation



What is a "visible particle"?

- Any definition of visibility must specify and control these critical variables:
  - Illumination
    - Intensity
  - Background
    - contrast
  - Duration
    - Inspection time, rate or pace
  - Agitation
    - Particle movement

Human Inspection Performance



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

Acceptance Criteria

- For Batch Release:
  - 100% inspection followed by acceptance sampling
  - ANSI/ASQ Z1.4-2008 or ISO 2859
  - AQL= 0.65%, UQL= 2.3-3.3% typical
- For Product with the Customer:
  - ANSI/ASQ Z1.4-2008 or ISO 2859
  - Special Level S-4, N = 1,201 – 500,000
  - n = 60, a = 1
  - AQL= 0.60%, UQL= 6.3%

Revisions to the Proposal based on Stakeholder Feedback

- Swirl and/or Invert
- Exempt proteins/biologicals. To be addressed in individual monographs.
- Revised sampling plan:
  - Two-stage plan (to conserve samples)
  - S1: n = 20, a = 0, r = 2, go to S2 if one unit observed with particle(s).
  - S2: n = 80, a = 0
  - AQL = 0.62%, UQL = 10.9%

The Risk of <10 µm Particles?

- "Overlooking Subvisible Particles in Therapeutic Protein Products: Gaps That May Compromise Product Quality"
  - *J. Pharm. Sci.* Vol. 98(4), April 2009, pgs 1201-1205
  - John Carpenter, et al
- Subvisible protein particles may cause immunogenic response

USP <788> Limits

- "Particulate Contaminants of Intravenous Medication and the Limits Set by USP General Chapter <788>"
  - *USP Pharmacopeial Forum* Vol. 30(6) Nov-Dec 2004, pgs 2272-2280
  - Nrapendra Nath, et al
- Analysis of 295 ANDA's (406 drug lots) from 1998-2002
  - ≥10µm = 219±415, ≥25µm = 15±43 (mean ± 1σ)
  - ≥10µm = 6,000, ≥25µm = 600 (current USP <788> limits)
- "We hope that this *Stimuli* article will help generate discussion about the need and usefulness of tighter limits based on recent data …"

How do we assess the risk a particle may pose to a patient?

- Chemical
  - Single 100um particle in 1mL dose is equivalent to an impurity level of 4 ppm (v/v)
- Microbiological
  - Particles can be carriers for microbiological contamination
- Process Control
  - Cosmetic assessment of quality
- Physiological

How do we assess the risk a particle may poses to a patient?

- Animal Studies
  - "Truly massive" particle doses (e.g. 10^5-10^9 particles/kg/injection)
  - Useful for studying circulation and deposition of particles in tissues
    - Smallest particles (1 um) trapped in liver, lungs and spleen
    - Larger particles generally do not migrate far from injection site
    - In long-term studies, gram quantities were required to produce pathology
  - Provide limited guidance in assessing human patient risk for small numbers of visible particles

How do we assess the risk a particle may poses to a patient?

- Human Studies
  - Lack of controlled human studies
  - Anecdotal studies
    - Foreign body emboli and granulomas most common result of particulate matter from IV solutions
    - Pulmonary emboli and granulomas observed in IV drug abusers who inject non-sterile slurries of ground tablets
    - No granuloma formation from 150-300um glass spheres used for surgical correction of vesicoureteral reflux
  - Consider route of administration (IM or sub-Q vs. IV)?

How do we use Acceptance Sampling in a visual inspection program?

- Sampling vs. 100% Inspection
  - Sampling preferred when:
    - Test is destructive
    - Test cost is high
    - Lot size is very large
  - 100% Inspection preferred:
    - To remove low numbers of randomly distributed defects
    - When risk of a defective unit is high

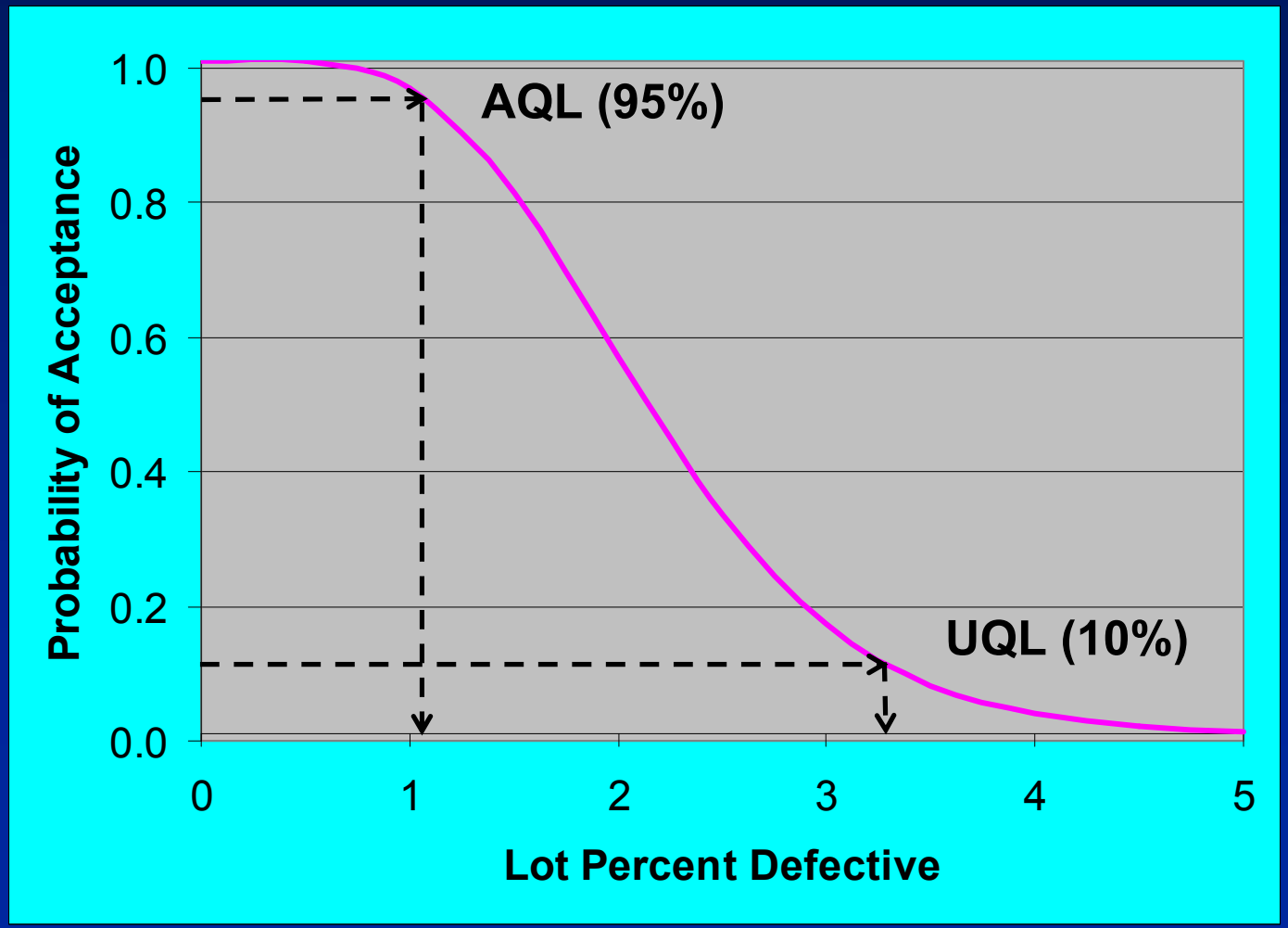
Acceptance Sampling

- Acceptable Quality Limit (AQL)
  - The defect level that will be routinely accepted by the sampling plan. 95% of the time, lots of this quality will be accepted. Defines the producer's risk.
- Unacceptable Quality Limit (UQL) or Lot Total Percent Defective (LTPD)
  - The defect level that will be routinely rejected by the sampling plan. 90% of the time, lots of this quality will be rejected. Defines the customer's risk.

Acceptance Sampling

- Operating Characteristic (OC) Curve
  - A plot of the probability of accepting a lot (y-axis) versus the lot percent defective (x-axis). This curve is descriptive of the protection provided by a given sampling plan.

Operating Characteristic Curve



Single

N = 50,000

n = 315

a = 6

AQL = 1.1%

UQL = 3.3%

Sampling Plans

	2008	2003	1996
• Firms w/ sampling plan based on:			
- ANSI Z1.4 (Mil Std 105E)	53%	70%	90%
- Mil Std 1916	11%	10%	0%
- ISO 2859.1	11%	10%	0%
- JIS Z9015	15%	5%	0%
- Dodge Romig	0%	5%	0%
- Other	10%	0%	10%

Sampling Plans (cont.)

- Typical lot size .. 1,500-150,000 / 33,000 median
  1,000-400,000 / 20,000 median
  2,200-300,000 / 65,000 median
- Typical sample size ..... 30-2,500 / 500 median
  1-1,000 / 315 median
  10-3,000 / 600 median

Sampling Plan AQL's

- Critical Defects ..... 0.00-1.0 / 0.10 median
  0.00-0.10 / 0.10 median
  0.006-0.10 / 0.035 median
- Major Defects ..... 0.10-3.0 / 0.65 median
  0.07-1.5 / 0.65 median
  0.25-2.5 / 0.83 median
- Minor Defects ..... 0.50-5.00 / 4.00 median
  0.4-4.0 / 2.5 median
  1.3-4.0 / 2.9 median

How do we use Acceptance Sampling in a visual inspection program?

- 100% (manual or automated) inspection followed by sampling inspection
  - 100% inspection provides high sensitivity for small numbers of random defects
  - Sampling inspection provides an assessment of the effectiveness of the inspection of a specific batch
    - Safety net

Is automated inspection better than manual inspection?

- Automated
  - Same or greater sensitivity for many (not all) visible defects
  - Better consistency
  - Better efficiency, higher throughput
  - Often higher false reject rate
  - Reduced ergonomic injury risk
  - High initial cost

Is automated inspection better than manual inspection?

- Human (Manual or Semi-automated)
  - More flexible
    - New products and packages
  - Quicker response to new defect types
  - More cost effective for small batches / many different product types
  - Reference standard for all compendia
  - Low initial cost

Inspection Method

	2008	2003	1996
• For Particulate Matter:			
- manual	33%	46%	33%
- semi-automated	24%	19%	20%
- automated	43%	35%	42%
• For Container / Closure Defects:			
- manual	36%	63%	48%
- semi-automated	26%	15%	42%
- automated	39%	20%	5%

Shift to Automated Inspection

	2008	2003	1996
• Firms with plans to replace manual inspection with automated systems in the next 1-2 years	67%	50%	68%
• Justification:			
- productivity	92%	92%	100%
- quality	75%	92%	92%
- Ergonomics / safety	0%	8%	17%

What's new in automated inspection technology?

- Leak Detection
  - Vacuum Decay
  - Headspace Analysis
  - High-Voltage
- X-Ray
  - Lyo cakes
  - Powders
  - Suspensions

Where can I get more information on visual inspection?

- PDA Visual Inspection Interest Group
  - Annual Meeting (Joint Meeting w/ Lyo IG)
  - European IG, May 25, 2011, Berlin Germany
  - PDA/FDA Joint Regulatory Conference
- PDA Glass Quality Conference
  - May 23-24, 2011, Arlington, VA
- PDA Visual Inspection Forum
  - October 3-4, 2011, Bethesda, MD
- PDA TRI Introduction to Visual Inspection
  - May 26-27, 2011, Berlin, Germany
  - October 5-6, 2011, Bethesda, MD

Remember, everyone is an inspector!

What are your

Hot Topics

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