# HOT TOPICS in the Visual Inspection of Injectable Products

John G. Shabushnig, Ph.D.
Pfizer Global Quality Operations

January 14, 2009

# Hot Topics …

- How do we assess the risk that particles may pose to the patient?
- Do glass particles pose a unique and different risk to patients?
- What is a “visible” particle?
- What does “essentially free” (USP) or “practically free” (EP) of visible particles mean?

# More Hot Topics …

- What is the appropriate classification (and associated AQL) for particles?
- How do we use acceptance sampling in a visual inspection program?
- Is automated inspection better than manual inspection?
- What are the regulatory authorities saying about inspection?

# Even More Hot Topics …

- What do we know about industry inspection practices ?
- Where can I get more information?

# 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)?

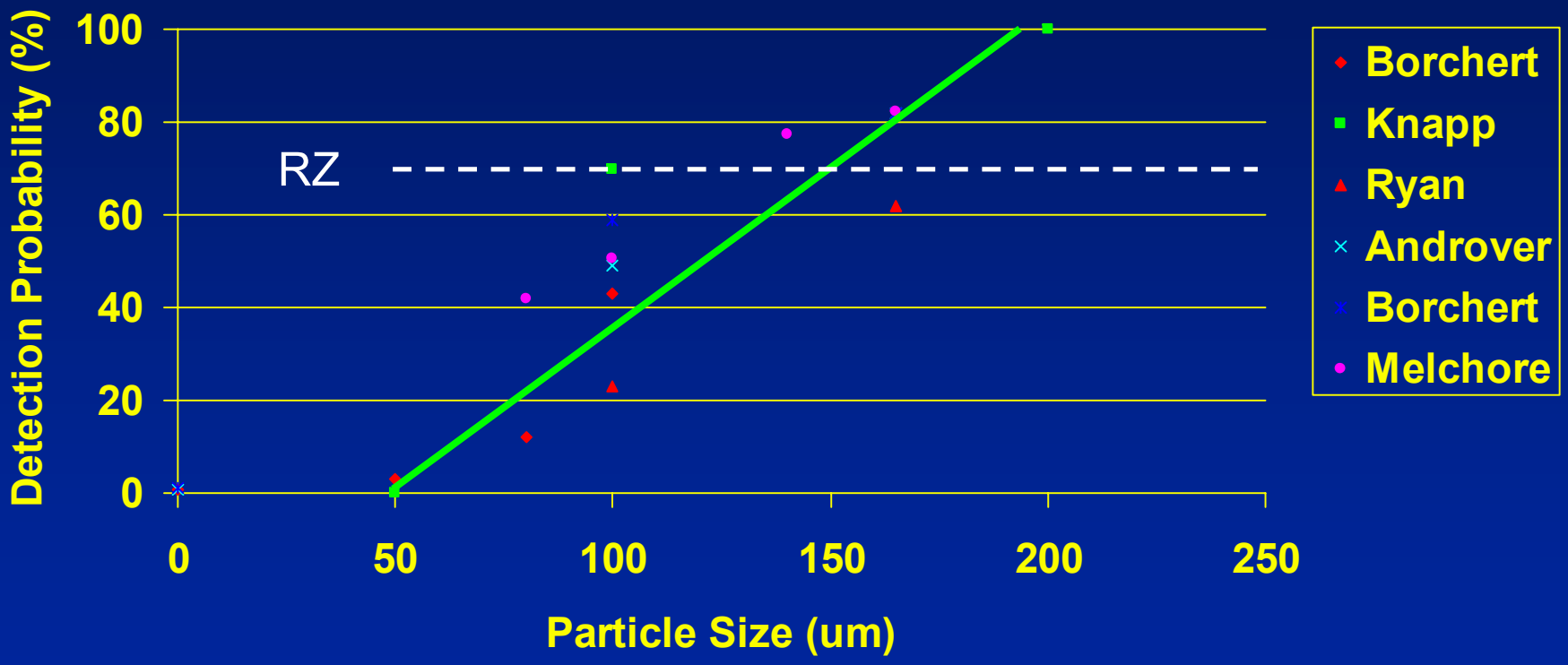
# Do glass particles pose a unique and different risk to patients?

- Size, quantity and route of administration appear to be important variables
- Composition does not appear to be as significant

# Particulate Matter vs. Foreign Matter

- Particulate matter is an intrinsic element of the manufacturing process.
- Intrinsic
  - Formulation, Processing Equipment, Primary Package
    - qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)
- Extrinsic
  - Environmental Contaminants
    - insect parts, hair, fibers, paint, rust

# What is a "visible" particle?

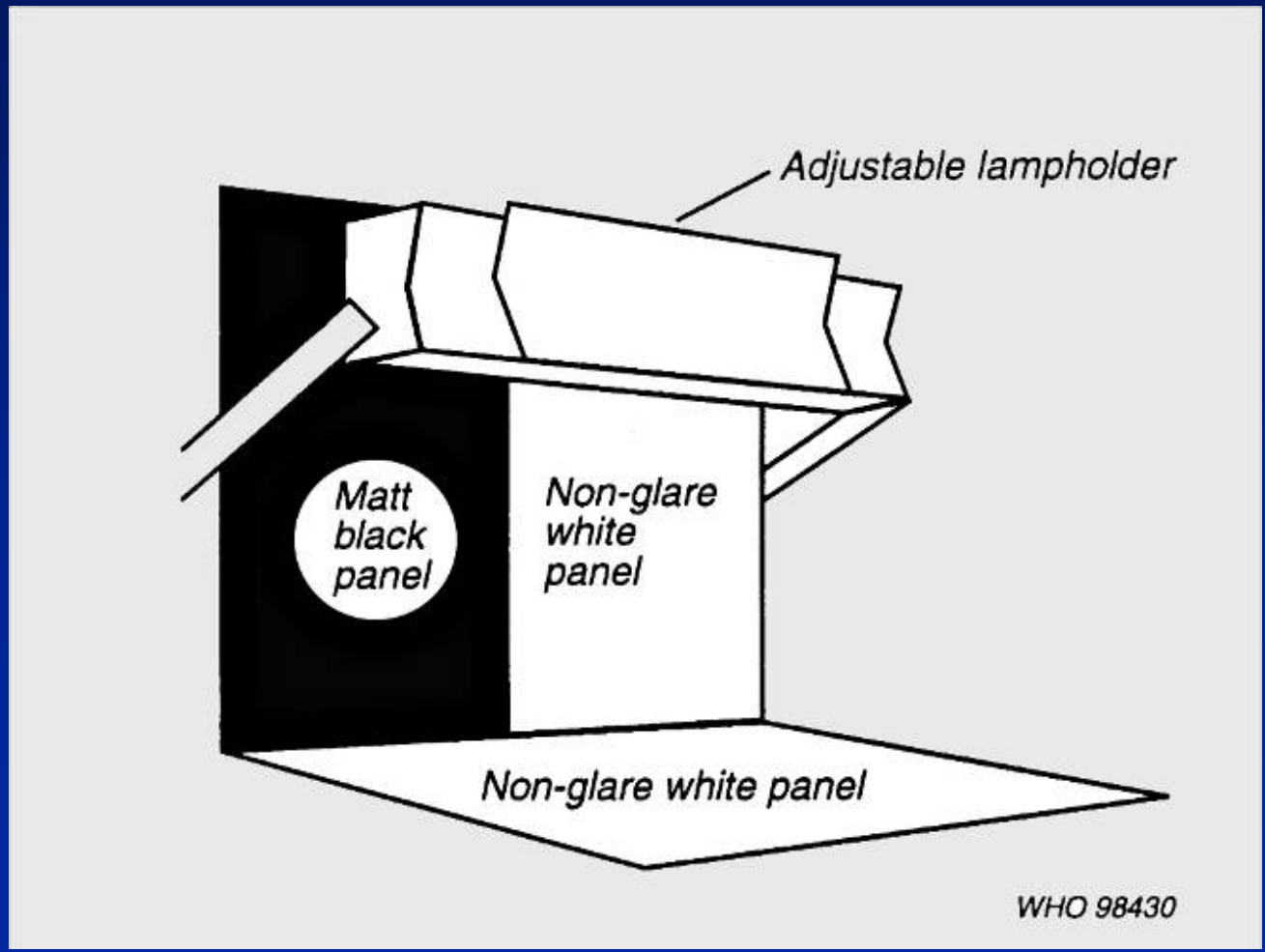



From Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995

# 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

# EP/WHO Inspection Workstation



# 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 process
  - 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

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

- Other precedents exist
  - Sterility Assurance provides a good model, recognizing the probabilistic nature of the test method
  - Current non-zero compendial limits exist for sub-visible particles

# 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

# USP Stimuli to the Revision Process

- Not for batch release.  Intended for testing of product in distribution.
- Inspection conditions defined
  - Harmonized with EP
  - 2,000-3750 lux
  - Black and white backgrounds
  - 5 sec viewing against each background
- ANSI/ASQC Z1.4
  - Special Level S-4, N = 1,201 – 500,000
  - n = 60, a = 1
  - AQL = 0.60%, UQL = 6.32

# What is the appropriate classification (and AQL) for visible particles?

- Common Defect Classifications
  - Critical
    - Safety risk, may cause permanent injury to patient
  - Major
    - Functional risk, product impossible or difficult to use
  - Minor
    - Cosmetic (appearance) defects

# 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

# 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

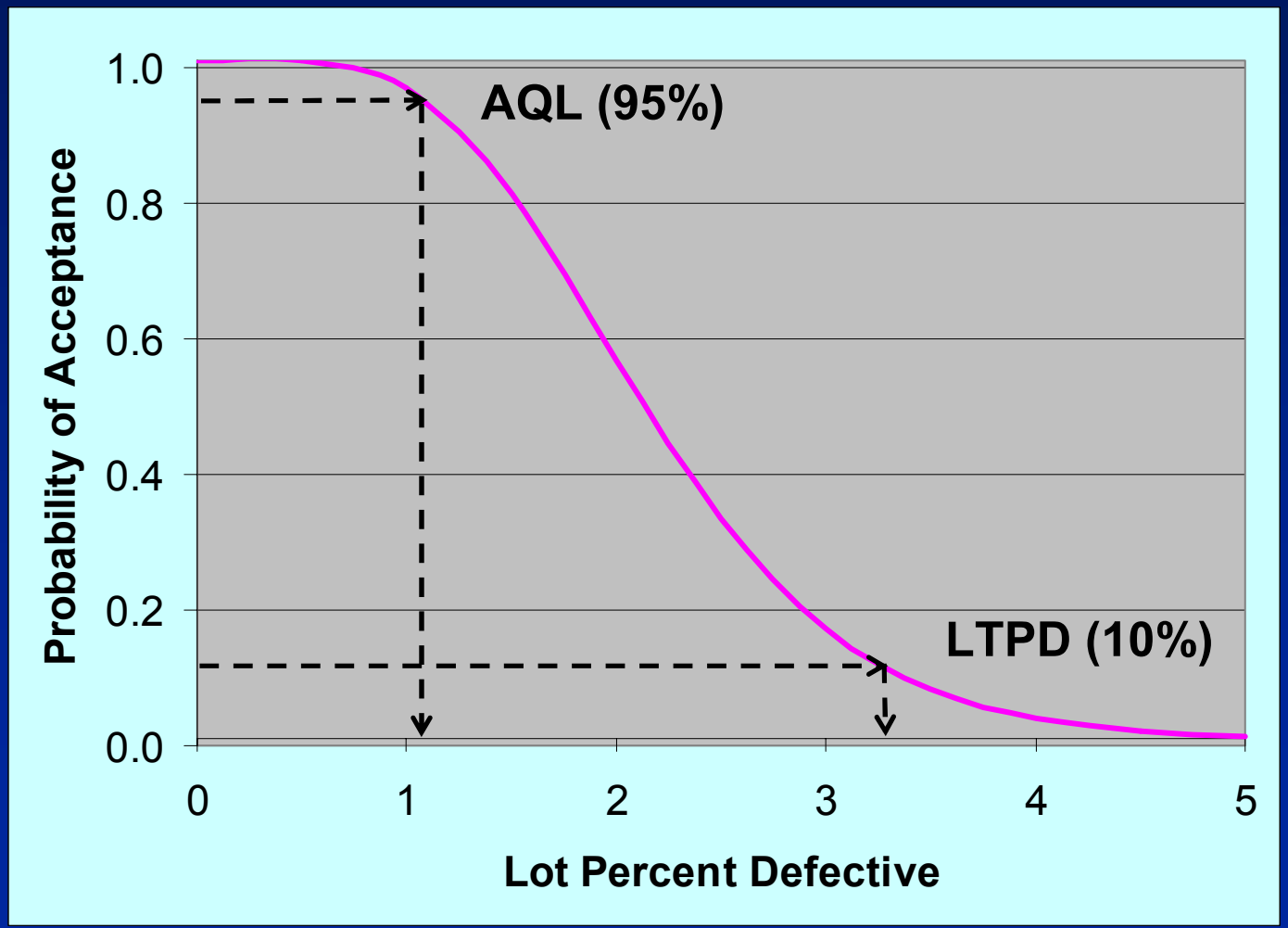
# Acceptance Sampling

- Acceptable Quality Level (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 Level (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%**

**LTPD = 3.3%**

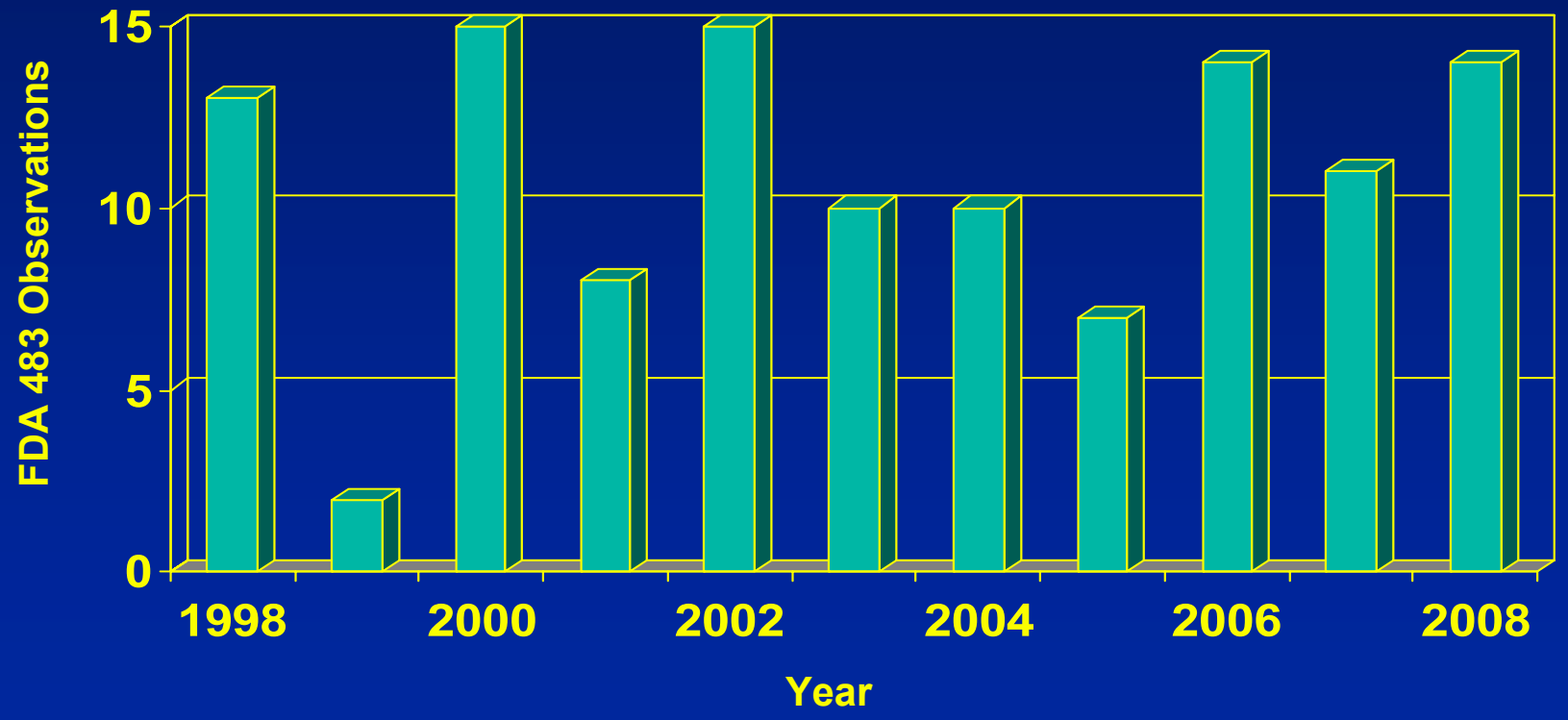
# Is automated inspection better than manual inspection?

- 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

# What are the regulatory authorities saying about inspection?



# 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.
- Must use statistically sound sampling plan for AQL inspection.
- Inspectors must be trained and training documented.
- Inspectors must be periodically recertified.
- Identify particulate matter when performing Investigations

# Top 10 Reasons for Recalls - 2006

1. Sub-potent product
2. **Defective container**
3. Lack of sterility assurance
4. Impurity / degradation products
5. cGMP deviations (failure to perform or document required activities)
6. Microbial contamination
7. Super-potent product
8. Stability data do not support expiration date
9. Labeling (incorrect expiration date)
10. Dissolution failure / Non-sterility / **Presence of particulate matter**

# What do we know about industry inspection practices?

- PDA surveys conducted in 1996, 2003 and 2008.
- Document current industry practice for visual inspection of injectable products.
- 57 questions, blinded response
- 230 companies/sites contacted
- 21 responded (9%)
  - 8 North America, 12 Europe, 1 South America
- 27 responded (14%) in 2003
  - 20 North America, 5 Europe, 2 Japan
- 20 responded (27%) in 1996
  - 20 North America

# Markets Served

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • North America ..... | 81% | 81% | 100% |
| • Europe ..... | 90% | 63% | 75% |
| • Asia / Pacific ..... | 81% | 56% | 70% |
| • South America ..... | 81% | 48% | 50% |
| • Africa ..... | 52% | 26% | 30% |

# Product Mix

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Human Health Drug ..... | 67% | 85% | 80% |
| • Biologicals / Biotech..... | 76% | 37% | 40% |
| • Veterinary ..... | 48% | 7% | 30% |
| • Diagnostics ..... | 5% | 4% | 10% |

# Product Type

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Solution ..... | 54% | 40% | 60% |
| • Lyophilized ..... | 25% | 30% | 27% |
| • Suspension ..... | 6% | 22% | 9% |
| • Powder ..... | 0% | 1% | 2% |
| • Ointment ..... | 1% | 0% | 1% |
| • Oil ..... | 9% | 3% | 1% |

# Production Volume

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • No response ..... | 3% | 0% | 5% |
| • <1 million units ..... | 14% | 19% | 10% |
| • 1 to 10 million units ..... | 29% | 32% | 20% |
| • 11 to 30 million units ..... | 29% | 4% | 35% |
| • 31 to 60 million units ..... | 10% | 15% | 15% |
| • 61 to 100 million units ..... | 5% | 30% | 15% |
| • > 100 million units..... | 10% | - | - |

# Location of Inspection

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Off-line ..... | 81% | 59% | 37% |
| • In-line with Filling ..... | 16% | 22% | 31% |
| • In-line with Packaging ..... | 3% | 17% | 42% |
| • Firms inspecting empty containers .. | 16% | 28% | 30% |

- molded or special containers
- customer requested

# Manual Inspection

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Paced ..... | 68% | 56% | 80% |
| • Magnification ..... | 26% | 31% | 45% |
| - (2-5x, 4x median) | | | |
| • Clip/Grouped ..... | 71% | 22% | 30% |
| - number per group (1-16, 4 median) | | | |
| • Polarizer ..... | 16% | 4% | 25% |

# Manual Inspection Rate

- Molded Glass Vials
  - 1 to 10 mL ..... 1-12 sec / 6 sec median
    0.7-4 sec / 2 sec median
    1-20 sec / 6 sec median
  - 11 to 100 mL ..... 2-15 sec / 4 sec median
    1-28 sec / 6 sec median
    0.5-20 sec / 7 sec median
  - >100 mL ..... No Data
    1-4 sec / 3 sec median
    1-20 sec / 7 sec median

# Manual Inspection Rate (cont.)

- Tubing Glass Vials
  - 1 to 10 mL ..... 1-17 sec / 5 sec median
    0.7-60 sec / 8 sec median
    0.5-20 sec / 7 sec median
  - 11 to 100 mL ..... 2-15 sec / 4 sec median
    1-60 sec / 15 sec median
    0.5-20 sec / 8 sec median
- Glass Ampoules ..... 3-10 sec / 5 sec median
  4-42 sec / 4 sec median
  3-20 sec / 11 sec median

# Lighting

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Fluorescent ..... | 68% | 56% | 45% |
| • Incandescent ..... | 16% | 15% | 25% |
| • Both ..... | 16% | 26% | 25% |

- Intensity at container:
  - 90-400 ft-candles / 270 ft-candles median
  - 65-750 ft-candles / 215 ft-candles median
  - 90-500 ft-candles / 225 ft-candles median
  - 900-4000 lux / 2700 lux median
  - 600-7,000 lux / 2,000 lux median
  - 850-4,650 lux / 2,100 lux median

# Break Interval

- Maximum duration of uninterrupted inspection:

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| - 15 min ..... | 16% | 12% | 5% |
| - 30 min ..... | 32% | 15% | 21% |
| - 60 min ..... | 32% | 62% | 32% |
| - 120 min ..... | 11% | 12% | 37% |
| - 240 min ..... | 0% | 0% | 5% |

# 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% |

# Typical Reject Rates

- Solution ..... 0.1-7.5% / 2.0% median
  0.5-5% / 2.5% median
  0.1-5% / 1.9% median
- Lyophilized ..... 0.1-8.0% / 1.0% median
  0.6-5% / 1.2% median
  0.1-2.5% / 1.0% median
- Suspension ..... 0.1-5.0% / 1.5% median
  0.2-6% / 2.0% median
  0.3-2% / 0.9% median

# Most Common Defects

- (1) (1) (1) Particulate Matter
- (2) (4) (4) Scratches
- (3) (3) (2) Crimp
- (4) (5) (5) Fill
- (5) (2) (3) Cracks
- (6) (7) (9) Cap
- (7) (8) (7) Leaks
- (8) (9) (8) Plug
- (8) (6) (6) Cake

# Most Common Particulate Matter Identified

- (1) (1) (1) Lint / Fiber
- (2) (2) (2) Glass
- (3) (4) (3) Product Related
- (4) (5) (5) Rubber
- (5) (3) (4) Metal

# 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

# Classification of Defects

- 45% of firms classify Particulate Matter as Major and 45% as Critical.
  - Categories may be sub-divided into additional categories e.g. Major A (PM) / Major B (other), Minor / Cosmetic.
- 63% of firms use the same AQL for all PM (including glass).

# Acceptance Criteria

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Firms that apply same criteria to veterinary and human health products..... | 100% | 83% | 100% |
| • Firms that apply same criteria to products destined for all markets ... | 68% | 87% | 90% |

- Those indicating no, (32%) have special criteria for products intended for the Japanese market.

# Alert/Action Limits on 100% Inspection Results

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Firms with established limits ..... | 85% | 76% | 85% |
| - Firms with same limit for all products | 44% | 32% | 82% |
| • Practice if limit exceeded: | | | |
| - investigate ..... | 70% | 95% | 80% |
| - reinspect ..... | 45% | 50% | 82% |
| - reject all or part of lot ..... | 5% | 36% | 45% |

# Alert/Action Limits on 100% Inspection Results (cont.)

| | 2008 | 2003 | 1996 |
|---|---|---|---|
| • Alert/Action Limits: | | | |
| - <1% ..... | 32% | 29% | 14% |
| - 1 to 2% ..... | 21% | 41% | 18% |
| - 3 to 5% ..... | 37% | 29% | 27% |
| - 5 to 10% ..... | 16% | 35% | 18% |
| - >10% ..... | 11% | 6% | 9% |

# Conclusions

- Limited changes have occurred in inspection practices since 1996 and 2003 surveys.
- Manual inspection is generally performed under controlled conditions, however these conditions still vary widely.
- Most firms expect tighter regulatory requirements to impact inspection practices in the future.

# Conclusions (cont.)

- Firms are planning to replace manual inspection with automated inspection to improve productivity and quality.
- Automated inspection is applied to particulate matter in solutions to the same extent as previously observed. The number of systems installed for cosmetic / container inspection has increased.

# Where can I get more information on visual inspection?

- PDA Visual Inspection Interest Group
  - October 19-20, 2009, Bethesda, MD
- PDA Visual Inspection Forum
  - Annual Meeting
  - PDA/FDA Joint Regulatory Conference
- PDA TRI Introduction to Visual Inspection
  - October 21-22, 2009, Bethesda, MD

# Acknowledgments


- Survey
  - Ron Leversee - Pfizer
  - Matthew Ostrowski - Pfizer
  - Iris Rice - PDA
- USP Stimulus
  - Russ Madsen - The Williamsburg Group
  - Roy Cherris - Bridge Associates International
  - Desond Hunt - USP

Remember, everyone is an inspector!

What are your


?