

# Lifting the Fog around the Visual Inspection of Injectable Products

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# Common Questions ...

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- 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 Questions ...

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- 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 Questions ...

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

A vertical decorative image on the left side of the slide showing a sunset over a layer of clouds. The sun is partially visible as a bright semi-circle on the horizon, with a gradient from orange to yellow.

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

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- **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?

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- **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  $\mu$ m) 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?

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- **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?

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

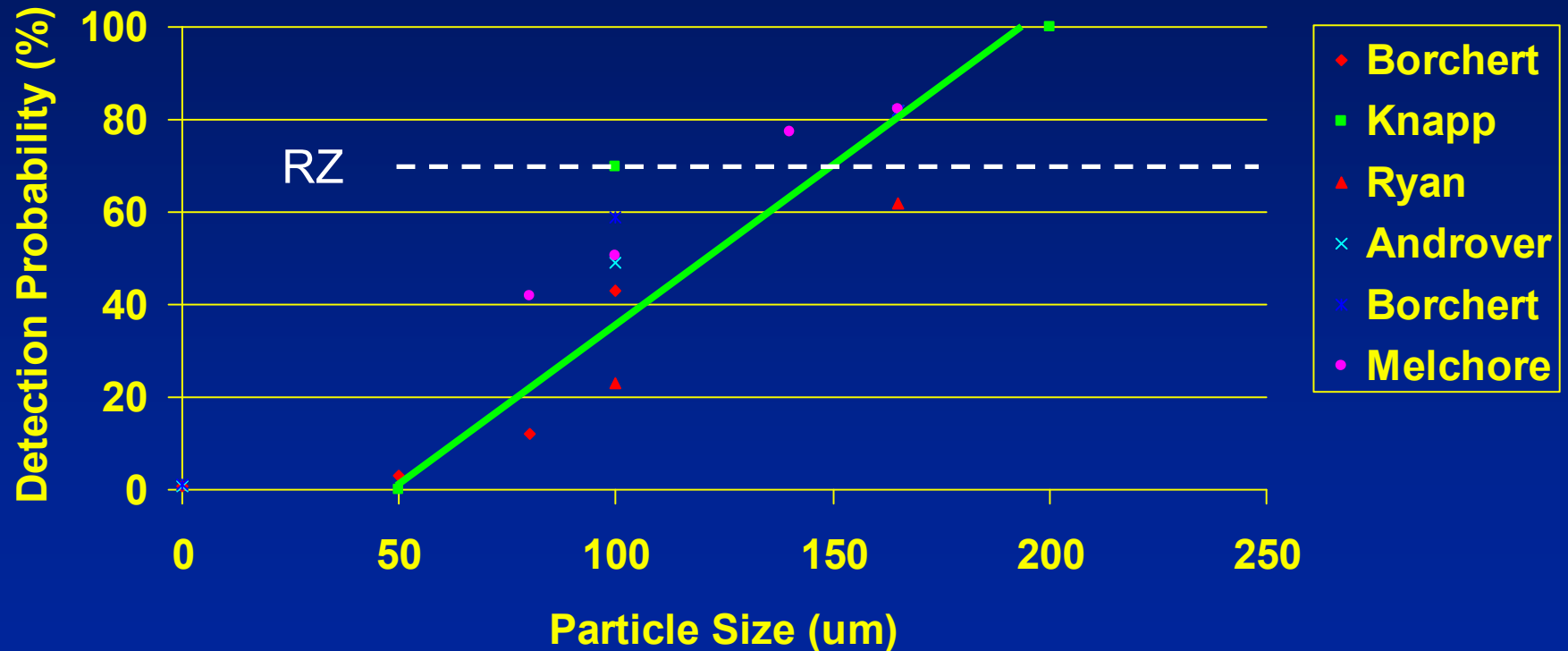


# Particulate Matter vs. Foreign Matter

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- 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

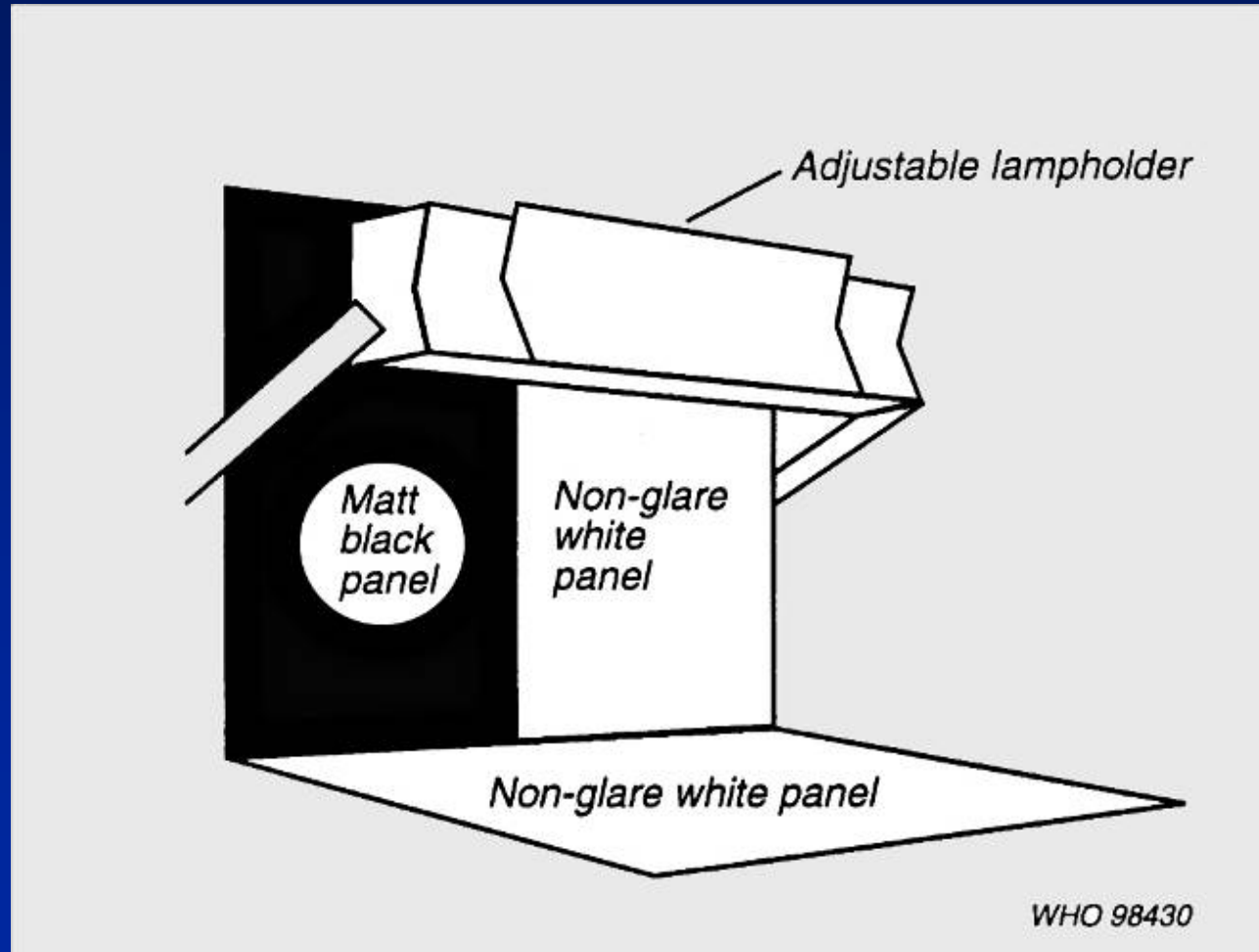


# What is a “visible particle”?

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- 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?

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- 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

A vertical strip on the left side of the slide shows a sunset over a layer of clouds. The sun is partially obscured by the clouds, and the sky is a mix of orange and red.

# What does “essentially free” or “practically free” mean?

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- 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

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- 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

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- 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

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

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- **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

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

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- **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

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

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- 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

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- **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.

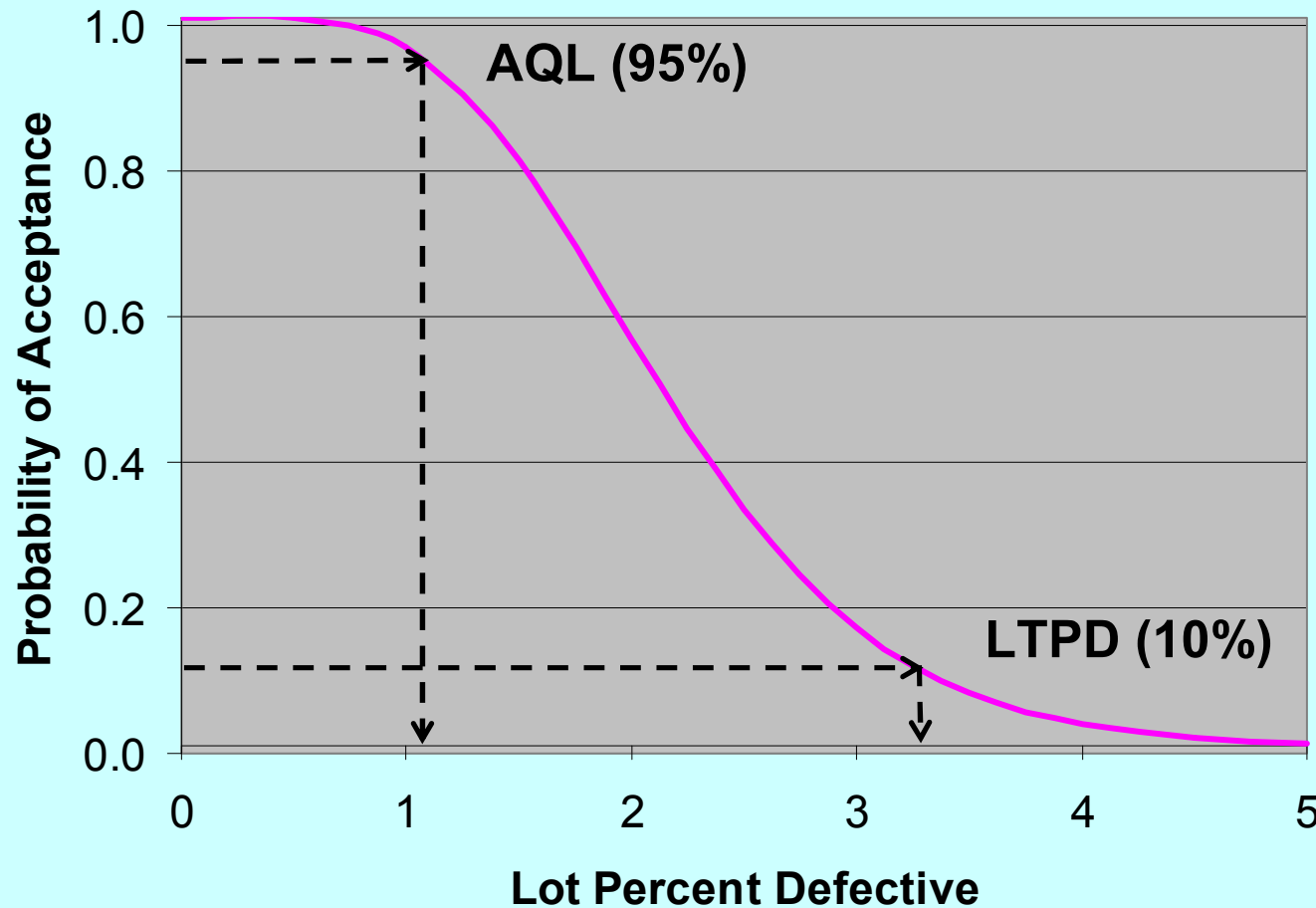
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# Acceptance Sampling

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- **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?

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- **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

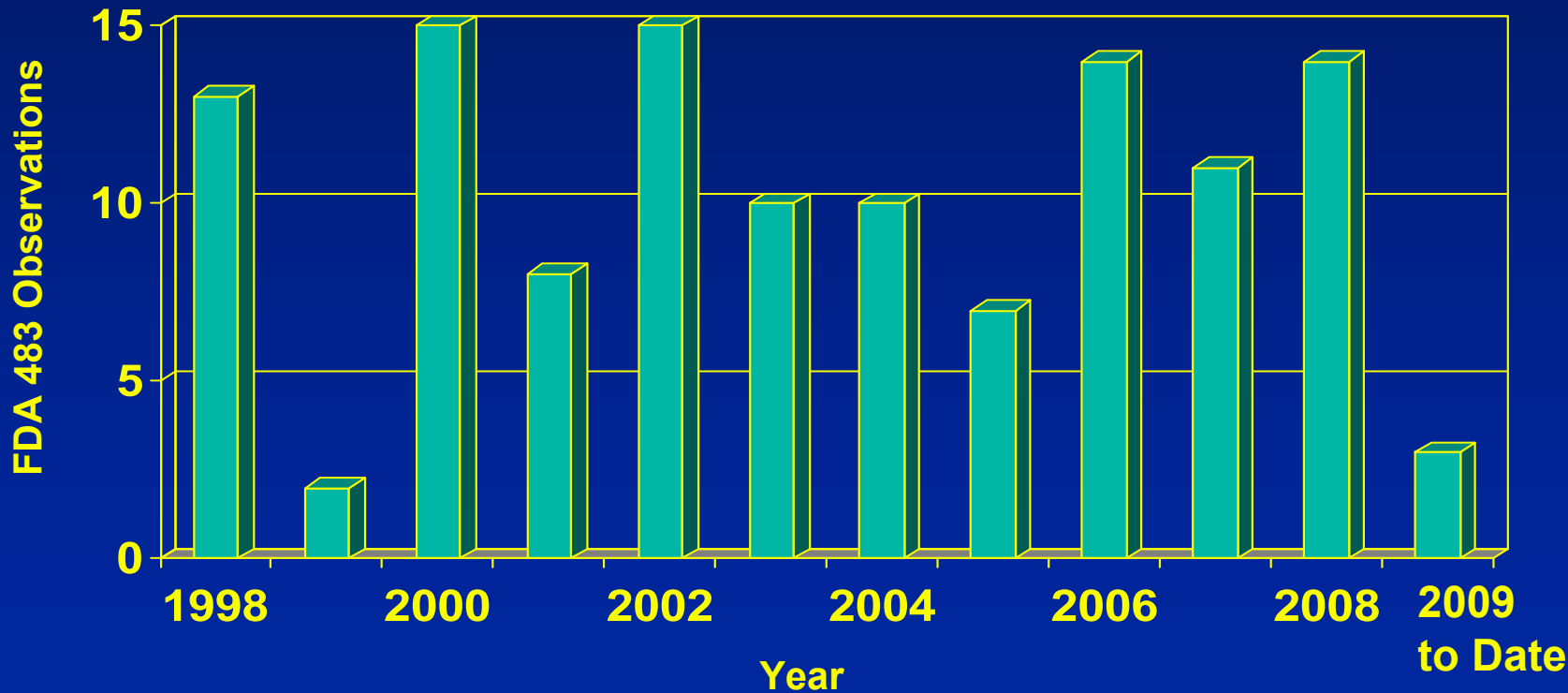


# Is automated inspection better than manual inspection?

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- **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

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- 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

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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?

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- 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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

# Product Type

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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- **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.)

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- **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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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- Maximum duration of uninterrupted inspection:

	<u>2008</u>	<u>2003</u>	<u>1996</u>
- 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

	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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- **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

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- (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

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

# Sampling Plans

	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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.)

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- 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

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- **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

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- 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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.)

	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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

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- 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.)

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- 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.

A vertical decorative image on the left side of the slide showing a sunset over a body of water with clouds.

# Where can I get more information on visual inspection?

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- **PDA Visual Inspection Interest Group**
  - PDA/FDA Joint Regulatory Conference, September 15, 2009, Washington, DC
- **PDA Visual Inspection Forum**
  - October 19-20, 2009, Bethesda, MD
- **PDA TRI Introduction to Visual Inspection**
  - October 21-22, 2009, Bethesda, MD



# Acknowledgments

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  - Desmond Hunt - USP



Remember, everyone is an inspector!

Questions?

