A Survey of Industry Practice for the Visual Inspection of Injectable Products

(Preliminary Report)

Ronald L. Leversee &

John G. Shabushnig, Ph.D.

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Survey Objective

- Document current industry practice for visual inspection of injectable products.
- Compare results with previous surveys conducted in 1996 and 2003.

Questionnaire and Response

- 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

Questionnaire Categories

- General
- Manual Inspection
- Automated Inspection
- Inspection Results
- Inspection Strategies
- Future Direction

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 Mix (cont.)

	2008	2003	1996
• 1 to 5 products	14%	44%	30%
• 6 to10 products	14%	19%	5%
• 11 to 20 products	29%	11%	10%
• >20 products	43%	26%	55%

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%

Primary Package Type

	2008	2003	1996
• Molded Glass Vials			
- 1 to 10 mL	2%	12%	12%
- 11 to 100 mL	13%	4%	14%
- >100 mL	0%	3%	9%
• Tubing Glass Vials			
- 1 to 10 mL	32%	34%	44%
- 11 to 100 mL	10%	14%	11%

Primary Package Type (cont.)

	2008	2003	1996
• Plastic Vials	2%	0%	0.1%
• Glass Ampoules	15%	7%	1%
• Glass Syringes	11%	0%	4%
• Plastic Syringes	1%	0%	0.5%
• Other	4%	18%	4%

  - glass cartridges
  - bags

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

Time Between Filling and Inspection

	2008	2003	1996
• <1 day	5%	8%	6%
• 1 to 2 days	32%	20%	17%
• 3 to 7 days	47%	36%	50%
• >7 days	16%	36%	28%

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

Inspector Qualification

	2008	2003	1996
• Training (56-160 hrs)	89%	96%	80%
• Testing (65-90% accuracy w/ test vials) .	100%	89%	80%
• Vision Test (20/20 corrected)	79%	85%	80%
• Color Vision	68%	-	-
• Education (HS or equiv. minimum)	26%	30%	25%
• Experience	37%	15%	30%
• Firms with same requirements for QA Inspectors	83%	82%	20%

Inspector Requalification

	2008	2003	1996
• Periodic Requalification Required	79%	92%	65%
• Requalification Interval:			
- monthly	5%	0%	8%
- quarterly	0%	0%	8%
- semi-annually	11%	8%	16%
- annually	63%	75%	69%
- bi-annually	0%	8%	0%

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%

Validation Criteria

	2008	2003	1996
• Equivalent to manual	38%	63%	50%
• Better than manual	31%	25%	31%
• Other, not compared to manual ..	31%	25%	19%

Routine Challenges

	2008	2003	1996
• Standards:			
- standard material	64%	64%	50%
- product samples	73%	36%	50%
• Frequency of challenges:			
- none	0%	0%	15%
- each shift	8%	13%	8%
- at set-up or for each batch.....	42%	75%	38%
- daily	25%	19%	23%
- weekly	0%	0%	8%

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

Typical Reject Rates (cont.)

- Oil ..... 0.1-1.0% / 1.0% median
  0.6-1% / 0.8% median
  0.3-2% / 0.9% median
- Powder ..... No data
  2.0% / 2.0% median
  0.1-1% / 0.6% 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

Transient Particulate Matter

	2008	2003	1996
• Firms having observed transient particulate matter (TPM).....	50%	60%	75%
• TPM Observed to:			
- appear after holding	50%	67%	20%
- disappear after holding	29%	29%	7%
- appear after handling / agitation	8%	22%	14%
- disappear after handling / agitation	29%	36%	27%
- appear w/ change in temperature	42%	11%	18%
- disappear w/ change in temperature ...	43%	35%	14%

Transient Particulate Matter (cont.)

- When TPM is known to occur in a product, the following practices are employed:

	2008	2003	1996
- reinspect w/ std. inspect. method ...	50%	50%	27%
- hold before inspection	10%	30%	41%
- accept as is	30%	10%	18%
- reinspect w/ mod. inspect. Method..	10%	10%	14%

Auditing Lot Quality

	2008	2003	1996
• Audit performed on every lot	85%	72%	90%
• Audit performed on selected lots	0%	8%	5%
• No audit performed	15%	20%	5%
• Audit performed by QA	74%	85%	89%
• Audit performed by Production	26%	15%	11%

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%

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

- What defects are included in calculating this limit?

	2008	2003	1996
- all	76%	77%	60%
- critical only	6%	9%	13%
- critical and major	18%	5%	27%

- Firms that correct results for false rejects 20% 15% 29%

Reinspection

- Firms that limit to number of inspections….. 63%
- Maximum number of times a lot can be inspected:
  - 1 …… 40%
  - 2 …… 0%
  - 3 …… 60%

Reinspection of Culled Units

	2008	2003	1996
• Firms which return units found acceptable to lot:			
- after manual reinspection	25%	22%	45%
- after automated reinspection	55%	38%	58%
• Same vs. tightened acceptance criteria for reinspection by:			
- manual inspection	80% vs. 20%	100% vs. 0%	82% vs. 18%
- automated inspection	88% vs. 12%	83% vs. 17%	50% vs. 50%

Regulatory Observations

- Firms that have been challenged on their inspection program in the last 2 years …. 42%

- Questions from regulatory agencies during audit:
  - Basis for Defect Limits
  - Validation methods for automated equipment
  - System Suitability Test before each batch
  - Composition of test sets
  - Trending of inspection results
  - Inspector training and qualification

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.

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