PDA Survey

2014 Visual Inspection

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2014 Visual Inspection

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2014 PDA Visual Inspection Survey — PDA Task Force

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Introduction and Overview

Visual inspection continues to be a critical step in the manufacture and release of high quality injectable medicines. There is limited specific guidance on inspection methods or acceptance criteria which has led to a wide range of industry practices. This diversity is also to be expected given the variety of products and packages currently being manufactured and thus inspected. In recent years we have also seen increased interest and activity by the regulatory authorities in this part of the process, providing additional incentive for consistent practices. In August of 2014, the fourth survey in a series of surveys was launched by PDA to better understand and document current industry practices in this important area. Past PDA Visual Inspection surveys in 1996, 2003 and 2008 have provided practical guidance and insight to those working in this field. The purpose of this survey was to document current industry practice for visual inspection of injectable products.

The survey was open to all PDA members and as well as non-members. For some questions, respondents were allowed to check multiple options, therefore the sum of the response percentage may exceed 100% in some instances and the total response count may exceed the number of respondents to the survey. All response percentages for a given question are based on the total number of those who answered that question. The most frequent response to a given question is highlighted in **RED.**

The results presented for the 2014 PDA Visual Inspection survey are based on 186 responses received between August 15 and November 1, 2014. Participants were asked to limit their response to one per manufacturing site, thus a single firm may have more than one response if they have multiple sites. PDA conducts its benchmarking surveys in a manner designed to protect the confidentiality of the gathered information and data. The identity of survey respondents was blinded and not revealed to the author or other PDA members, or in any publication or presentation of the final results developed with the survey. The same population was sampled for each survey year, but the specific companies and manufacturing sites that responded each year are different. This limits to some degree the identification of trends. The survey documents current industry practice; readers should not infer these are best practices.

The numbering in this report does not coincide with the numbering of the questions in the original questionnaire. Preliminary results from this survey were originally presented at the PDA Visual Inspection Forum held October 21-22, 2014 in Berlin, Germany.

Summary of Results

This survey represents practices in the global pharmaceutical industry with a good distribution of geographic plant locations. The predominant responses came from North America (48%), Europe (29%) and Japan and the Asia/Pacific region (19%). Good geographic representation also extended to the markets supplied by these plants with North America (82%), Europe (72%), Japan (58%), Asia/Pacific region (54%) and South America (52%) all above 50%. Small and large manufacturers were also well represented with small (<1M units/year) accounting for 15% of the respondents and large (>100M units/year) accounting for 22%.

The majority (77%) of surveyed products inspected is for human use and includes a significant amount (54%) of biological/biotech products. Most are aqueous solutions (84%) or lyophilized powders (59%).

These products are mostly packaged in tubing (70%) and molded (55%) glass vials, with a significant number in glass syringes (40%) and ampoules (29%).

Manual inspection continues to be the most used method for both particles (46%) and the container/closure system (50%). There is continued interest in using automated inspection with 50% of firms having plans to implement systems in the next two years. Similar results have been observed in previous surveys. Automated systems are validated with production defects (83%) to be equivalent to manual inspection (51%).

Most firms (73%) control manual inspection time and do not use magnification or polarized light. 55% of firms inspect more than a single container at a time. The median inspection time was 6-10 sec per container which agrees with the current European Pharmacopeia (EP) and United States Pharmacopeia (USP) inspection conditions. Illumination intensity is typically 2,000-4,000 lux (60%) which agrees with the current EP and USP inspection conditions with some (28%) using higher values.

Inspection continues to be performed most often (79%) off-line, but a significant amount (58%) is also performed in-line with packaging. Training (94%), a test of visual acuity (91%) and inspection performance (90%) are part of the typical inspector qualification process. Annual requalification (79%) continues to be the typical time interval used for human inspectors.

Test sets with 100-300 units (50%) with a defect rate of 5-10% (35%) are used most often for inspector qualification. Inspectors are given a 5 minute (50%) break every 60 minutes / 1 hour (47%) or every 30 minutes (33%). Most firms use the same inspection conditions for different regions (78%), veterinary products (77%) or clinical supplies (86%).

The typical total reject rate is 1-2% for aqueous solutions and <1% for lyophilized powders. Differences in typical rejects rates are likely due to detection ability rather than underlying quality. Particles, and specifically lint/fibers, continue to be the most common defects observed.

After 100% inspection, lots are routinely (92%) audited most often (71%) by quality assurance (QA) per equivalent standards ANSI/ASQ Z1.4, ISO 2859 or JIS Z9015. The median values for acceptable quality limits (AQL's) used with these plans are 0.065% for Critical, 0.65% for Major and 2.5% for Minor. The high number of responses of 0 for the AQL for Critical defects suggests misunderstanding of AQL values and acceptance sampling plans. These responses are likely the accept number for these sampling plans and not the AQL value. There was a shift in the median AQL value used for Critical defects from 0.10% to 0.065% and for Minor defects from 4.0% to 2.5% between 2008 and 2014.

Conclusions

Inspection continues to be performed with a variety of methods. The rapid increase in the use of automated inspection for container/closure systems in previous years was likely driven by technological development. In the current survey year, the choice to use manual, semi-automated or automated inspection technology for particle and/or container/closure inspection is likely a function of the volume of product to be inspected rather than significant differences in inspection performance. Specifically, larger volumes support the significant capital cost and validation expense of automated systems. Smaller volumes and more diverse product mix likely leads to manual inspection with semi-automated inspection filling the space between.

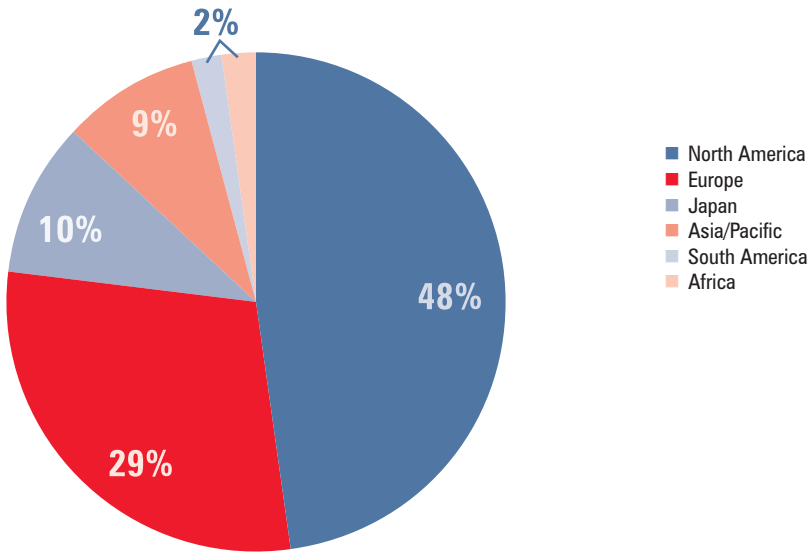
There has been a shift to a Critical classification for particles likely due to regulatory pressure but this is not consistent with the new USP General Chapter <790> *Visible Particulates in Injections* (official August 1, 2014). More firms (56%) classify glass particles as Critical versus Major (37%). Many firms have established alert/action limits based on 100% inspection results (89%) and investigate (88%) and/or reinspect (69%) when these limits are exceeded.

The publication of USP <790> appears to be moving firms to align with the manual inspection conditions specified therein and also found in the EP or Pharm Eur 2.9.20 *Particulate Contamination: Visible Particles*.

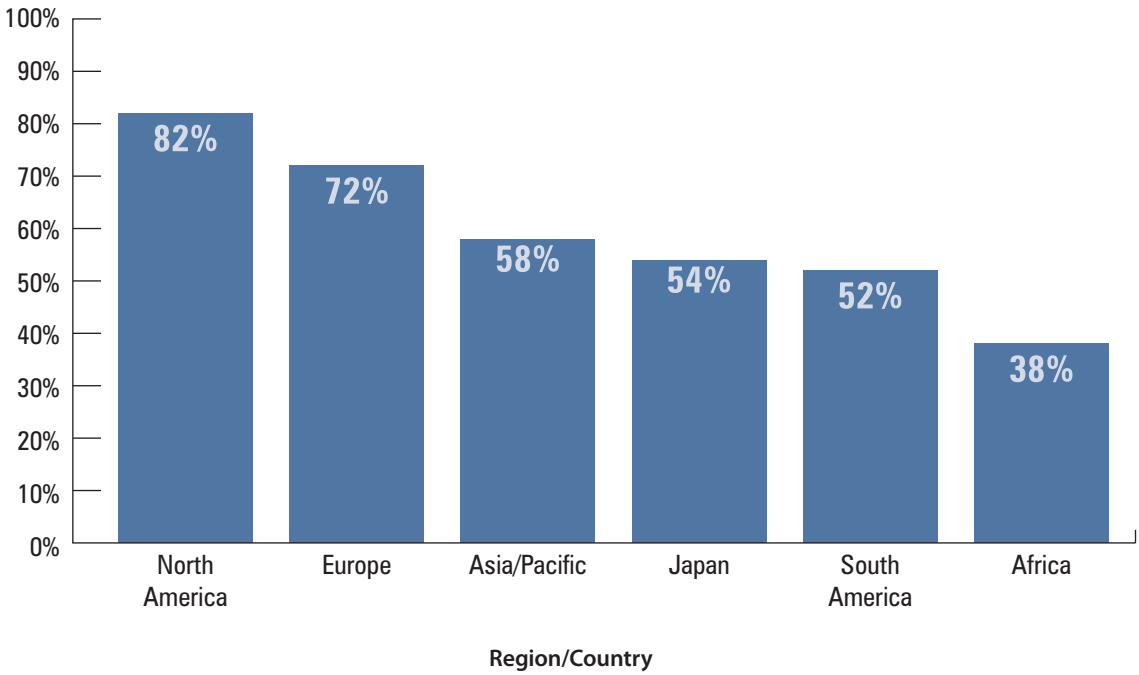
Finally, 44% of firms have been challenged by a regulatory inspector on their inspection method or acceptance criteria in the last two years. 38% of firms expect changes in customer expectations in the next five years. Specifically, a tightening of visible particle limits. 79% of firms expect changes in regulatory expectations in the next five years as well; again with a tightening of visible particle limits.

1. General Information (Questions 1–10)

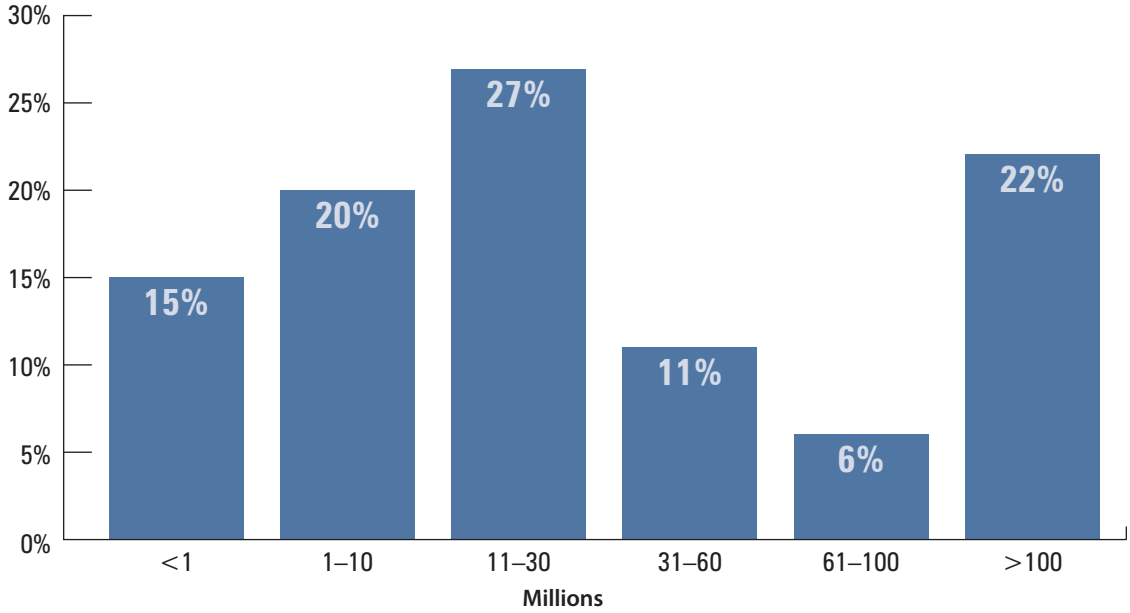
1. In what geographic region is this facility located?



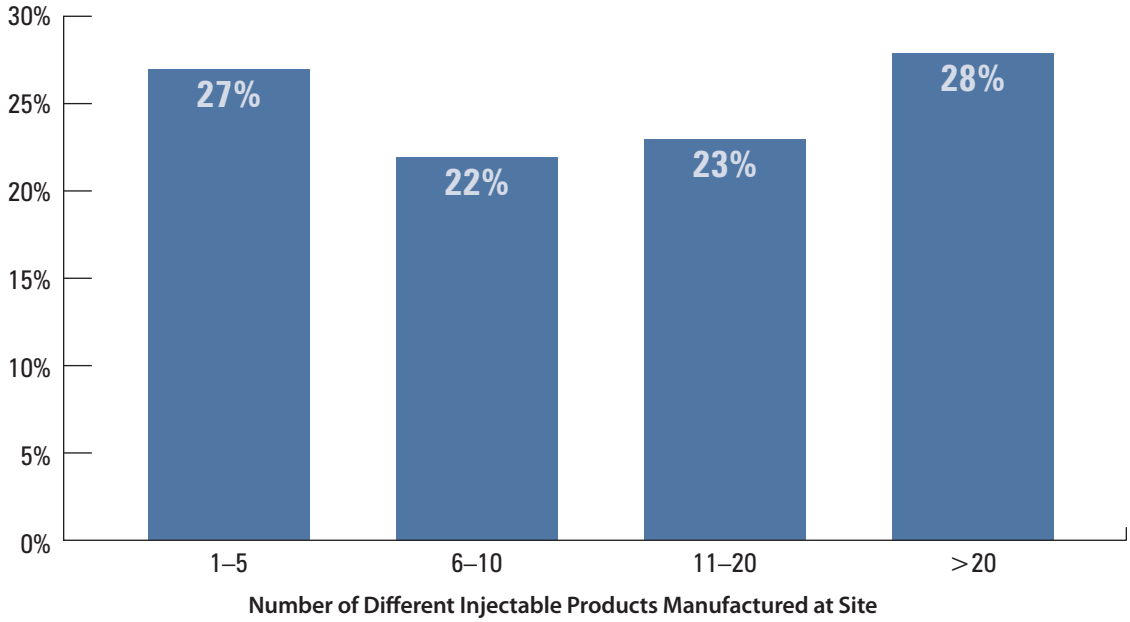
2. To what geographic regions are products manufactured at this facility distributed?



3. What is the approximate total number of injectable units produced at this facility per year?



4. How many different injectable products are produced at this facility?



5. What are the product types produced at this facility?

	2014	2008	2003	1996
Human Health	**77%**	67%	85%	80%
Biological/Biotech	54%	76%	37%	40%
Device/Combination	22%	ND	ND	ND
Diagnostic	15%	5%	4%	10%
Animal Health	14%	48%	7%	10%

ND = No Data, question not asked in survey from this year

6. What are the product formulations produced at this facility?

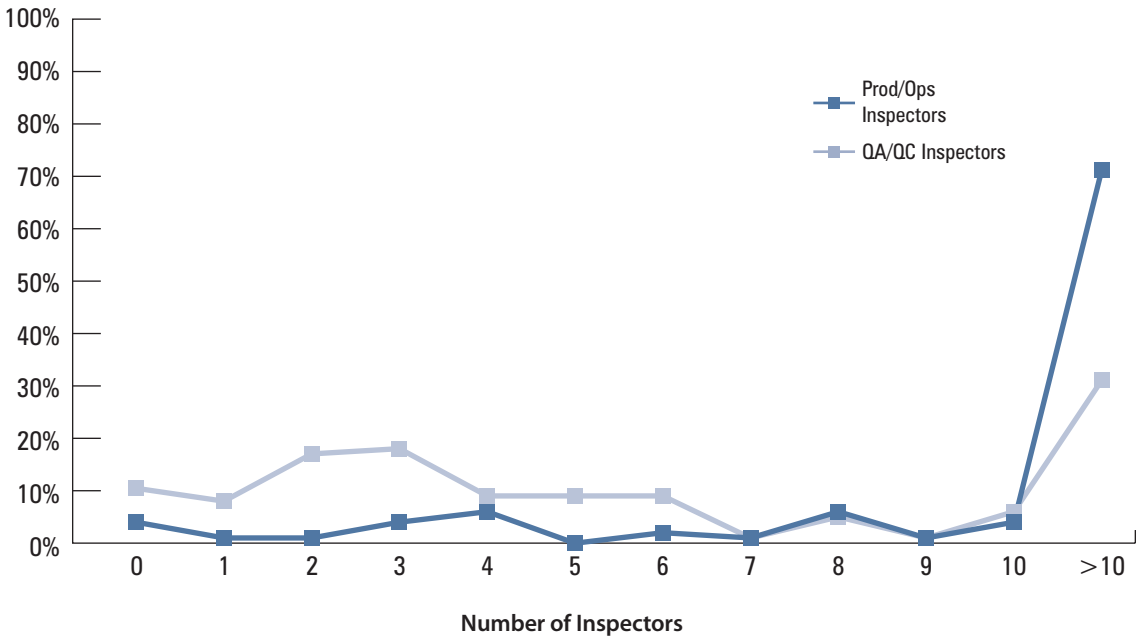
	2014	2008	2003	1996
Aqueous Solutions	**84%**	54%	40%	60%
Lyophilized	59%	25%	30%	27%
Suspension	34%	6%	22%	9%
Powder	17%	0%	1%	2%
Oils and Emulsions	10%	9%	3%	1%

7. What are the product package types produced at this facility?

	2014	2008	2003	1996
Tubing Glass Vial	**70%**	42%	48%	55%
Molded Glass Vial	55%	15%	19%	35%
Glass Syringe	40%	11%	0%	4%
Glass Ampoule	29%	15%	7%	1%
Cartridges	20%	ND	ND	ND
Plastic Syringe	15%	1%	0%	1%
Plastic Vial	14%	2%	0%	0%
Flexible Bags	6%	ND	ND	ND
Blow-Fill-Seal	5%	ND	ND	ND

ND = No Data, question not asked in survey from this year

8. How many full-time inspection employees do you have at this facility?



9. Where do you perform 100% inspection?

	2014	2008	2003	1996
Off-Line	**79%**	81%	59%	37%
In-line with Filling	43%	16%	22%	31%
In-line with Packaging	58%	3%	17%	42%

10. What technique is used for inspection for particles or inspection of the container/closure?

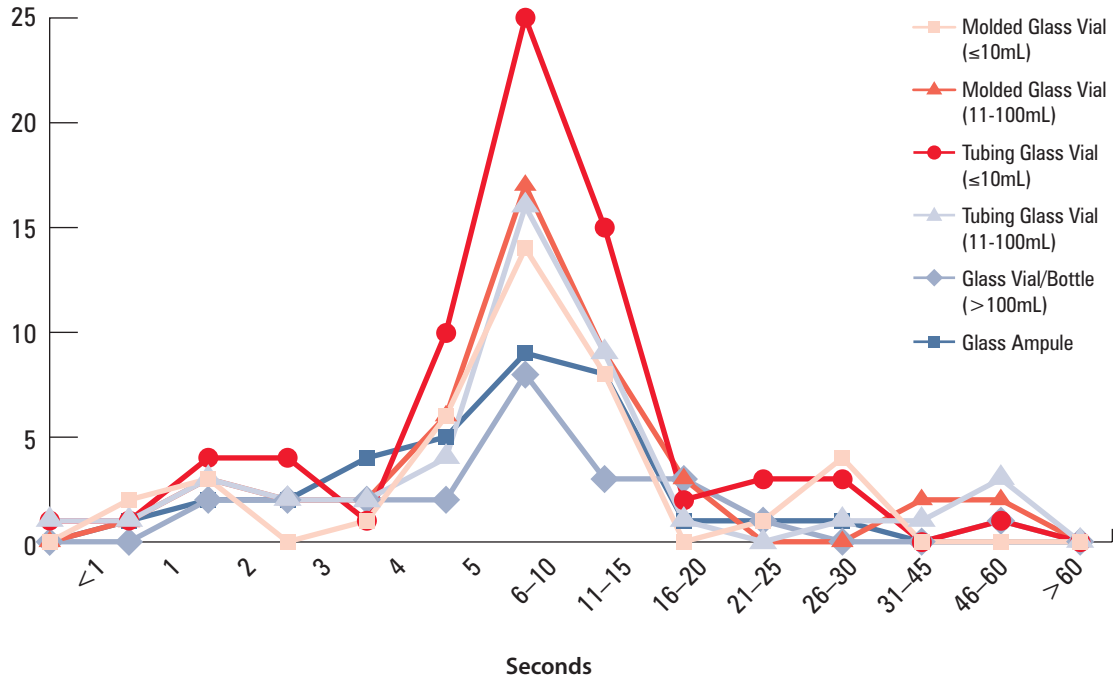
	2014	2008	2003	1996
Particles				
Manual	**49%**	33%	46%	33%
Semi-Automated	17%	24%	19%	20%
Automated	33%	43%	35%	42%
Container/Closure				
Manual	**54%**	36%	63%	48%
Semi-Automated	18%	26%	15%	42%
Automated	28%	39%	20%	5%

2. Manual Inspection (Questions 11–21)

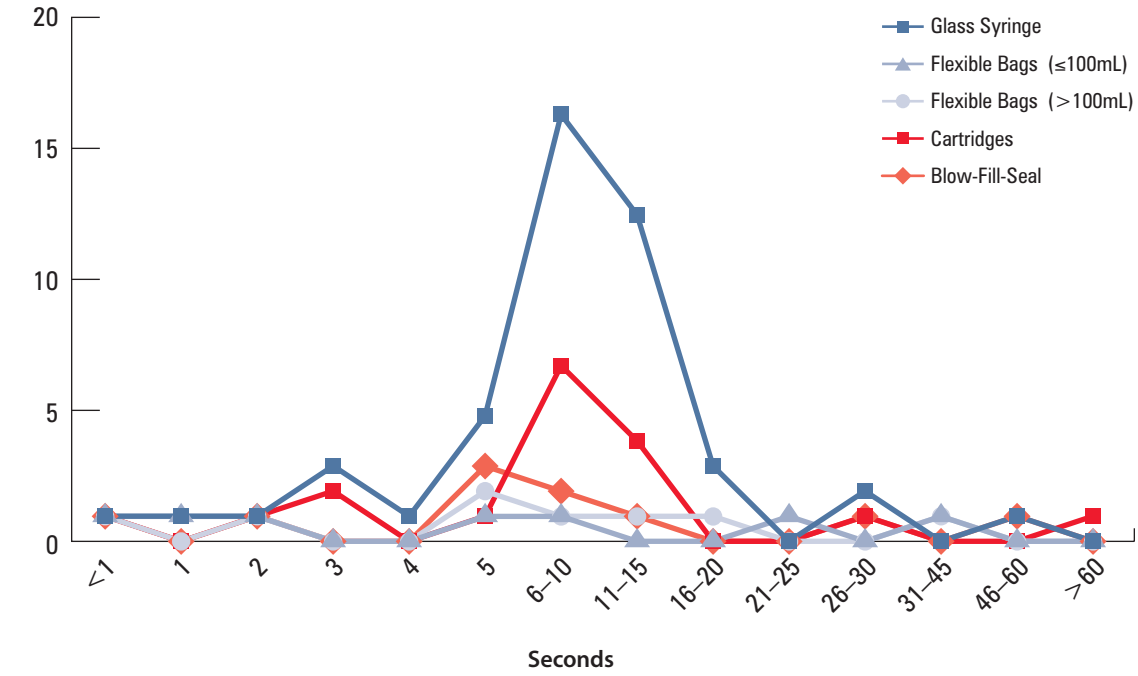
11. Summary of responses regarding manual inspection conditions.

- 73% control inspection time or the pace of inspection.
  - — **46% with Timer**
  - — 29% by SOP
  - — 24% with Conveyor
- 26% use a magnifier.
  - — **44% 2X,** 25% 3X, 8% 4X, 8% 5X, 14% >5X
- 6% use a polarizer.
- Light Source used:
  - — **73% Fluorescent,** 18% Incandescent, 19% LED

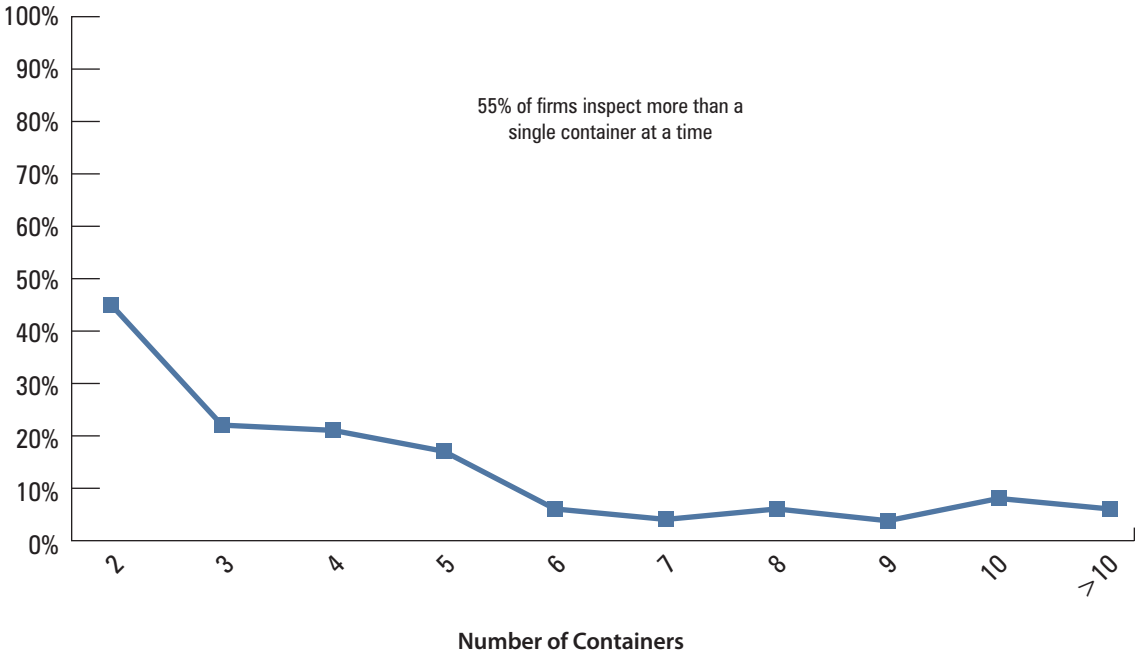
12. What is the average inspection time for this container type?



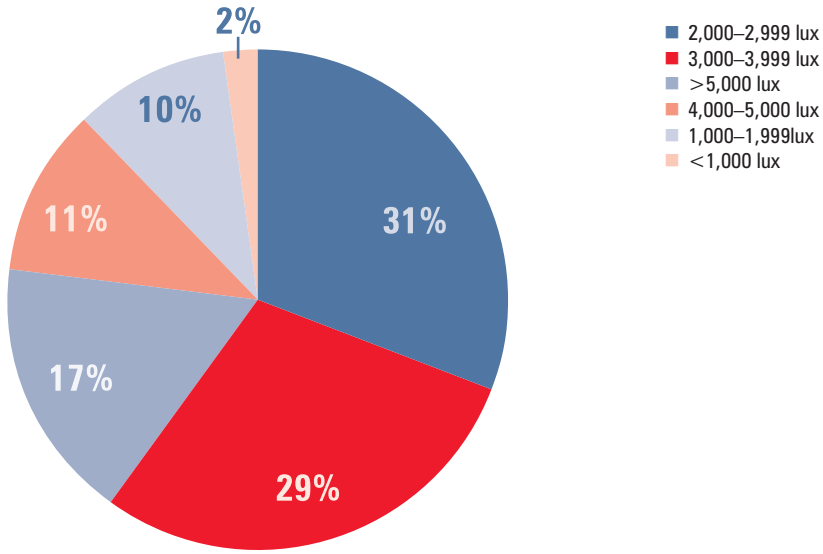
13. What is the average inspection time for this container type?



14. If more than one container is inspected at a time, how many are inspected?



15. What is the average illumination intensity at the container during manual inspection?



16. Summary of responses regarding inspector selection criteria.

	2014	2008	2003	1996
Training	94%	89%	96%	80%
Visual Acuity	91%	79%	85%	80%
Test of Inspection Ability	90%	100%	89%	80%
Color Vision	74%	68%	ND	ND
Education	41%	26%	30%	25%
Experience	32%	37%	15%	30%

(ND = No Data, question not asked in survey from this year)

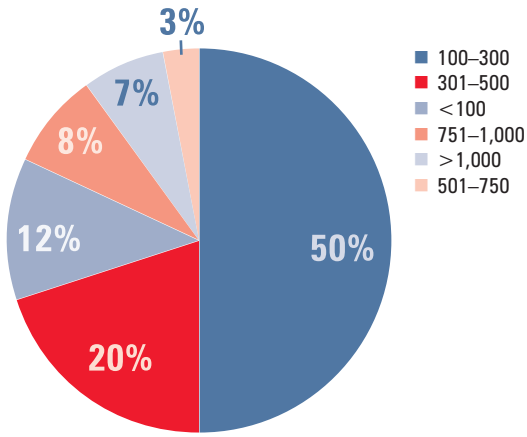
17. How are inspectors qualified?

- 98% describe defects and inspection conditions in a written procedure.
- Qualification conditions?
  - — **Simulated: 75%**
  - — Actual Manufacturing: 45%
- Standards?
  - — **Production Defects: 91%**
  - — Non-Spherical Standards: 40%
  - — Spherical Standards: 33%

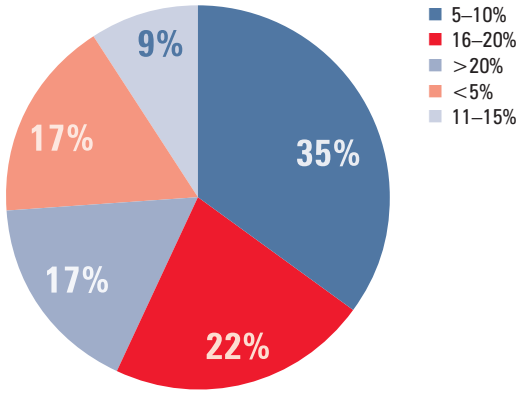
18. How often are inspectors requalified?

	2014	2008	2003	1996
Never	5%	21%	8%	35%
Monthly	1%	5%	0%	8%
Quarterly	4%	0%	0%	8%
Semi-Annually	10%	11%	8%	16%
Annually	**79%**	63%	75%	69%

19. The composition of test kits used to qualify inspectors.



Total Units in Test Kit



Defect Rate in Test Kit

20. How frequently do inspectors take a break or rotate to a non-inspection task?

	2014	2008	2003	1996
Never	2%	ND	ND	ND
<30 min	2%	16%	12%	5%
30 min	33%	32%	15%	21%
45 min	3%	ND	ND	ND
60 min	**47%**	32%	62%	32%
2 hrs	9%	11%	12%	37%
4 hrs	4%	0%	0%	5%

(ND = No Data, question not asked in survey from this year)

21. How long are these breaks?

	2014	2008	2003	1996
5 min	**50%**	ND	ND	ND
10 min	17%	ND	ND	ND
15 min	20%	ND	ND	ND
>15 min	13%	ND	ND	ND

(ND = No Data, question not asked in survey from this year)

3. Automated Inspection (Questions 21–23)

21. Does your firm have plans to replace manual inspection with automated inspection?

	2014	2008	2003	1996
Shift to Automated Inspection	50%	67%	50%	68%
Justification:				
Quality	85%	75%	92%	92%
Productivity	87%	92%	92%	100%

22. Summary of responses regarding automated inspection validation.

- 100% validate automated inspection equipment.
- Validation Criteria:
  - **Equivalent to manual: 51%**
  - Better than manual: 28%
  - Other, Not compared to manual: 21%
- Samples used for routine challenge:
  - **Production Defects: 79%**
  - Spherical Standards: 40%
  - Non-Spherical Standards: 44%
- In case of equipment failure:
  - **Use manual inspection: 47%**
  - Delay production until repair: 43%
  - Either manual or delay: 10%

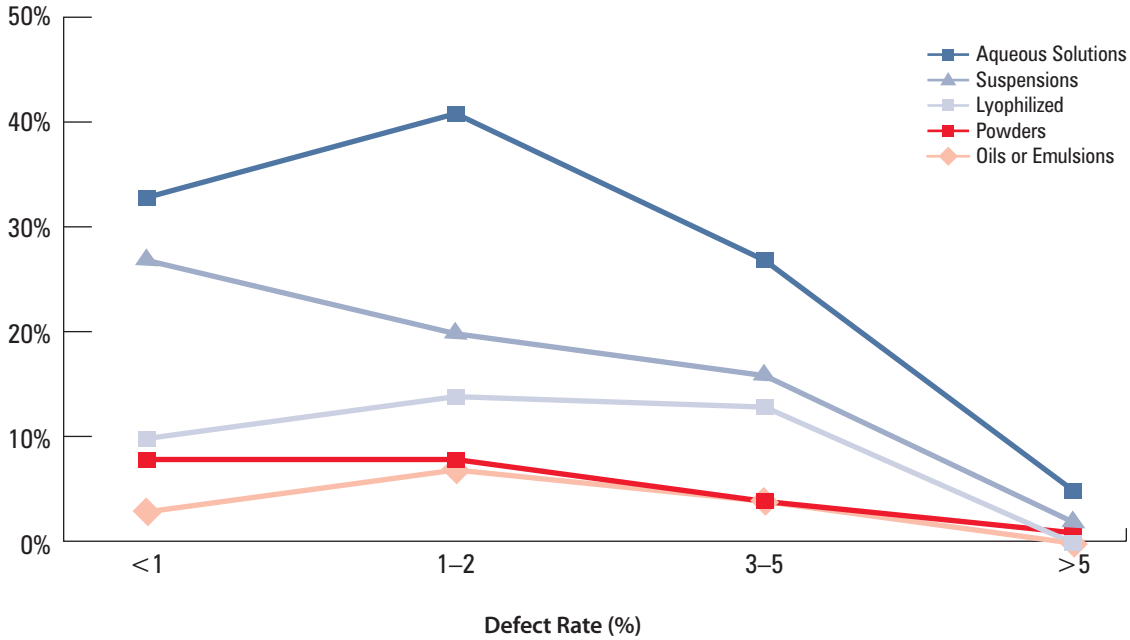
23. How frequently do you challenge or retest automated inspection equipment?

	2014	2008	2003	1996
Never	1%	0%	0%	15%
Each Shift	1%	8%	13%	8%
Start of Lot	**46%**	42%	75%	38%
Start and End of Lot	8%	ND	ND	ND
Daily	15%	25%	19%	23%
Weekly	2%	0%	0%	8%
Monthly	2%	ND	ND	ND
Quarterly	1%	ND	ND	ND
Annually	19%	ND	ND	ND

(ND = No Data, question not asked in survey from this year)

4. Inspection Results (Questions 24–26)

24. What is the average reject rate for this product formulation?



25. What are the most common defects found during visual inspection? (Rank order with 1 most frequent)

	2014	2008	2003	1996
Particles	**1**	1	1	1
Scratches	2	2	4	4
Crimp Seal	3	3	3	2
Cracks/Chips	4	5	2	3
Cap	5	6	7	9
High/Low Fill	6	4	5	5
Stopper/Plug	7	8	9	8
Cake	8	8	6	6
Leaks	9	7	8	7

26. What are the most common types of particles found during visual inspection? (Rank order with 1 most frequent)

	2014	2008	2003	1996
Lint/Fiber	**1**	1	1	1
Glass	2	2	2	2
Product Related	3	3	4	3
Rubber/Elastomer	4	4	5	5
Metal	5	5	3	4

5. Acceptance Sampling and Inspection Strategies (Questions 27–40)

27. Summary of responses on particle risk classification.

- In 2014 glass particles are classified as:
  - **Critical: 56%**
  - Major: 37%
  - Minor: 2%
- Other: 6% (size dependent)
- In 2008:
  - 45% of firms classified particles as Critical and 45% as Major.
  - 63% of firms use the same AQL for all particles (including glass).

28. Do you audit or perform a sampling inspection (AQL inspection) after 100% inspection?

	2014	2008	2003	1996
Audit every lot	**92%**	85%	72%	90%
Audit selected lots	0%	0%	8%	5%
No audit	8%	15%	20%	5%

Who performs the audit?

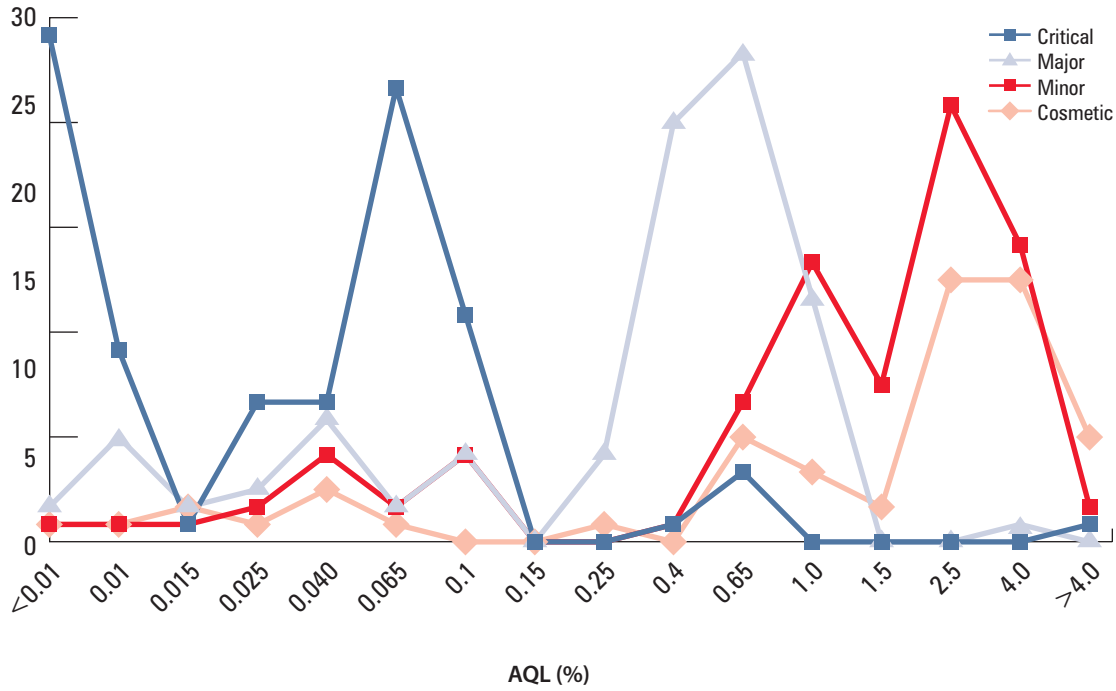
	2014	2008	2003	1996
Audit by QA	**71%**	74%	85%	89%
Audit by Production	29%	26%	15%	11%

29. What sampling plan does your facility use?

	2014	2008	2003	1996
ANSI/ASQ Z1.4	**65%**	53%	70%	90%
ISO 2859	23%	11%	10%	0%
JIS Z9015	7%	15%	5%	0%
Mil Std 1916	3%	11%	0%	0%
Dodge Romig	1%	0%	5%	0%
Other	2%	10%	0%	10%

30. What AQL value (in %) do you use for acceptance sampling of these defect categories?

	2014	2008	2003	1996
Critical	0.065	0.10	0.10	0.035
Major	0.65	0.65	0.65	0.83
Minor	2.5	4.0	2.5	2.9



31. Do you use medical/patient risk to help determine the acceptance criteria or AQL values used in the inspection program?

- In 2014, 50% of firms use medical/patient risk to help determine the acceptance criteria or AQL values used in the inspection program.

32. Do you have Alert/Action limits for 100% inspection results and what is done when the limit is exceeded?

	2014	2008	2003	1996
Firms with Limits	89%	85%	76%	85%
Same for all Products	40%	44%	32%	82%
Practice if Limit exceeded:				
Investigate	**88%**	70%	95%	80%
Reinspect	69%	45%	50%	82%
Reject	29%	5%	36%	45%
Change Sampling Plan	26%	ND	ND	ND

ND = No Data, question not asked in survey from this year

33. What are typical values used for Alert/Action limits for 100% inspection results?

	2014	2008	2003	1996
<1%	19%	32%	29%	14%
1 to 2%	**36%**	21%	41%	18%
3 to 5%	29%	37%	29%	27%
5 to 10%	14%	16%	35%	18%
>10%	3%	2%	11%	9%

34. Is there a limit to the number of times a lot may be reinspected?

	2014	2008	2003	1996
Have a Limit	99%	63%	ND	ND
Typical Limit used:				
1	**58%**	40%	ND	ND
2	35%	0%	ND	ND
3	6%	60%	ND	ND
>3	1%	ND	ND	ND

ND = No Data, question not asked in survey from this year

35. If you have an Alert/Action limit, which defects are included in the calculation of this limit?

	2014	2008	2003	1996
All	**74%**	76%	77%	60%
Critical only	7%	6%	9%	13%
Critical and Major	14%	18%	5%	27%
Other	7%	ND	ND	ND

ND = No Data, question not asked in survey from this year

36. Do you reinspect and return containers that are found to be acceptable after being culled out or rejected during initial inspection?

	2014	2008	2003	1996
After Manual Inspection	13%	25%	22%	45%
After Automated Inspection	48%	55%	38%	58%

37. What acceptance criteria do you use if you reinspect and return containers after being culled out or rejected during initial inspection?

- Acceptance Criteria
  - Manual: **53% Same**, 47% Tightened
  - Auto: **78% Same**, 22% Tightened

38. Does your firm use the same inspection methods and acceptance criteria for…?

	2014	2008	2003	1996
Different Geographic Regions	78%	67%	87%	90%
Veterinary Products	77%	100%	83%	100%
Clinical Supplies	86%	ND	ND	ND

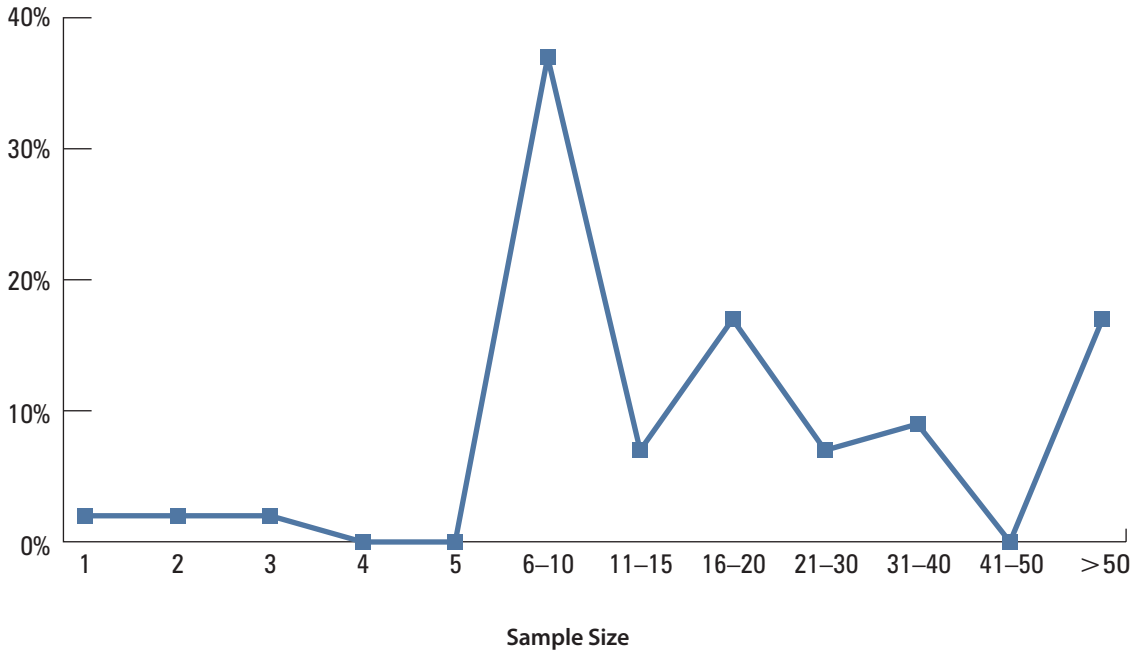
ND = No Data, question not asked in survey from this year

39. Summary of responses regarding special inspections.

	2014	2008	2003	1996
Inspect empty containers	15%	16%	28%	30%
For firms with applicable products:				
Reconstitute lyo/powder	**86%**	16%	28%	30%
Insp. after filling/before lyo	14%	ND	ND	ND
Transfer to clear container	14%	ND	ND	ND

ND = No Data, question not asked in survey from this year

40. If you perform destructive testing on difficult to inspect products and/or containers, what is the typical sample size?



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