A Survey of Visual Inspection Practices for Injectable Drug Products

Final Results for the period August 15 to November 1, 2014

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Survey Format and Participation

- Objective:
  - Document current industry practice for visual inspection of injectable products.
- On-line survey with multiple choice responses
- 77 questions with blinded responses
- Open to PDA members and non-members
- Response requested by site, so may have multiple entries for the same company
- 186 Participants

Please keep in mind …

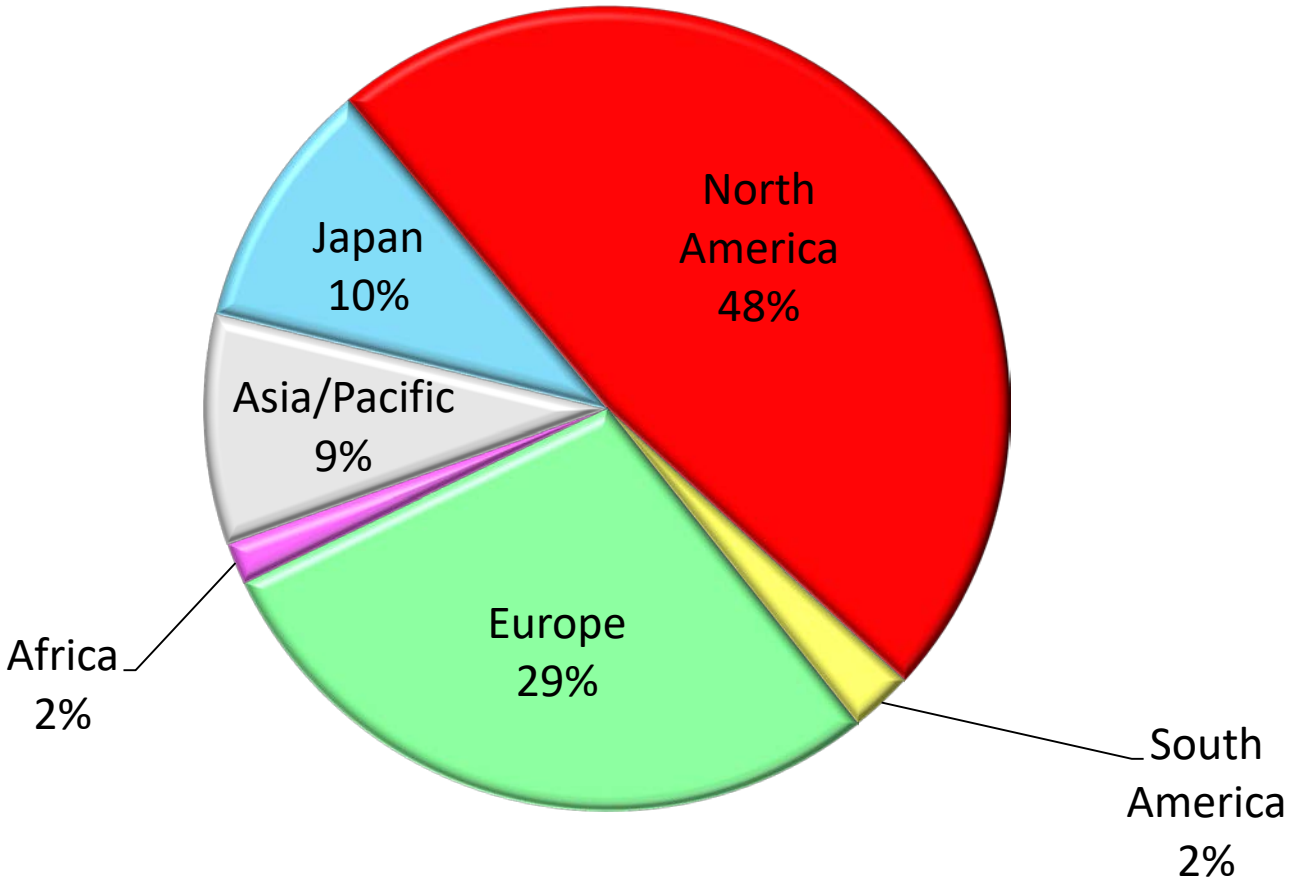
- The same population (PDA Members) was sampled for each survey, but the specific companies and manufacturing sites that responded each year are different. This limits to some degree the identification of trends.
- The survey documents current industry practice, but does not indicate if these are good or bad practices.

Topics

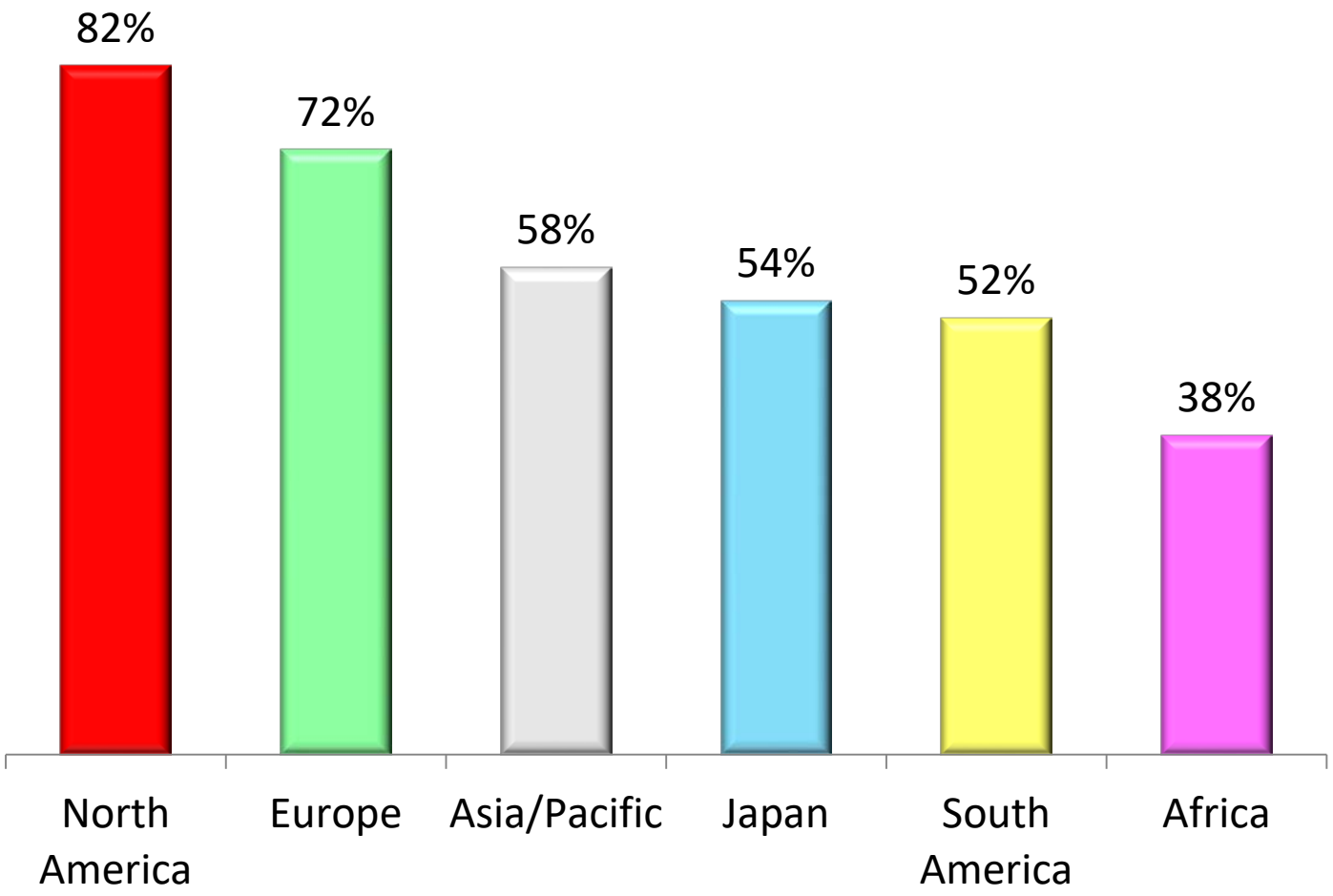
- General Information
- Manual Inspection
- Automated Inspection
- Inspection Results
- Acceptance Sampling and Inspection Strategies
- Future Direction

General Information

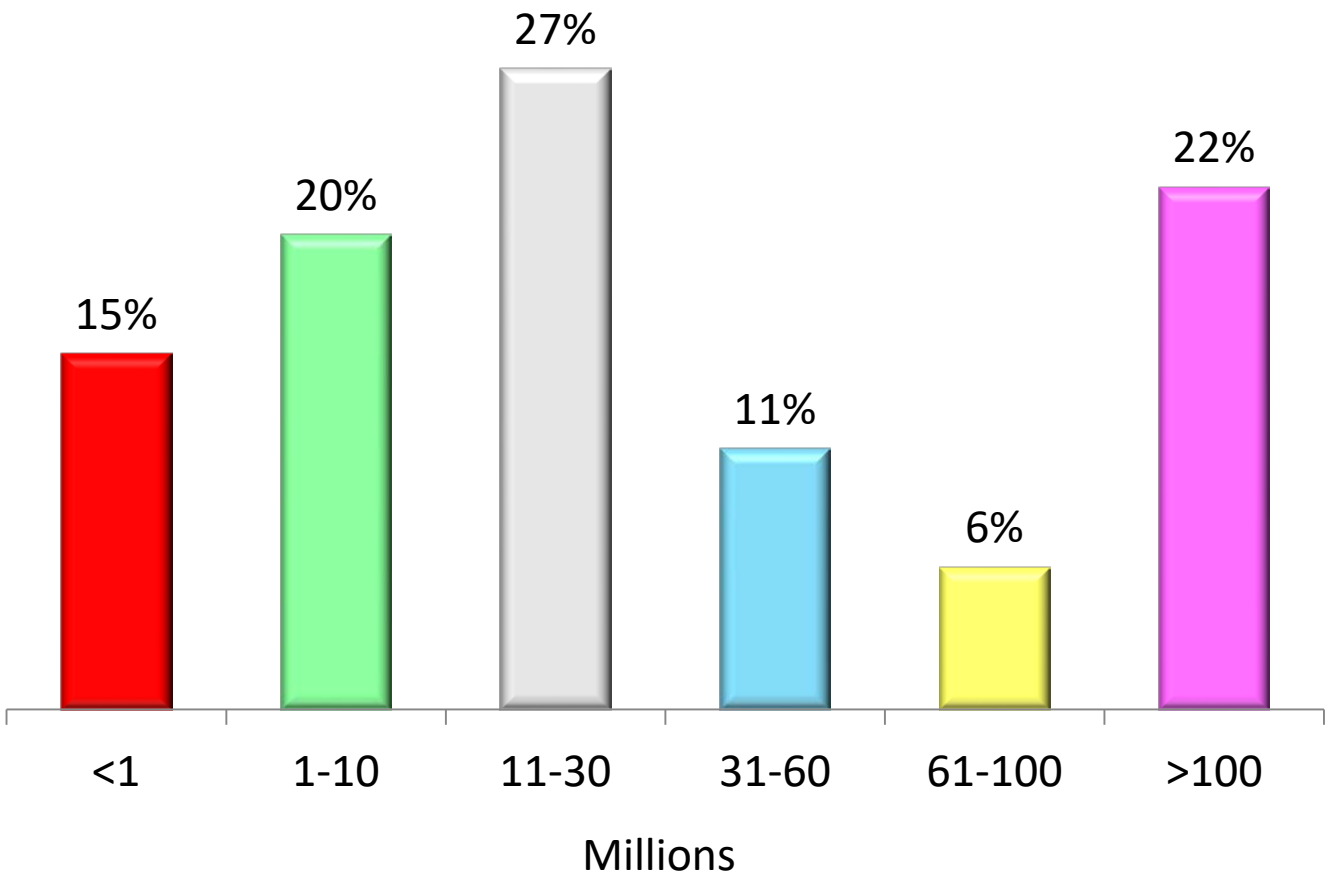
In what geographic region is this facility located?



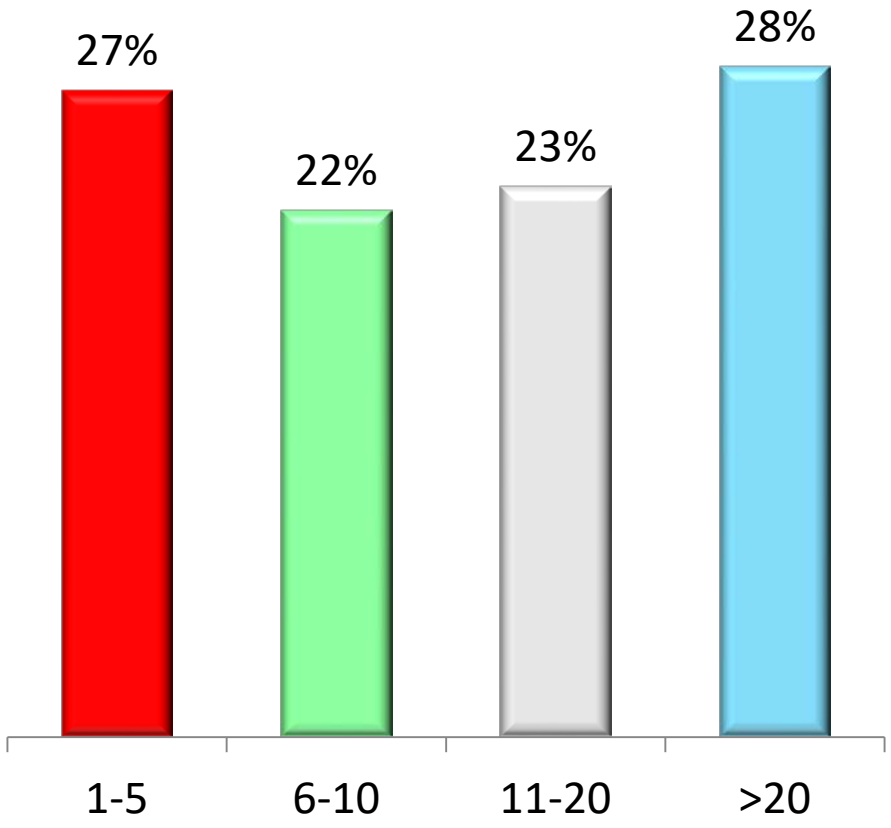
To what geographic regions are products manufactured at this facility distributed?



What is the approximate total number of injectable units produced at this facility?



How many different injectable products are produced at this facility?



Different Injectable Products Manufactured at Site

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

What are the product formulations produced at this facility?

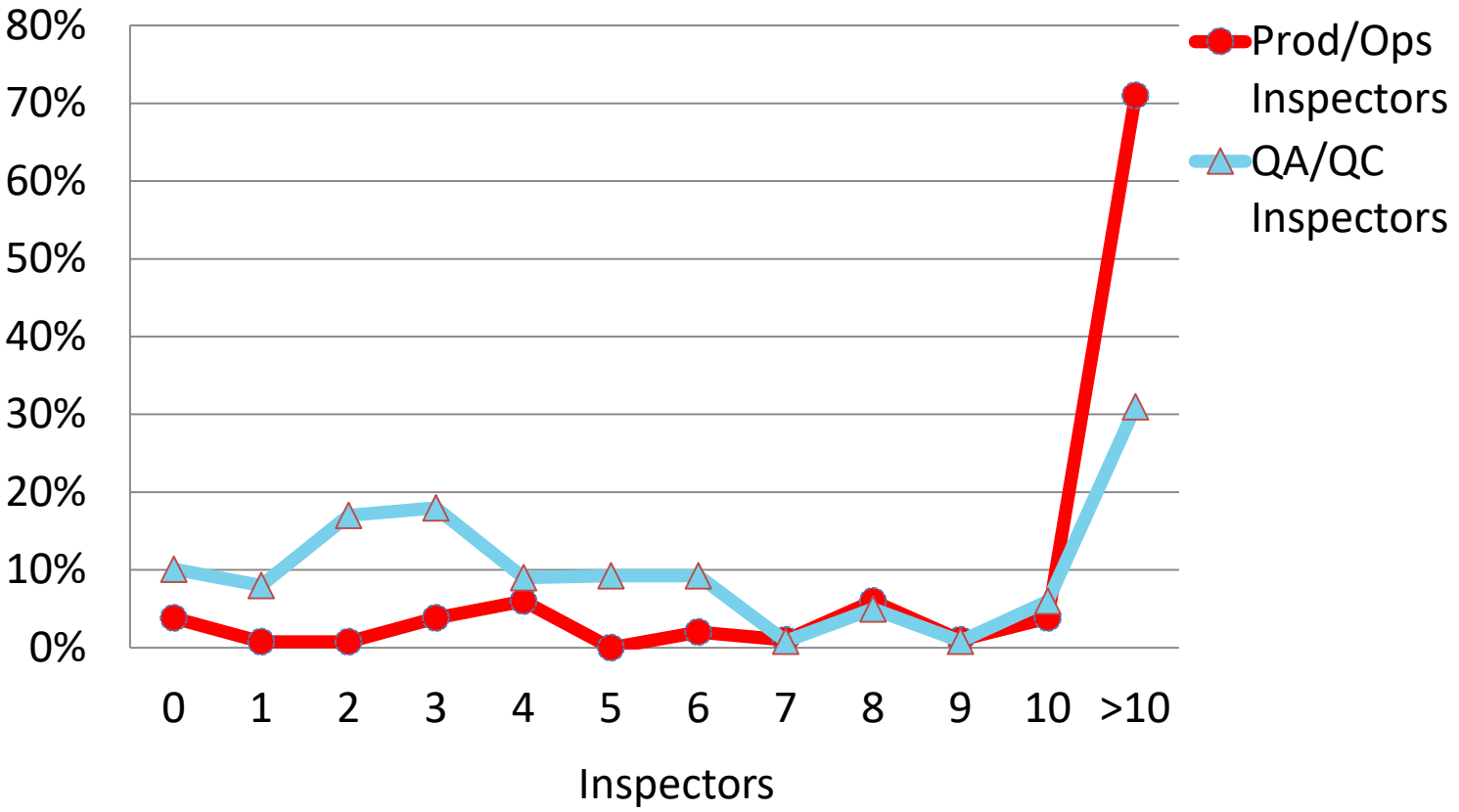
	2014	2008	2003	1996
Aqueous Solutions	**84%**	54%	40%	60%
Lyophilized	**59%**	25%	30%	27%
Suspension	**34%**	6%	22%	9%
Powder	**17%**	0%	1%	2%
Oils and Emulsions	**10%**	9%	3%	1%

What are the product 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

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



What technique is used for inspection for / of …

	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%

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%

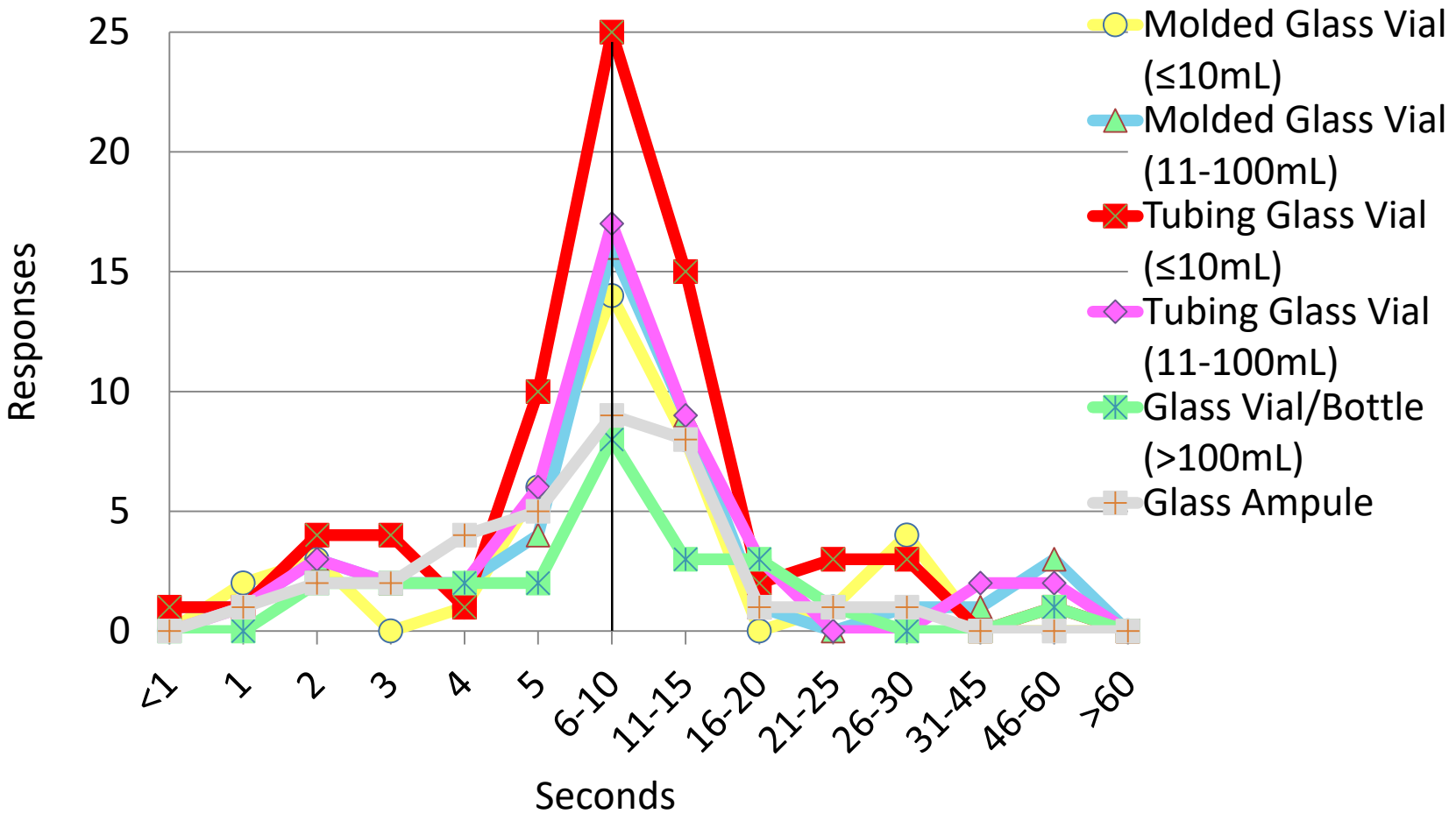
Note: In 2014 more than one response could be chosen for this question.

Manual Inspection

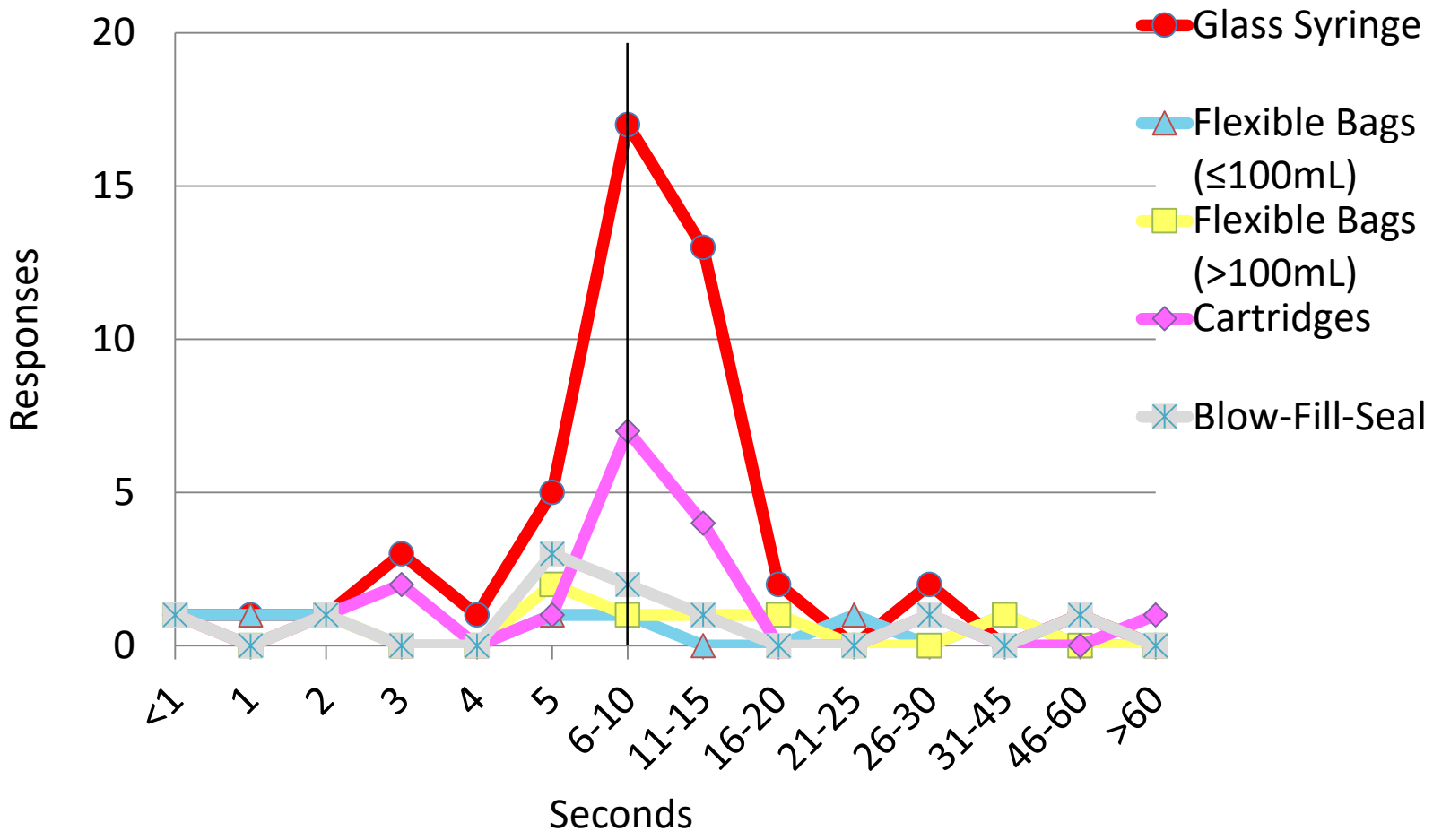
Manual Inspection Conditions

- 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

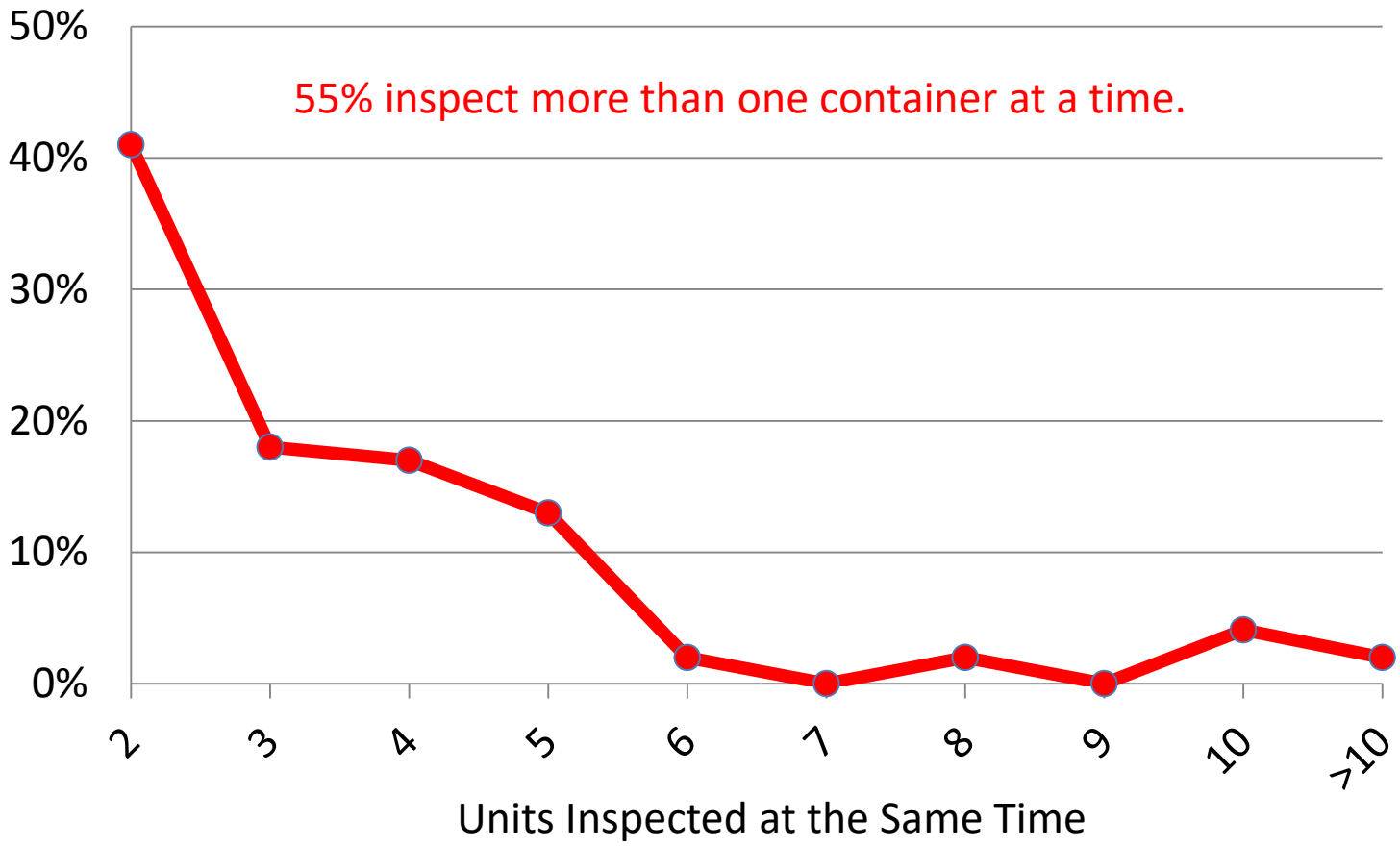
What is the average inspection time for this container type?



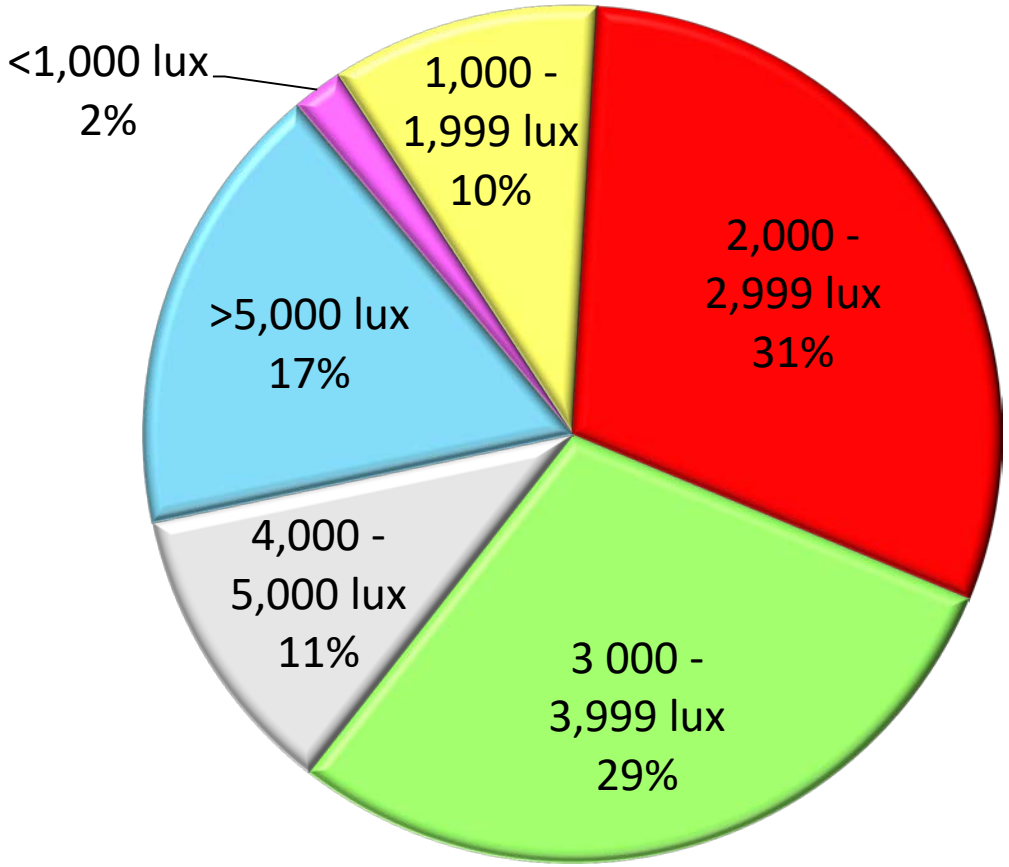
What is the average inspection time for this container type?



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



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



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%

- 78% have the same selection and training criteria for Production and QA inspectors?

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

Inspector Qualification

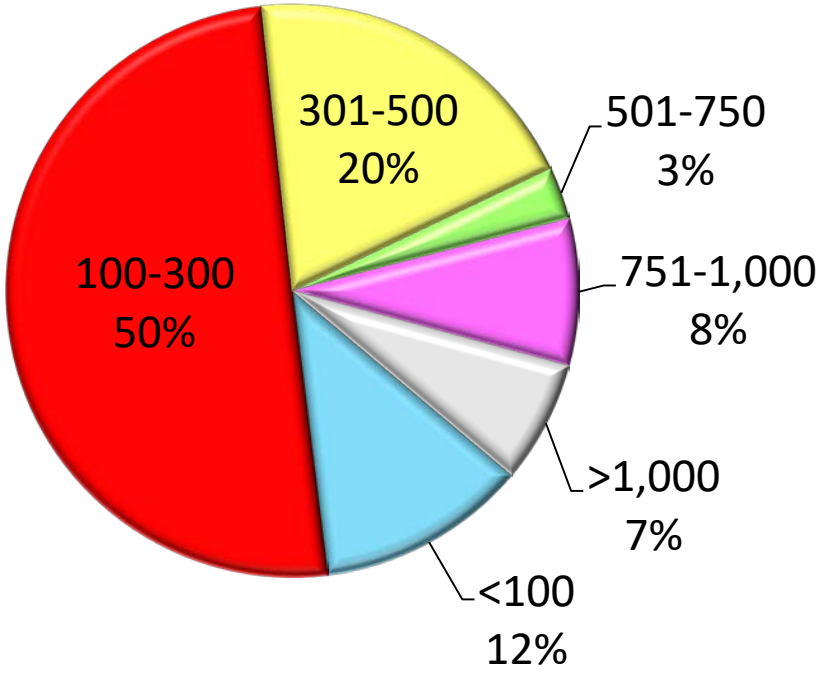
- 98% describe defects and inspection conditions in a written procedure.
- Qualification conditions?
  - Simulated: 75%
  - Actual Manufacturing: 45%
- Standards?
  - Production Defects: 91%
  - Non-Spherical Standards: 40%
  - Spherical Standards: 33%

How often are inspectors requalified?

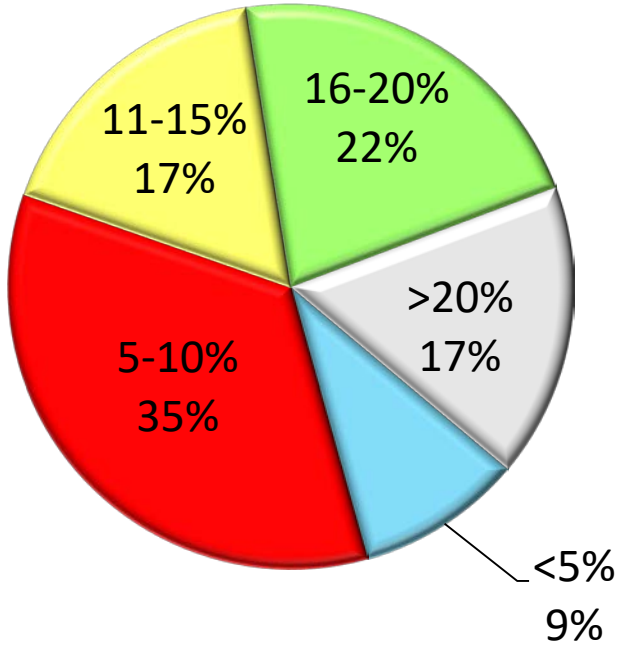
	2014	2008	2003	1996
Never	**5%**	21%	8%	35%
Monthly	**1%**	5%	0%	8%
Quarterly	**4%**	0%	0%	8%
Semi-Annually	**10%**	11%	8%	16%
Annually	**79%**	63%	75%	69%

The composition of test kits used to qualify inspectors.

Total Units in Test Kit



Defect Rate in Test Kit



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

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

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Automated Inspection

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%

Automated Inspection Validation

- 100% validate automated inspection equipment.
- Validation Criteria:
  - Equivalent to manual: 51%
  - Better than manual: 28%
  - Other, Not compared to manual: 21%

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

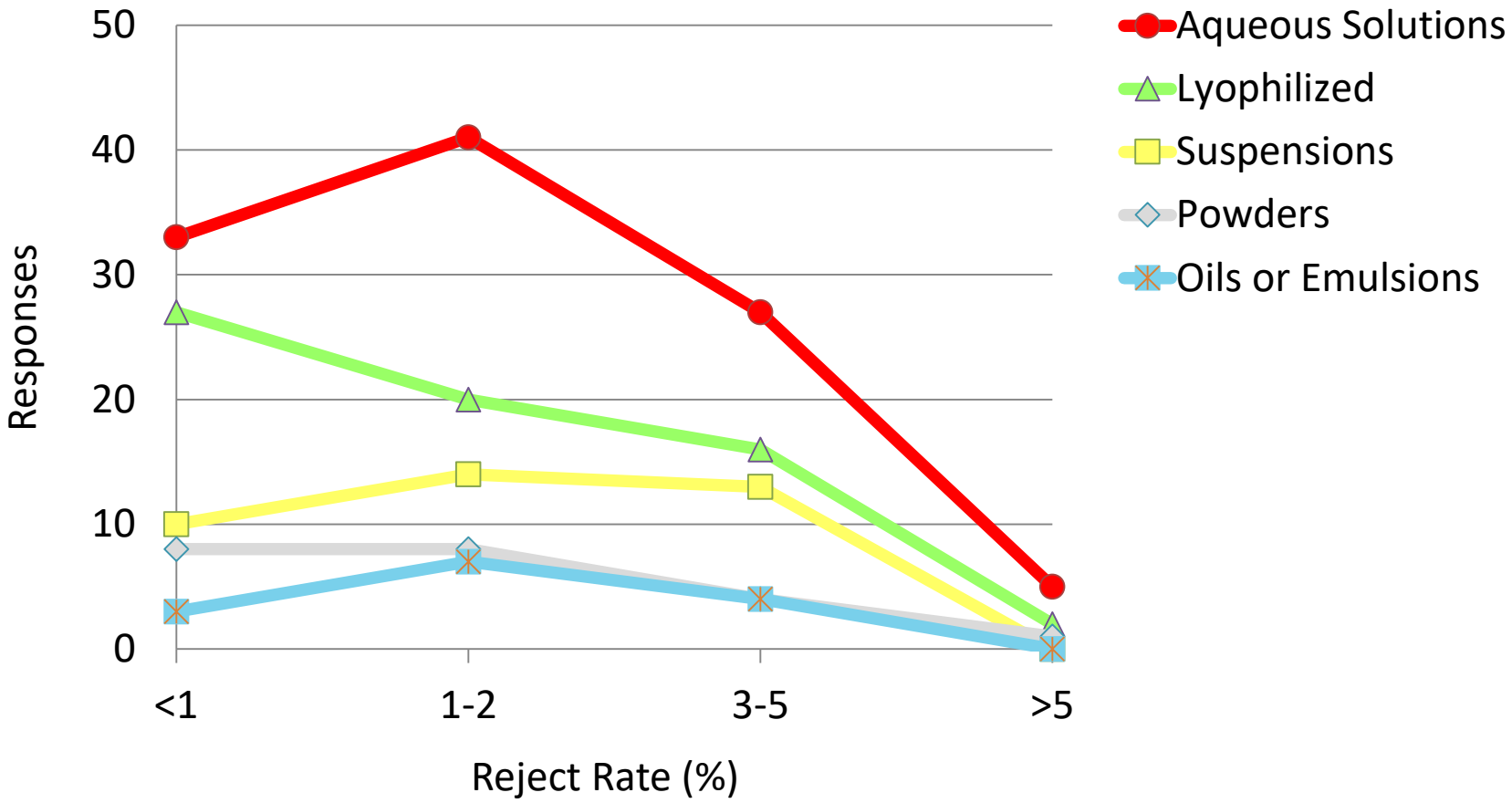
ND = No Data, question not asked in survey from this year

Automated Inspection Practices

- 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%

Inspection Results

What is the average reject rate for this product formulation?



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

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

Acceptance Sampling and Inspection Strategies

What classification do you use for Glass Particles?

- 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).

Acceptance Sampling

	2014	2008	2003	1996
Audit every lot	**92%**	85%	72%	90%
Audit selected lots	**0%**	0%	8%	5%
No audit	**8%**	15%	20%	5%
Audit by QA	71%	74%	85%	89%
Audit by Production	**29%**	26%	15%	11%

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%

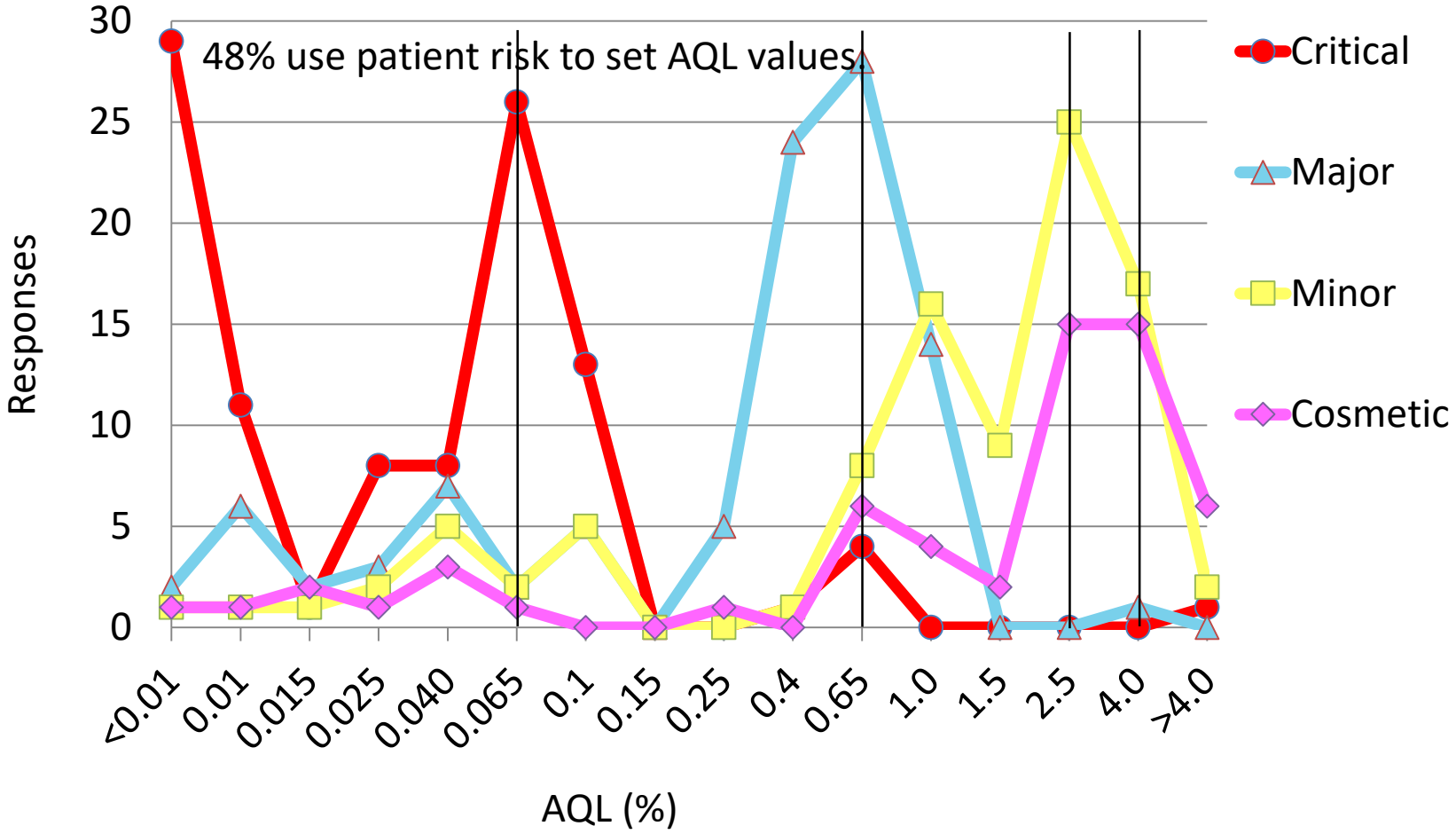
What AQL value (in %) do you use for acceptance sampling of these defect categories?

	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

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

Note: median values shown

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



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

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%

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

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

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%

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

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

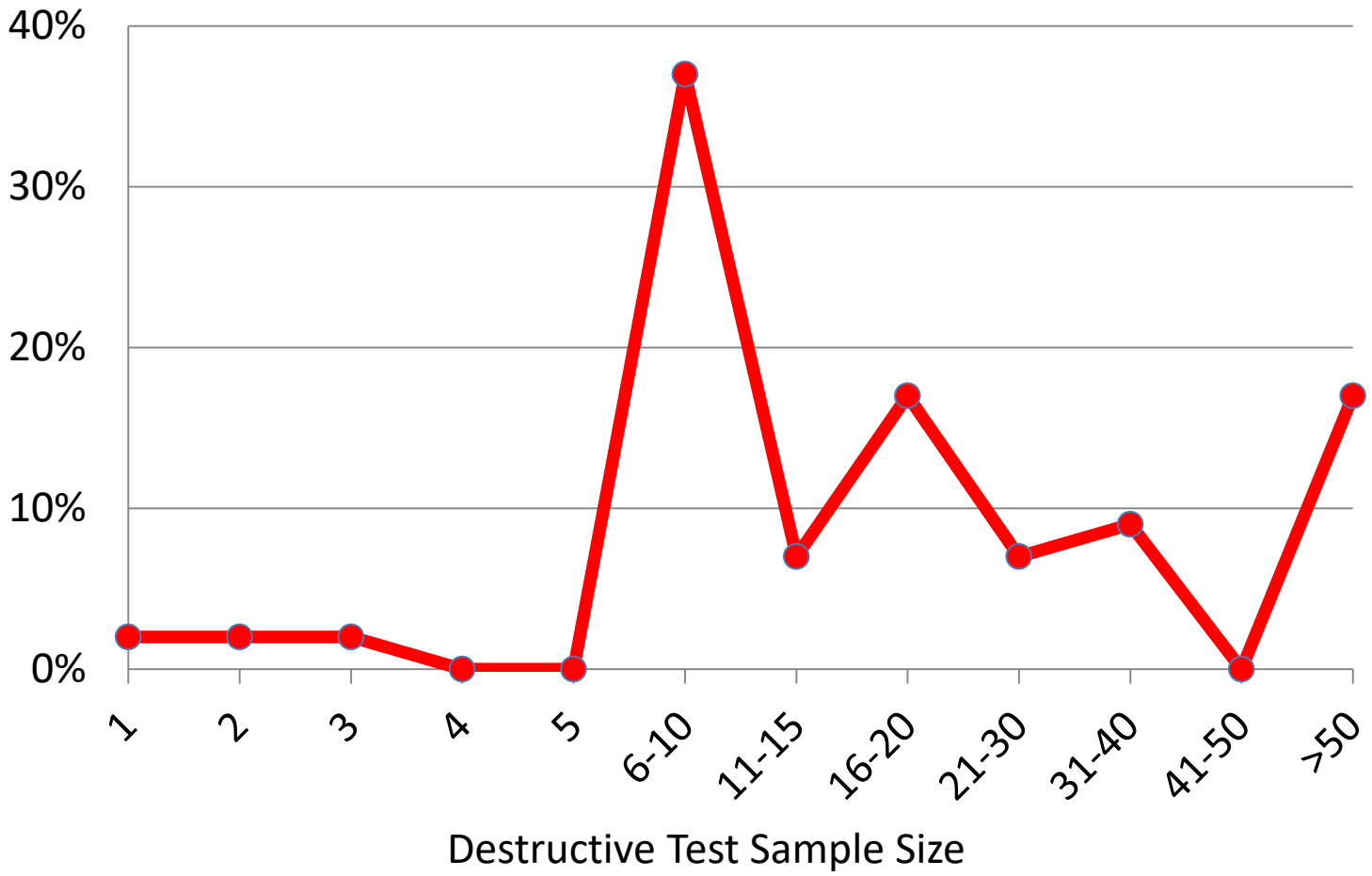
ND = No Data, question not asked in survey from this year

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

If you perform destructive testing on difficult to inspect prod/cont, what is the typical sample size?



Summary and Conclusions

Summary and Conclusions

- Good geographic representation in plant location with NA (48%), EU (29%) and Japan + A/P (19%).
- Good geographic representation of markets supplied with NA (82%), EU (72%), Japan (58%), A/P (54%) and SA (52%).
- Good representation of small (<1M units/year) to large (>100M units/year) manufacturing sites.

Summary and Conclusions

- The majority (77%) of surveyed products inspected are for human use and include a significant amount (54%) of biological/biotech products.
- The majority of surveyed products inspected 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%).

Summary and Conclusions

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

Summary and Conclusions

- Most firms (73%) control manual inspection time and do not use magnification or polarized light.
- The median inspection time was 6-10 sec per container which agrees with the current EP and 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.

Summary and Conclusions

- 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.

Summary and Conclusions

- 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%).

Summary and Conclusions

- 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.

Summary and Conclusions

- After 100% inspection, lots are routinely (92%) audited most often (71%) by QA per equivalent standards ANSI/ASQ Z1.4, ISO 2859 or JIS Z9015.
- The median values for AQL's used with these plans are 0.065% for Critical, 0.65% for Major and 2.5% for Minor.
- 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.

Summary and Conclusions

- More firms (56%) classify glass particles as Critical versus Major (37%)
- 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 <790>.
- Firms have established alert/action limits based on 100% inspection results (89%) and investigate (88%) and/or reinspect (69%) when these limits are exceeded.

Regulatory Experience and Future Expectations

- 44% have been challenged by a regulatory inspector on their inspection method or acceptance criteria in the last two years.
  - Various reasons
- 38% expect changes in customer expectations in the next five years.
  - Tighter particle limits
- 79% expect changes in regulatory expectations in the next five years.
  - Tighter particle limits

Acknowledgments

- Morgan Holland - PDA
- Janie Miller - PDA
- Participants!

Thank you for supporting this project to better understand our industry.