



Hot Topics in Visual Inspection on a Cold January Night

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Agenda

- Why Inspect?
- US FDA Recalls and 483's
- USP <790> and <1790>
- PDA Benchmark Survey
- Conclusions and Acknowledgements



Why inspect?



Why Inspect?

- Patient Risk
 - Physiological Implications
 - Chemical and Microbiological Implications
- Compendial Requirements
- Regulatory Requirements
- Process Knowledge and Continuous Process Improvement



Particulate Matter Concerns

- Patient Risk Factors to Consider:
 - Particle Size
 - Is the size in the range that will pass through the needle?
 - Quantity
 - Many vs. Single
 - Composition
 - Single 100 μm particle in 1 mL dose is equivalent to an impurity level of 4 ppm (v/v)
 - Generally not a tox concern
 - Extrinsic vs. Intrinsic
 - Inert?
 - Biological?



Particulate Matter Concerns (cont.)

- Sterility
 - Extrinsic vs. Intrinsic
 - Aseptic Process vs. Terminal Sterilization
- Duration of Exposure
 - Chronic vs. Single Dose
- Route of Administration
 - IV vs. IM vs. Sub-Q
 - Intrathecal, Intraocular
- Antigenic Potential
 - 1-10 μ m protein particles
- Intended Patient Population
 - Infant vs. Adult
 - Compromised vs. Healthy



Particulate Size Ranges

<100 nm

Nanometer

100 - 1,000 nm

Sub-micron

1 - 100 μm

Sub-visible

>100 μm

Visible

- SEC (Size Exclusion Chromatography)
- FFF (Field Flow Fractionation)
- SDS-Page Gels
- AUC (Analytical Ultra-Centrifugation)

- Light Obscuration
- Microscopy
- Flow Microscopy
- Coulter Counter

- Manual / Human
- Semi-Automated
- Automated

Narhi, et al. J Pharm Sci, 2012



Particulate Matter Definitions

- Extrinsic (from outside the process)
 - Environmental Contaminants
 - insect parts, hair, fibers, paint, rust
- Intrinsic (from within the process)
 - Processing Equipment, Primary Package
 - qualified product contact materials (e.g. stainless steel, glass, rubber, silicone oil)
- Inherent (part of the formulation)
 - Protein agglomerates



RISK



US FDA



US FDA

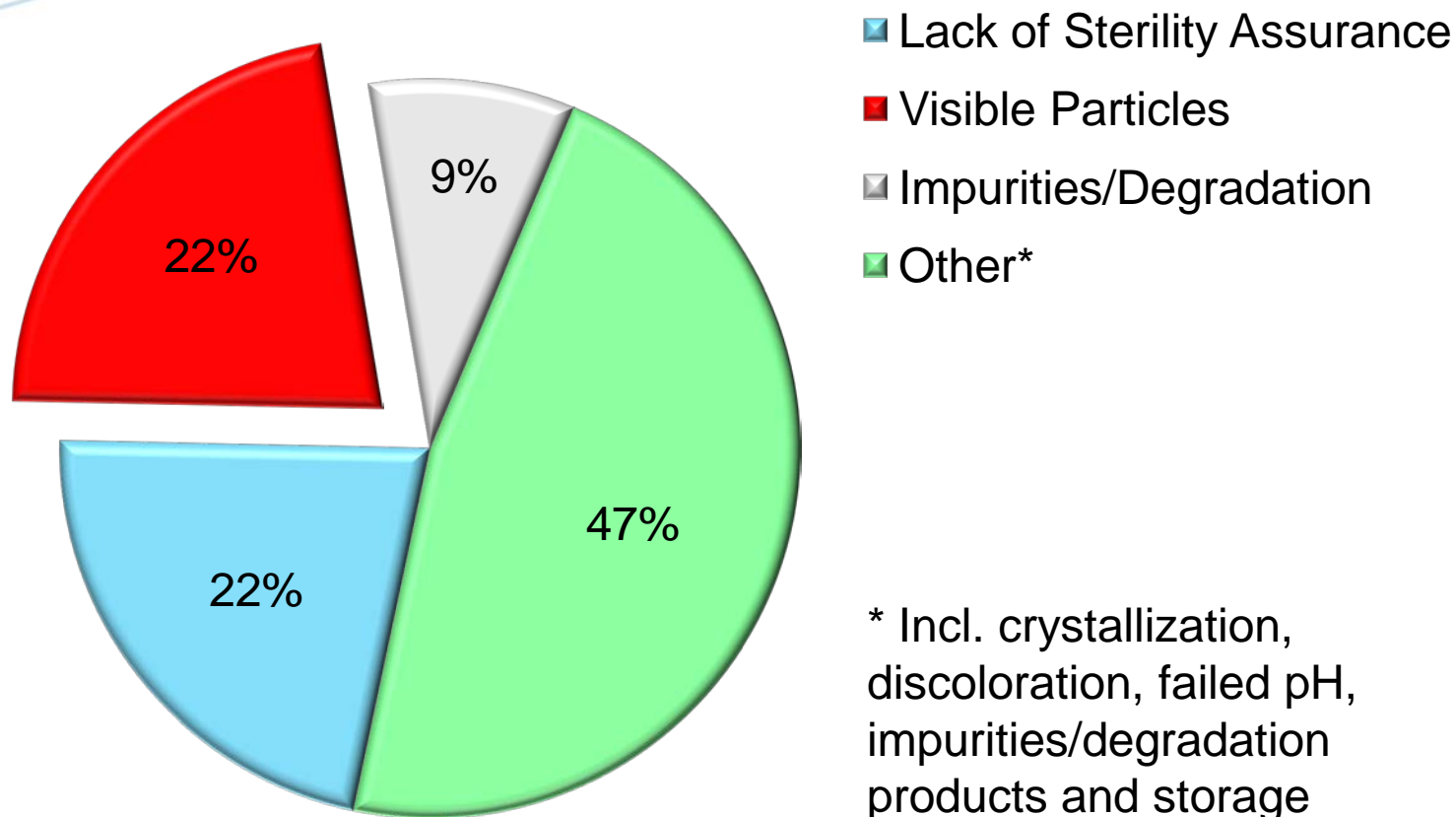
“I’m sure you’ve cringed when you heard some of the stories – **glass shards and other particulates in products, leaking IV bags, too much medication in syringes**; bacterial and endotoxin contamination found in products manufactured in aging sterile injectables facilities These are not the norm, but they are warning signals that we can and must do more”

Margaret Hamburg, FDA Commissioner

February 12, 2013



FDA Sterile Injectable Drug Recalls 2008-2012



- Lack of Sterility Assurance
- Visible Particles
- Impurities/Degradation
- Other*

* Incl. crystallization, discoloration, failed pH, impurities/degradation products and storage temp excursions.

Steven Lynn, FDA Office of Manufacturing and Product Quality, March, 14, 2013

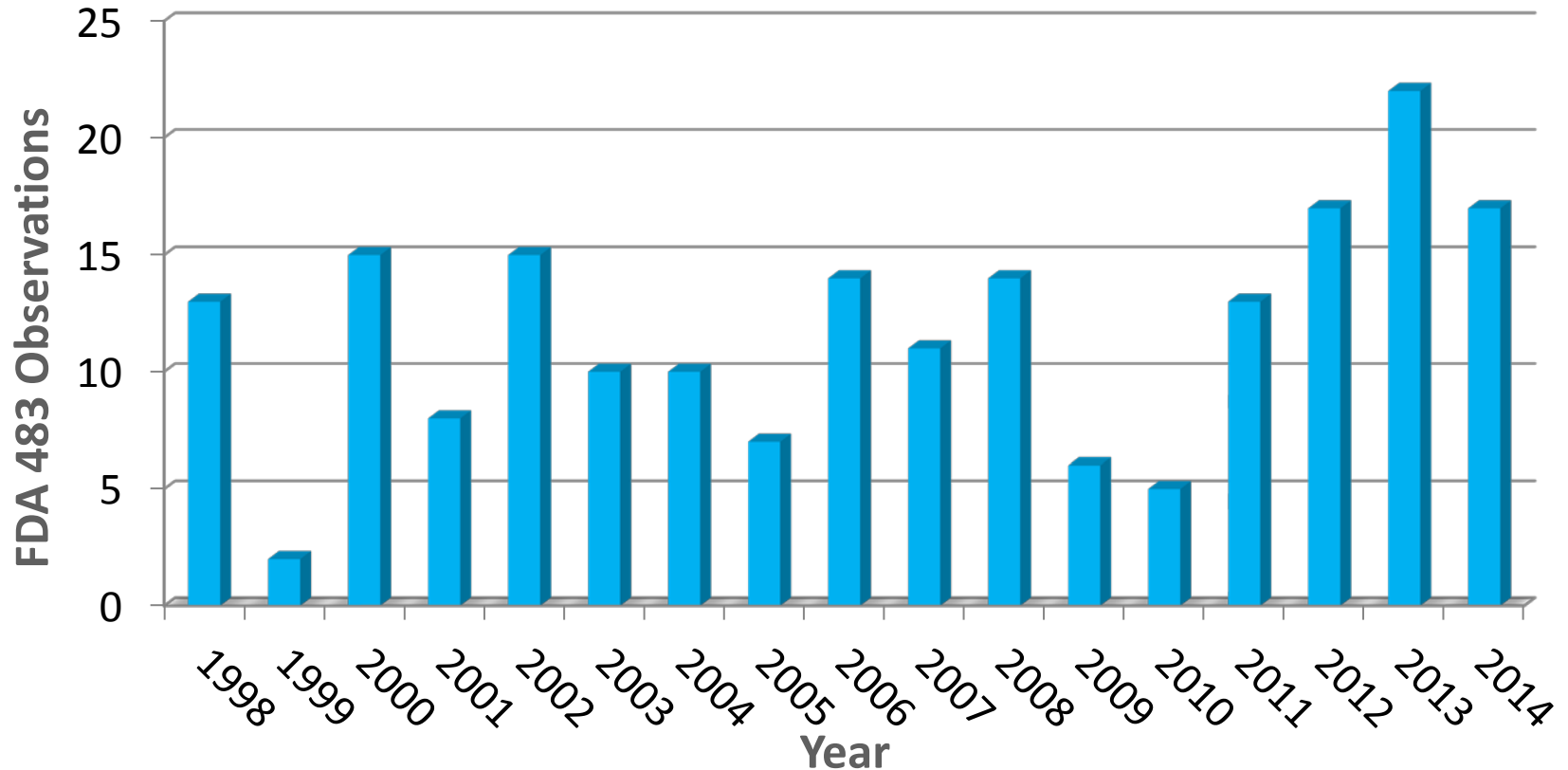


Recent FDA Recalls

- 10-16-2014 ... Hospira Announces Voluntary Nationwide Recall of One Lot of 1% Lidocaine Injection ... Due to the Presence of Particulate Matter
 - Human hair
- 8-13-2014 ... Baxter Voluntarily Initiates U.S. Recall of Two Lots of Peritoneal Dialysis Solution Due to the Presence of Particulate Matter
 - Oxidized stainless steel, garment fiber, PVC
- 8-13-2014 ... Amgen Issues Voluntary Recall of Aranesp[®] ... Due to the Presence of Particulate Matter
 - Cellulose and/or polyester
- 8-6-2014 ... Cubist Pharmaceuticals Issues Voluntary U.S. Recall of Certain Lots of CUBICIN ... Due to the Presence of Particulate Matter
 - Glass



US FDA 483 Observations Regarding Visual Inspection



from *GMP Trends*



US 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.
- Inspectors must be trained and training documented.
- Inspectors must be periodically recertified.
- Training and certification conditions must align with routine 100% inspection conditions.
- Address inspection fatigue during qualification.



US FDA 483 Themes

- Must conduct thorough investigations. Identify particulate matter when performing investigations.
- Must use statistically sound sampling plan(s) for AQL inspection.



USP



US Pharmacopoeia

- USP 37: <1> Injections - Foreign and Particulate Matter

All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* <788> and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed “visible particulates”) in its contents.



US Pharmacopoeia

- USP 37: <1> Injections - Foreign and Particulate Matter (cont.)

The inspection process shall be designed and qualified to ensure that **every lot of parenteral preparations is essentially free from visible particulates**. Qualification of the inspection process shall be performed with reference to **particulates in the visible range of a type that might emanate from the manufacturing or filling process**. **Every container that shows evidence of visible particulates shall be rejected.**



US Pharmacopoeia

- USP 37: <1> Injections - Foreign and Particulate Matter (cont.)

The **inspection for visible particulates may take place when inspecting for other critical defects**, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the **nature of the contents or the container-closure system permits only limited capability for inspection** of the total contents, the **100% inspection of a lot shall be supplemented** with the inspection of constituted (e.g. dried) or withdrawn (e.g. dark amber container) contents of a sample of containers from the lot.



USP <790> Visible Particulates in Injections

- Inspection conditions defined
 - Harmonized with EP
 - 2,000-3,750 lux
 - Black and white backgrounds
 - No magnification
 - 5 sec viewing against each background
 - Swirl and/or invert sample
- Applies to *Extrinsic* and *Intrinsic* particles
- *Inherent* particles addressed in individual monographs or approved regulatory filings



USP <790> Acceptance Criteria

- At Time of Batch Release
 - 100% inspection followed by acceptance sampling
 - ANSI/ASQ Z1.4-2003 or ISO 2859
 - AQL= 0.65%, UQL= 2.3-3.3% typical
 - Alternate and equivalent plans acceptable
- For Product in Distribution
 - $n = 20, a = 0$
 - AQL= 0.26%, UQL= 10.9%



USP <790>

- Published in USP 37 1st Supplement
 - Official August 1, 2014
- Clarifications added:
 - A smaller sample (such as the Special sampling plans in the standards) is appropriate for destructive testing of powders and suspensions
 - Now states that this chapter does not add a new requirement for stability testing
 - Alternative light sources such as LED's are acceptable
 - The light intensity range stated is intended to establish a lower limit of 2,000 lux, but that it may be appropriate to inspect at levels above 3,750 lux



USP <1790>

- <1790> *Visual Inspection of Injections*
 - Information Chapter in development
 - Key elements of an inspection process
 - Patient Risk
 - Elements of a good inspection process
 - Lifecycle / Continuous Improvement
 - Visible Defect Types
 - Extrinsic, Intrinsic and Inherent
 - Inspection Technologies
 - Published as draft for comment in PF 41(1) January 2015



PDA Benchmark Survey



Survey Format and Participation

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

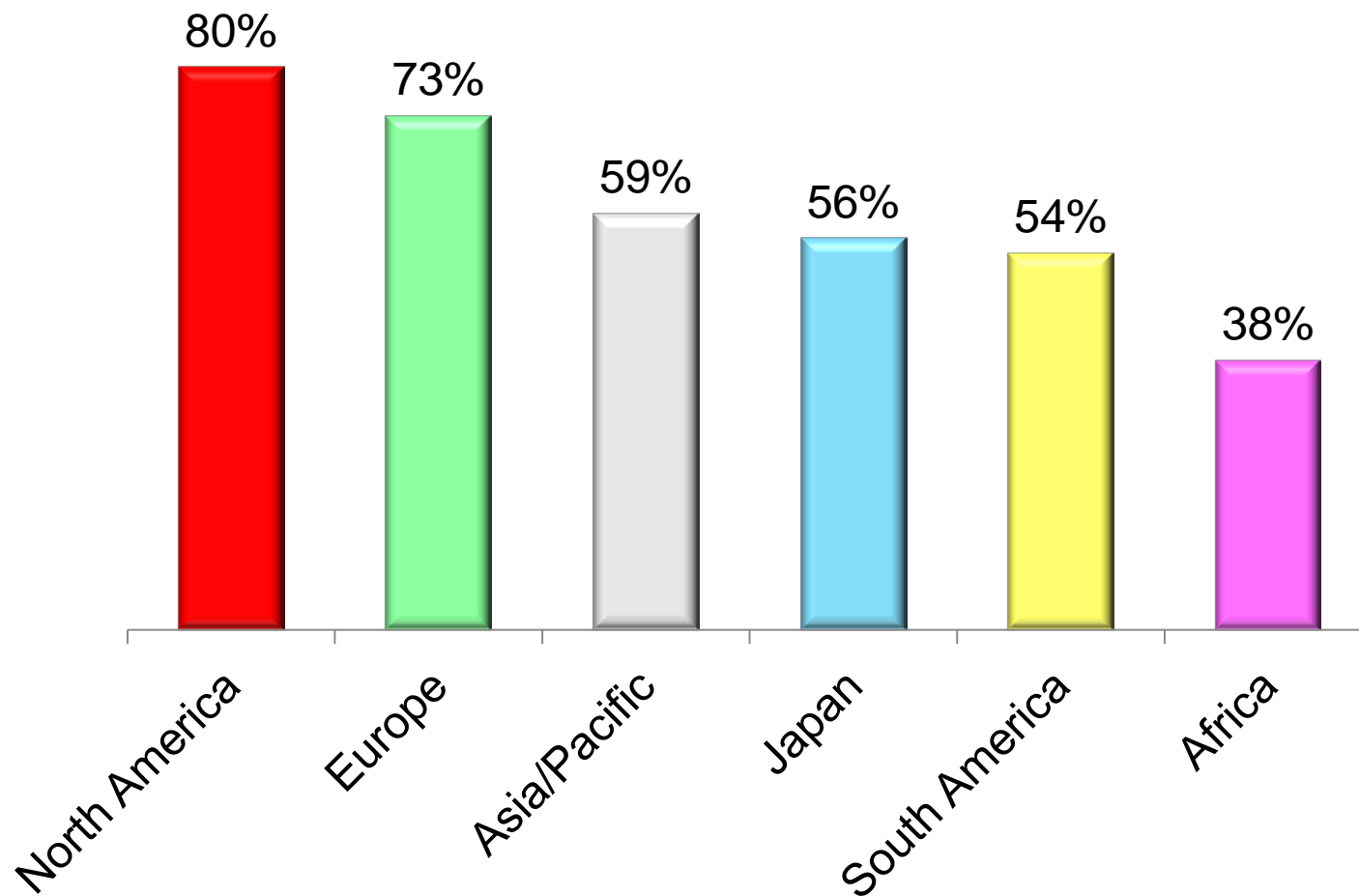


Please keep in mind ...

- 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.

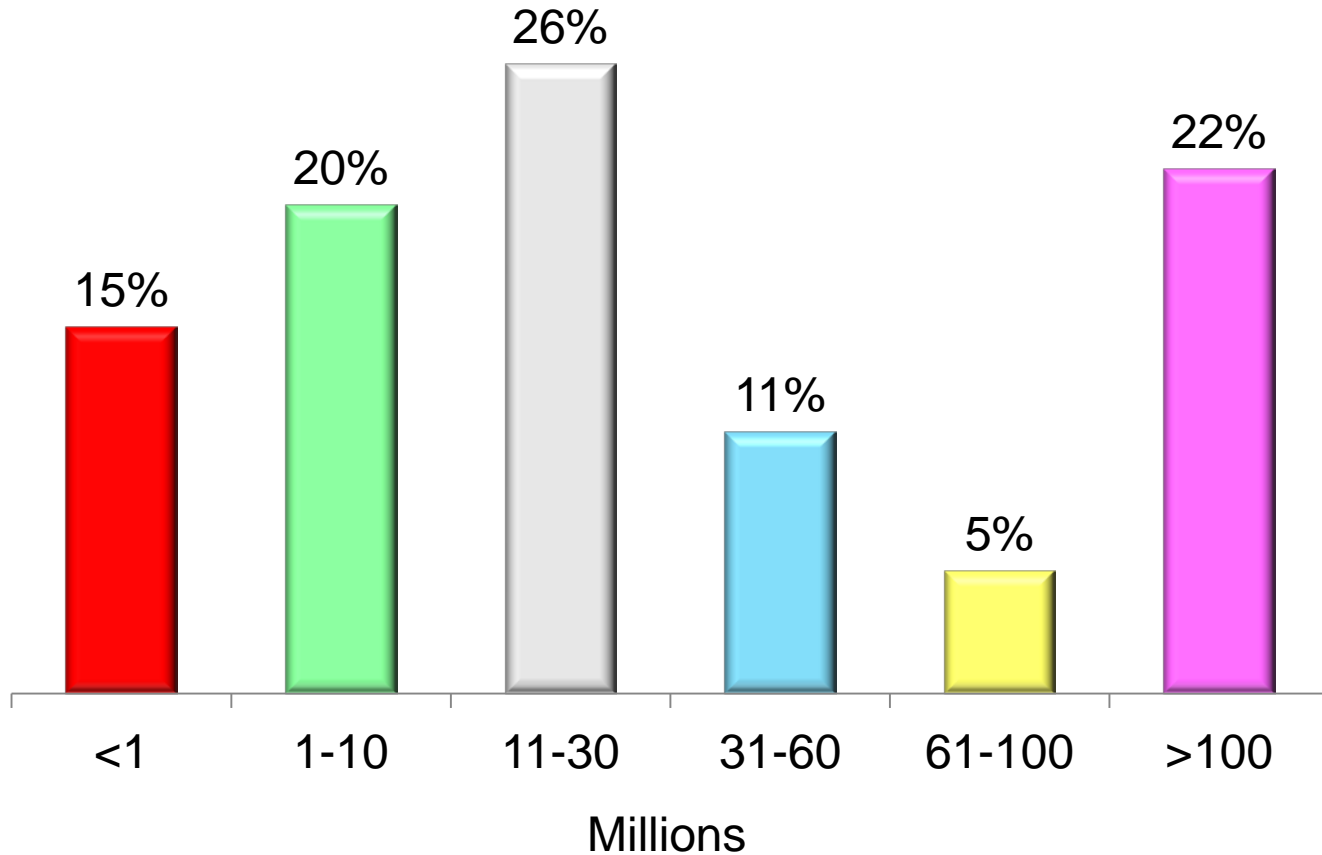


To what geographic regions are products manufactured at this facility distributed?





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





What are the product types produced at this facility?

	<u>2014</u>	<u>2008</u>	<u>2003</u>	<u>1996</u>
• Human	76%	67%	85%	80%
• Biological/Biotech	57%	76%	37%	40%
• Device/Combination ...	22%	ND	ND	ND
• Animal	17%	48%	7%	10%
• Diagnostics	12%	5%	4%	10%

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



What technique is used for inspection for / of ...

	<u>2014</u>	<u>2008</u>	<u>2003</u>	<u>1996</u>
• Particles				
– Manual	46%	33%	46%	33%
– Semi-Automated	23%	24%	19%	20%
– Automated	31%	43%	35%	42%
• Container / Closure				
– Manual	50%	36%	63%	48%
– Semi-Automated	26%	26%	15%	42%
– Automated	24%	39%	20%	5%



Where do you perform 100% inspection?

	<u>2014</u>	<u>2008</u>	<u>2003</u>	<u>1996</u>
• Off-line	79%	81%	59%	37%
• In-line w/ Filling	42%	16%	22%	31%
• In-Line w/ Packaging	60%	3%	17%	42%

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

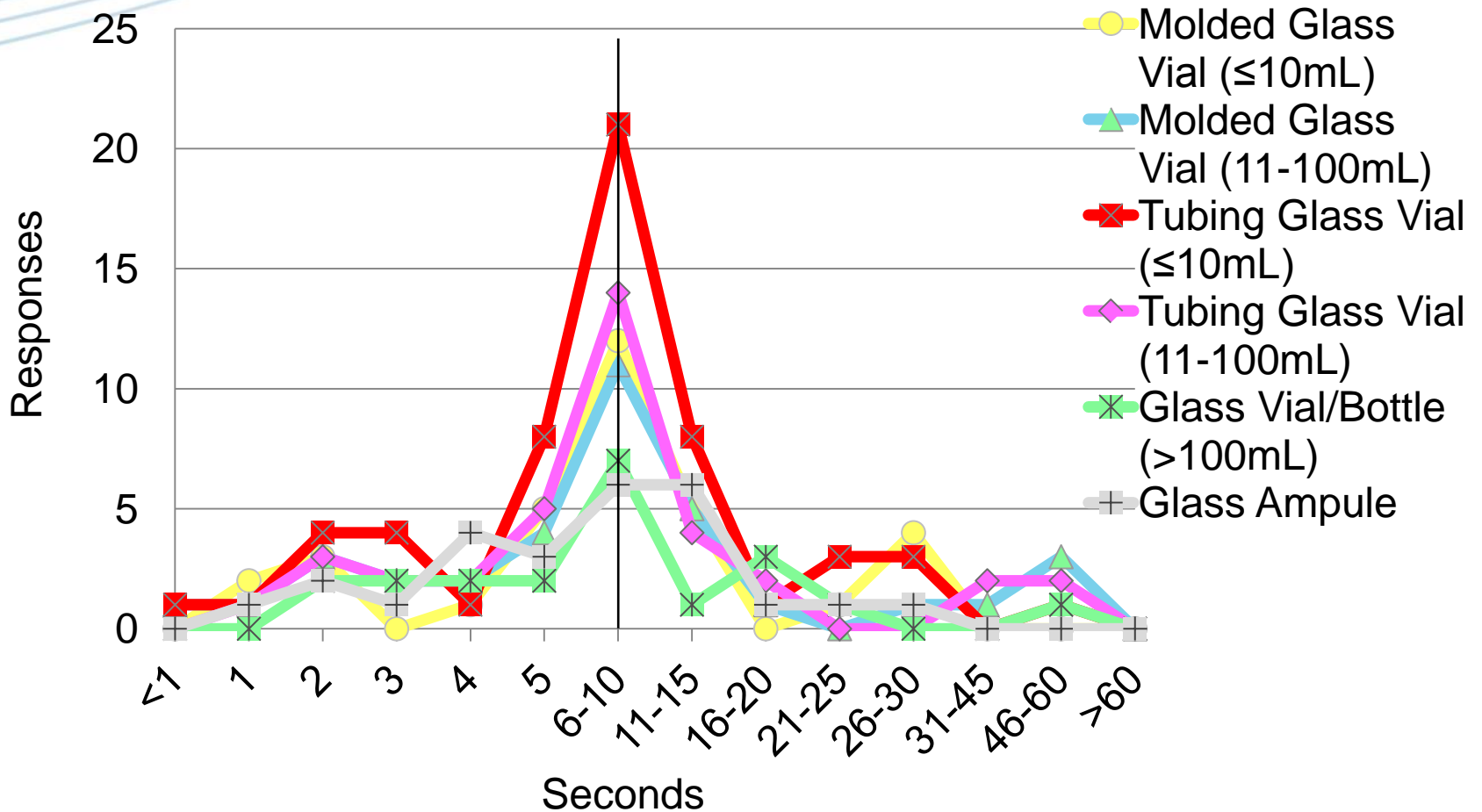


Manual Inspection Conditions

- 69% control inspection time or the pace of inspection.
 - 45% with Timer
 - 39% by SOP
 - 27% with Conveyor
- 27% use a magnifier.
 - 44% 2X, 25% 3X, 9% 4X, 9% 5X, 13% >5X
- 5% use a polarizer.
- Light Source used:
 - 65% Fluorescent, 18% Incandescent, 17% LED

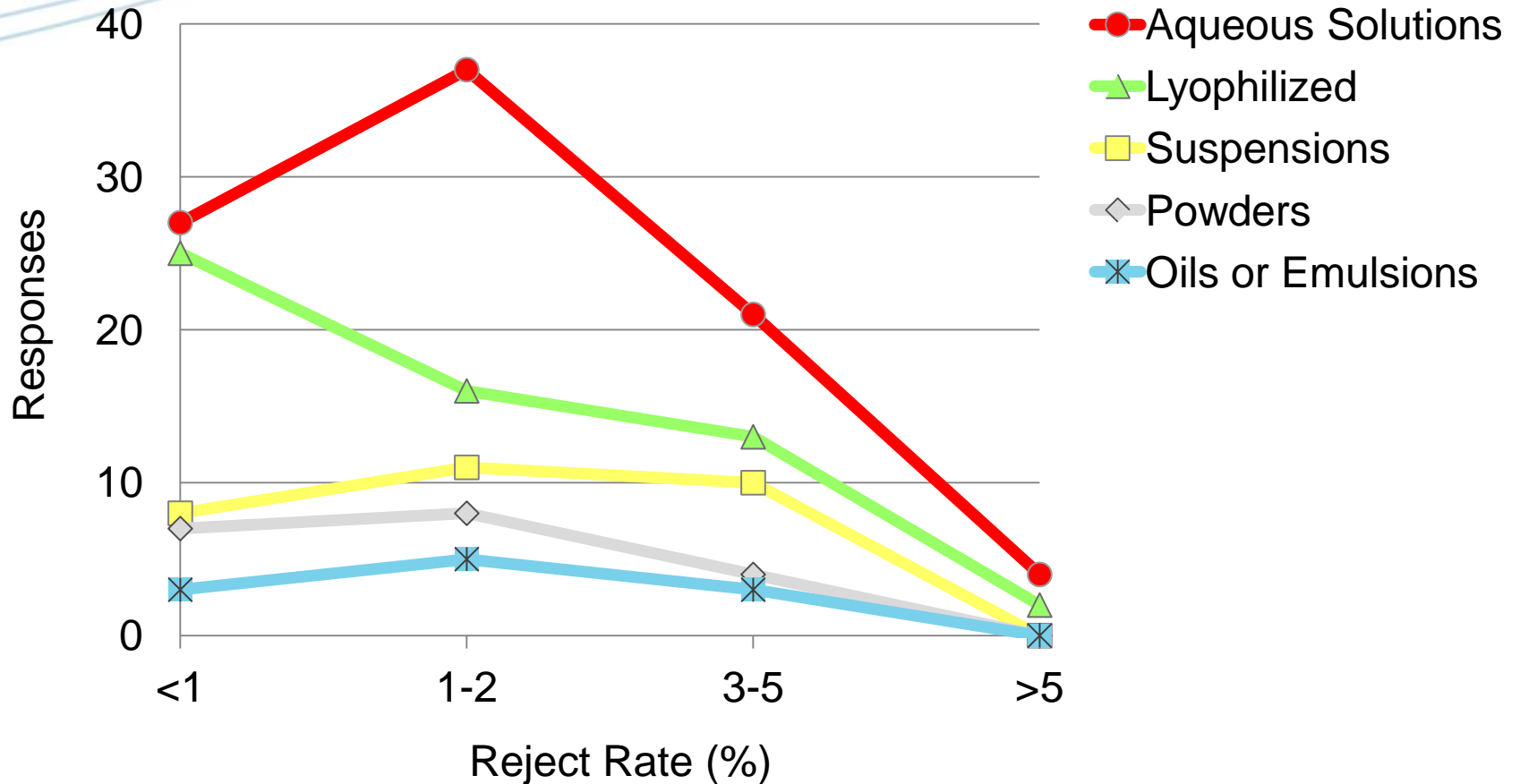


What is the average inspection time for this container type?





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)

	<u>2014</u>	<u>2008</u>	<u>2003</u>	<u>1996</u>
• 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
• Hi/Lo Fill	6	4	5	5
• Stopper/Plug	7	8	9	8
• Cake	8	8	6	6
• Leaks.....	9	7	8	7

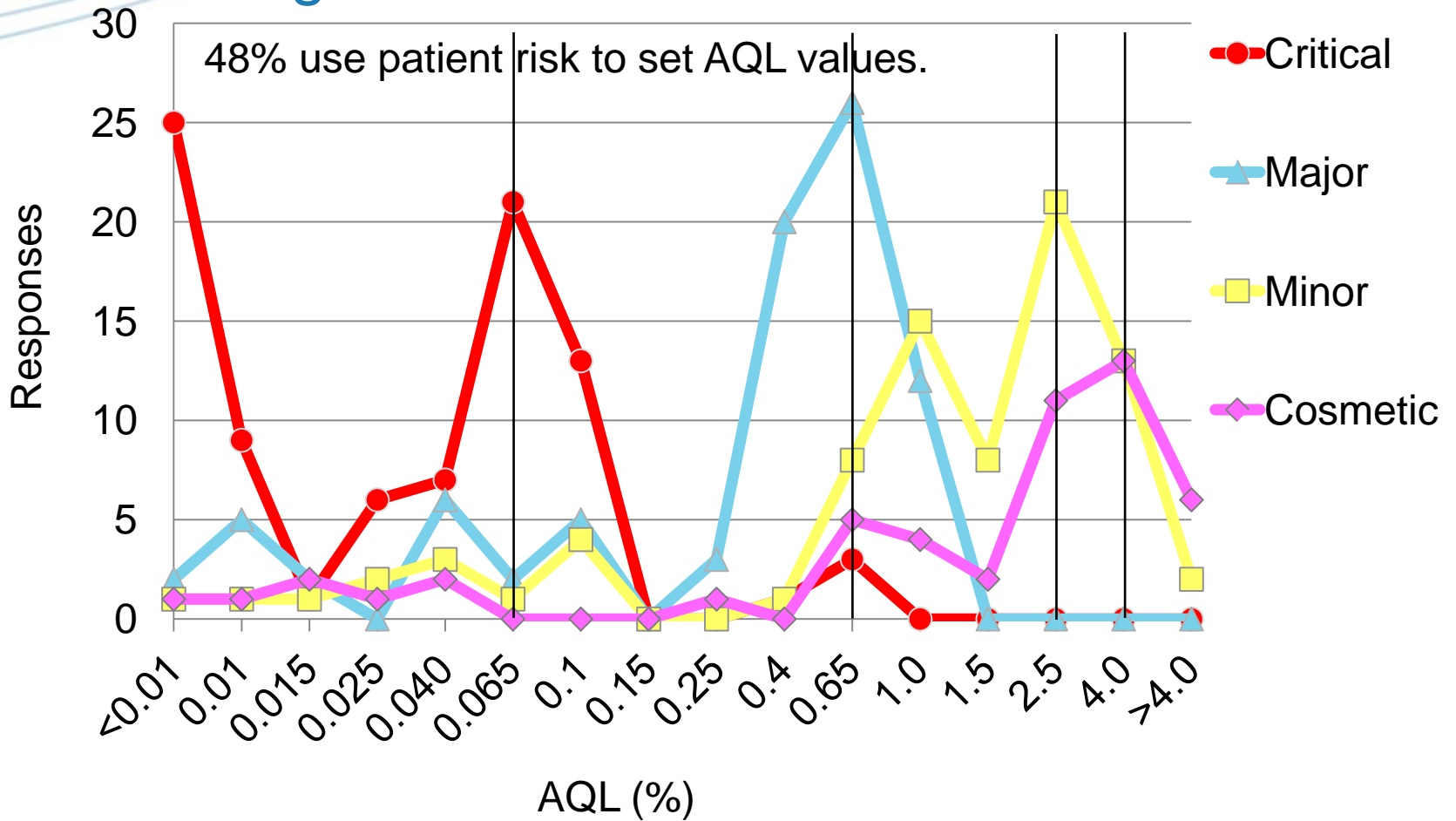


What are the most common types of particles found during visual inspection? (Rank order with 1 most frequent.)

	<u>2014</u>	<u>2008</u>	<u>2003</u>	<u>1996</u>
• Lint / Fiber	1	1	1	1
• Glass	2	2	2	2
• Product Related	3	3	4	3
• Metal	4	5	3	4
• Rubber	5	4	5	5



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





Conclusions and Acknowledgements



Conclusions

- Current industry performance is generally at or beyond the limits of medical risk.
- Compendial guidance is ambiguous, but getting better.
- “Zero defects” is a valuable goal, not a practical limit for particulate matter.
- Need to develop practical limits based on risk assessment and process capability measures.



Conferences, IG and Training

- PDA Visual Inspection Forum
 - October 26-27, 2015, Bethesda, MD
- PDA Visual Inspection of Parenterals Interest Group (IG)
 - NA meets at PDA Annual Meeting and PDA/FDA Conference
 - EU meets annually, April 14, 2015, Berlin
 - PDA Connect
- PDA Training and Research Institute (TRI)
 - Introduction to Visual Inspection
 - February 10-11, 2015



Acknowledgments

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 - Russell E. Madsen – The Williamsburg Group
- PDA Staff
 - Morgan Holland - PDA
 - Janie Miller - PDA
- Others
 - Stephen J. Borchert – Pfizer, retired
 - D. Scott Aldrich – Ultramikro
 - Markus Lankers – Rap.ID Particle Systems



Remember, everyone is an inspector!

