Visual Inspection Execution & Documentation of Defects and Container/Closure Integrity

SUSAN BAIN DRSC

CFR tells us……

§ 211.94 Drug product containers and closures

- **(a)** Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity…….
- **(b)** Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination…….
- **(c)** Drug product containers and closures shall be clean and……

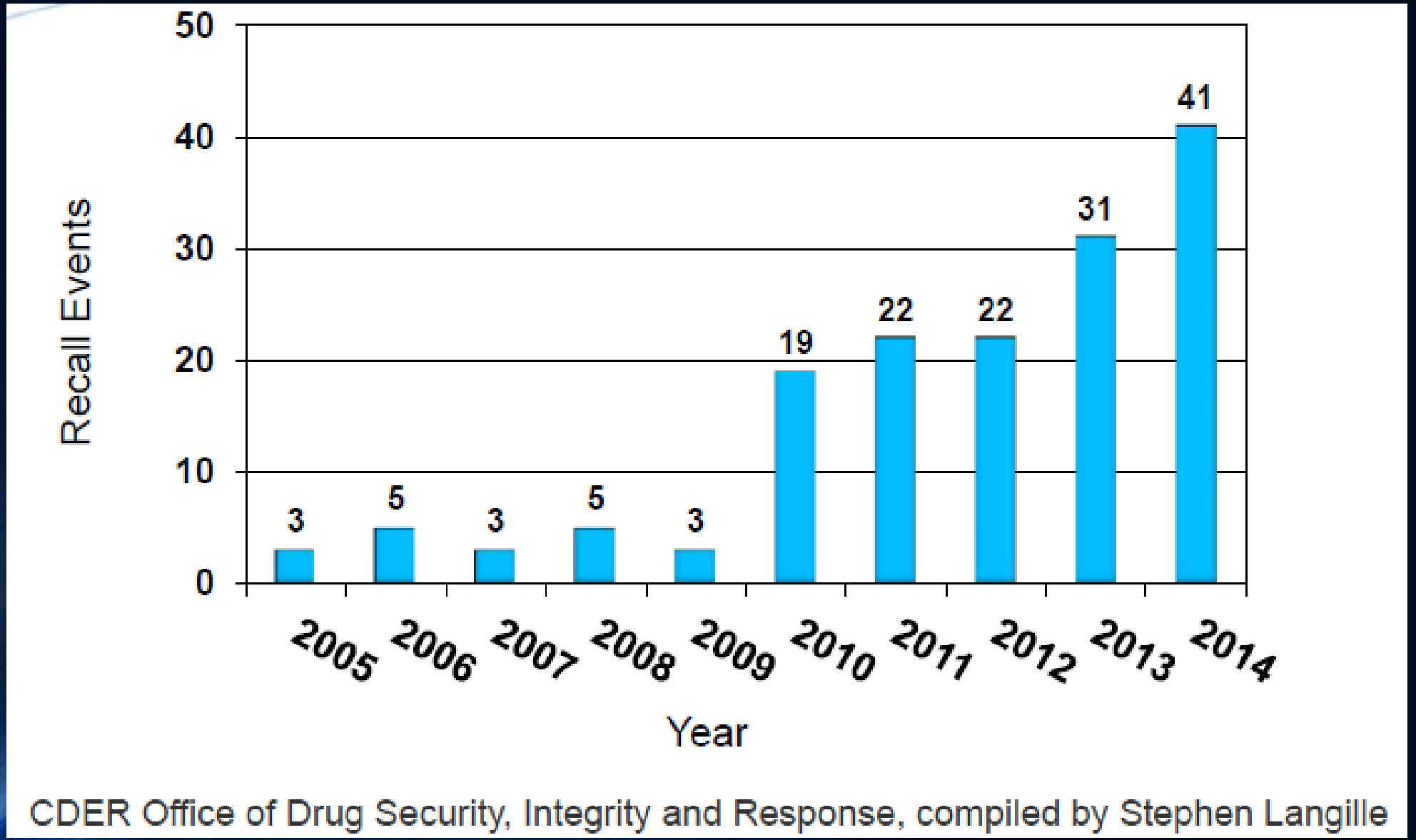
§211.165 Testing and release for distribution

- (f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Sterile Drug Products Produced by Aseptic Processing-Good Manufacturing Practices - 2004:

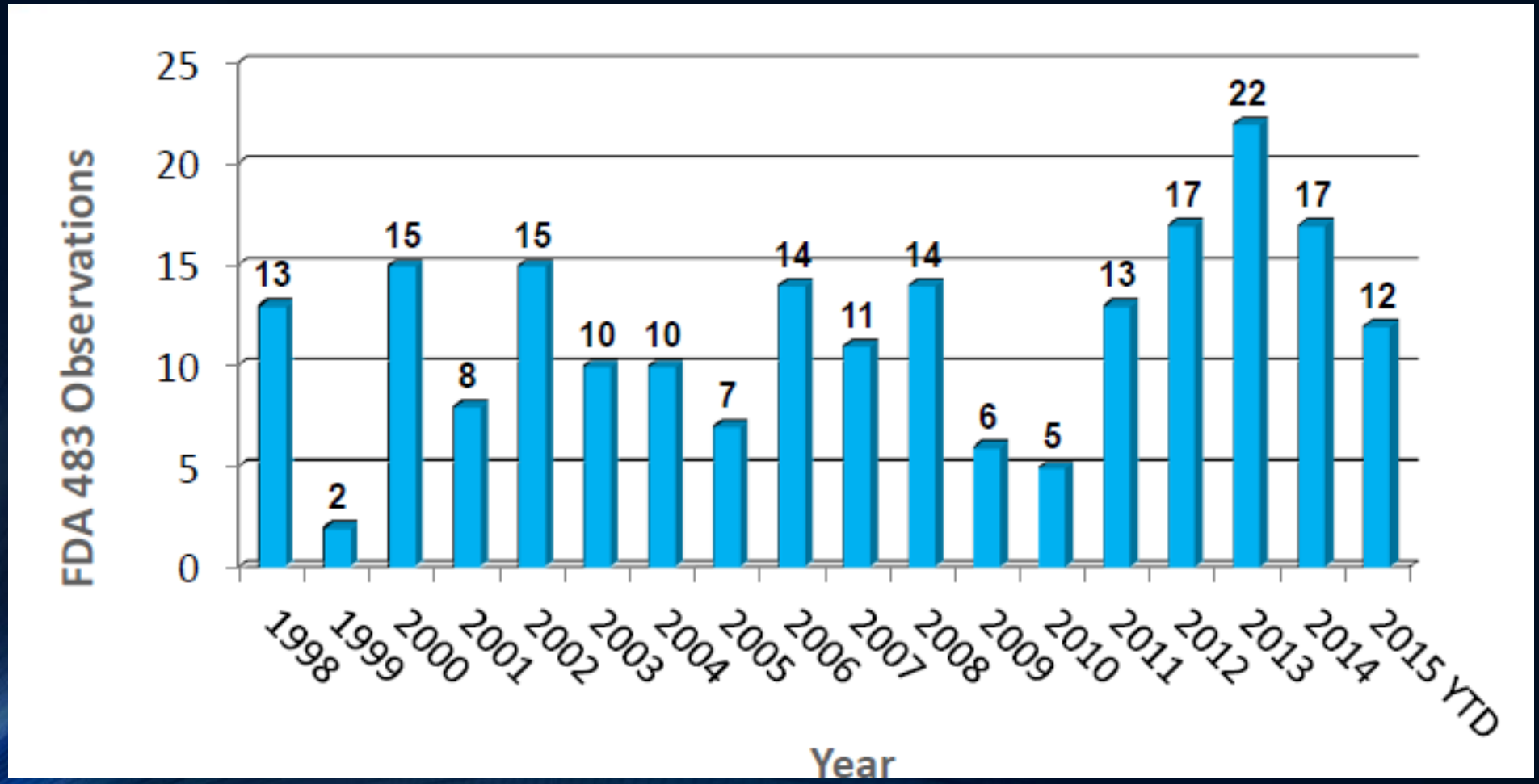
Inspection of Container Closure System……Any damaged or defective units should be detected, and removed, during inspection of the final sealed product…….. Any defects or results outside the specifications established for in-process and final inspection are to be investigated in accord with § 211.192

Recalls for Visible Particulates



CDER Office of Drug Security, Integrity and Response, compiled by Stephen Langille

483 Observations for Visible Inspection Issues



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What concerns FDA?

- Inspectors must receive documented training using known sample defects
- Inspectors must be recertified at regular intervals
- Inspection protocol must address Inspector fatigue
- Procedure must be in place for re-inspection activities (ex. Number of re-inspections allowed)
- All particulates found must be identified
- Must use AQL sampling plans and rejection rates

Human vs. Automated Inspections

Human manual inspection is still the reference standard for visual inspection and is the method stated in the European Pharmacopoeia of the Council of Europe (Ph. Eur.) and USP <790>

- Human inspectors are flexible and can respond to something they have never seen before or something that “doesn’t look right”
- Can more easily tolerate normal variation in containers, especially those formed by molding, reducing the number of falsely rejected good product
- Humans are more limited in the speed of inspection (i.e., the number of containers per minute or hour that they can inspect)
- Humans require frequent breaks to minimize fatigue
- Limitations lead to greater variation in manual inspection results, but can be minimized through good training and operating procedures

Vision Machines have the advantage of speed

- Can detect visible particulates in solutions, as well as container and seal defects.
- Less flexible with container variation, especially molded containers
- High cost must be justified based on product volume
- Best suited for high volume, limited number of products

PDA Visual Inspection Survey conducted in 2014 revealed some interesting findings…….

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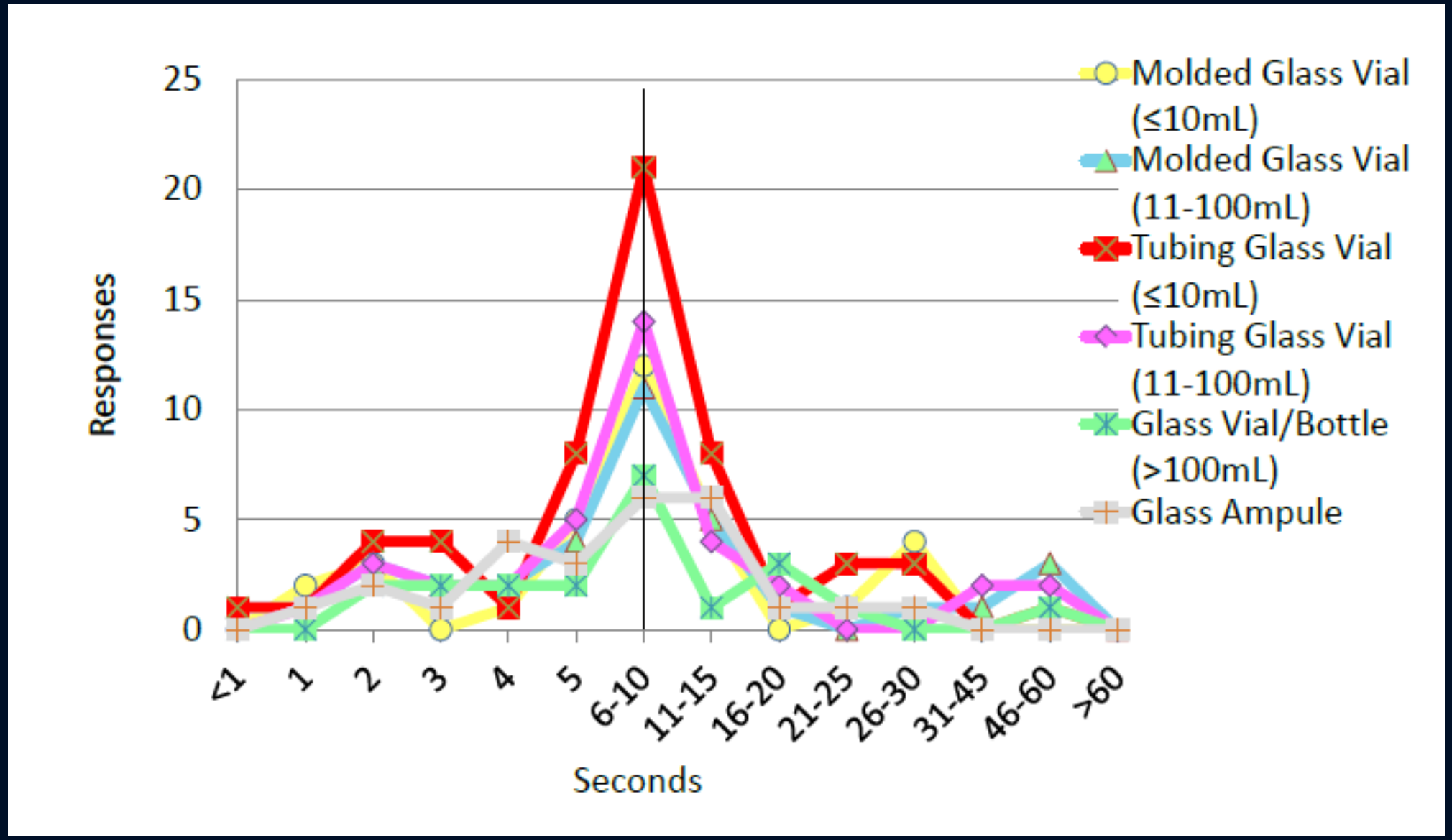
"PARTICULATE MATTER AND VISUAL INSPECTIONS: INDUSTRY TRENDS 2015"

- 171 respondents world-wide, ranging from production of <1 mil units/year to >100 mil units/year
- Manual inspection is most used method for particles (46%) and container/closure (50%) inspections
- 84% of inspections were aqueous solutions; 63% lyophilized powders
- Filled into tubing (70%) and molded glass vials (55%)
- Most firms (69%) do not use polarized light or magnification and control time (6-10 sec.) which agrees with EP and USP inspection conditions

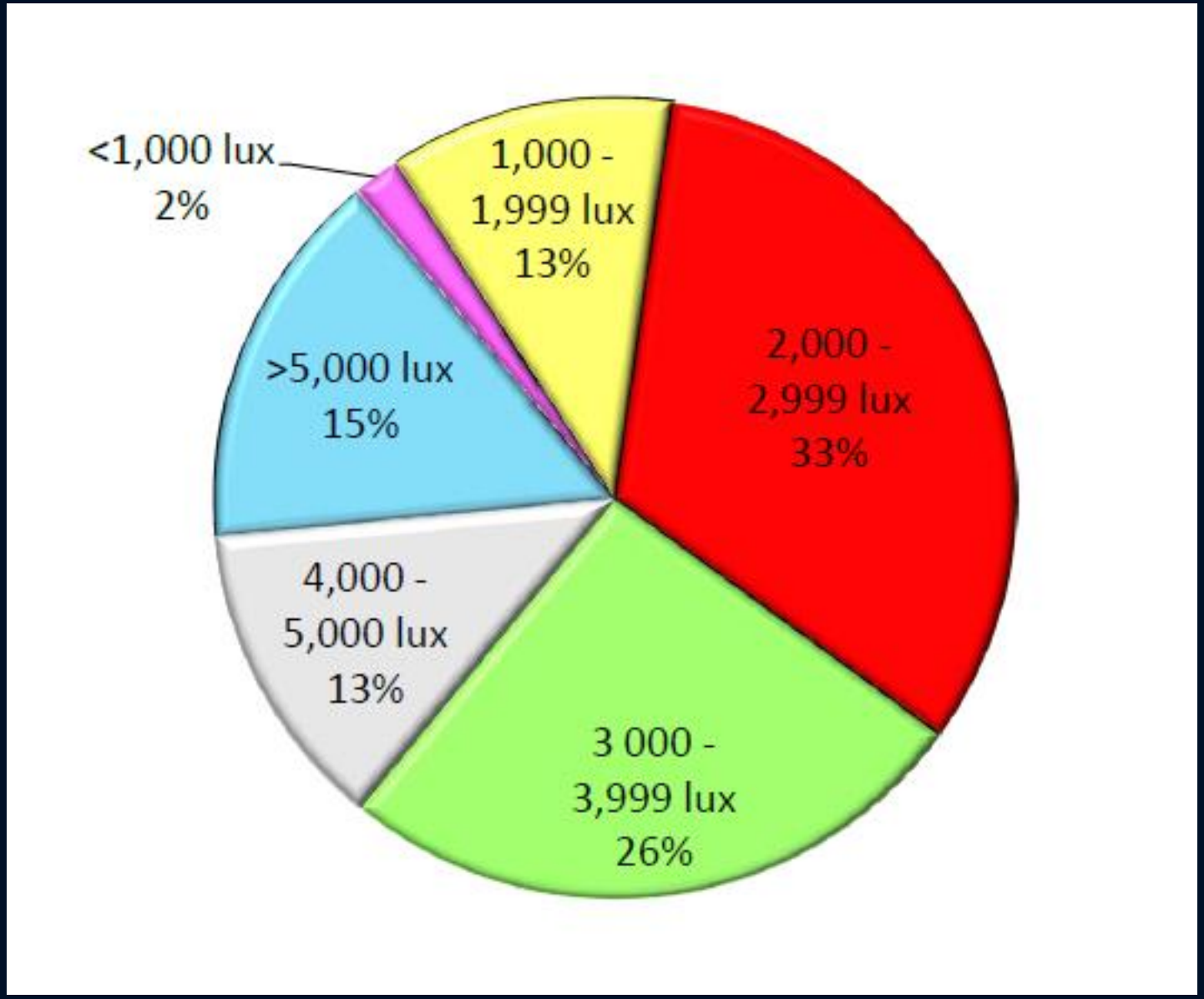
PDA Visual Inspection Survey conducted in 2014 revealed some interesting findings (cont'd)……..

- 59% use Illumination intensity 2,000-4,000 lux which agrees with EP and USP. 28% of firms use higher
- 79% inspections performed off-line
- 49% Inspectors given a break every 60 min.; 27% every 30 min.
- Rejection rates – 1-2% particulates in aqueous solutions; <1% lyophilized product (detection rather than quality???)
- Particles and specifically lint/fiber continues to be most common defect
- After 100% inspection, 92% are routinely audited using ANSI/ASQ Z1.4, ISO 2859 or JIS Z9015
- There has been a shift in median AQL between 2008 and 2014 – Critical defects from 1.0% (2008) to 0.065% (2014); Major 0.65%; Minor defects from 4.0% (2008) to 2.5% (2014)……not consistent with new USP <790> classification…..Regulatory pressures???

Inspection Times



Inspection Illumination



USP<790> Visual Particulates

- 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

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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%

Key Take-aways

- FDA is looking for well justified AQL inspection plans with thorough identification and investigations of particulates and/or container closure issues
- United States Pharmacopeia (USP) General Chapter <790> 'Visible Particulates in Injections' became official in August 2014
  - Inspection conditions defined
    - Example: lighting, black/white backgrounds, harmonization with EP, swirl and/or invert, no magnification
  - Inspection requirements at batch release
    - Example: ANSI/ASQ Z1.4 or ISO 2859, 100% visual inspection followed by AQL acceptance sampling
  - Applies to intrinsic and extrinsic particles
- USP <1790> (revised draft 12/2015)
  - Contains discussion of the key elements of an effective inspection process
  - Addresses visual inspection in general, including container and closure defects
    - Includes detection of other visible defects; including container integrity defects such as cracks, misplaced stoppers, or incomplete seals
  - Discusses particulates, which are the central focus of *USP* <790>
  - Details the evaluation of marketed products where anomalies had been observed regarding particles
  - Discussion of patient risk and risk factors

Visual inspection will never result in 100% defect free products!!!

Practical limits; Patient Risk and Process Capability are guiding factors

Thank you!

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